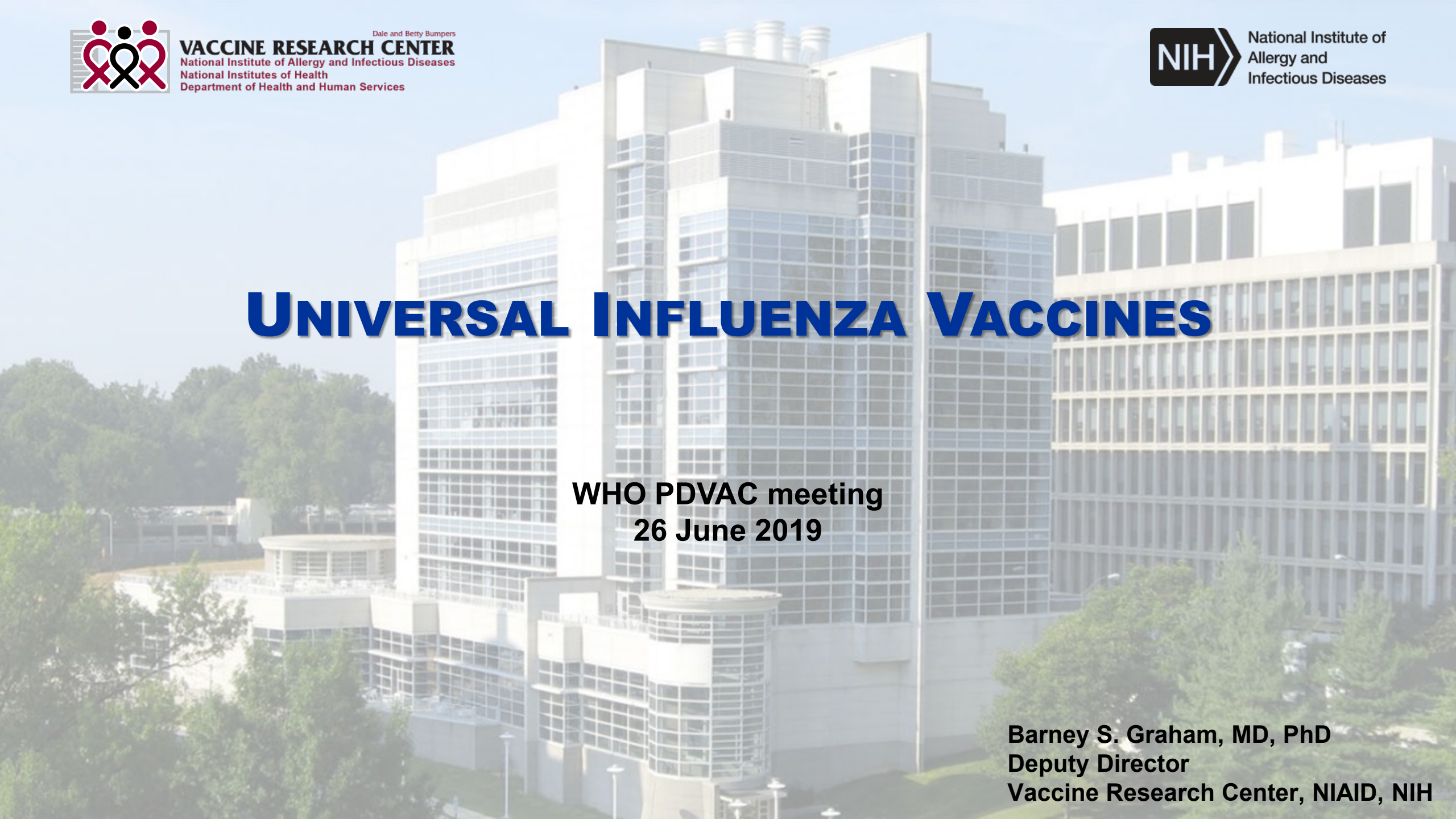


Dale and Betty Bumpers
VACCINE RESEARCH CENTER
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Department of Health and Human Services

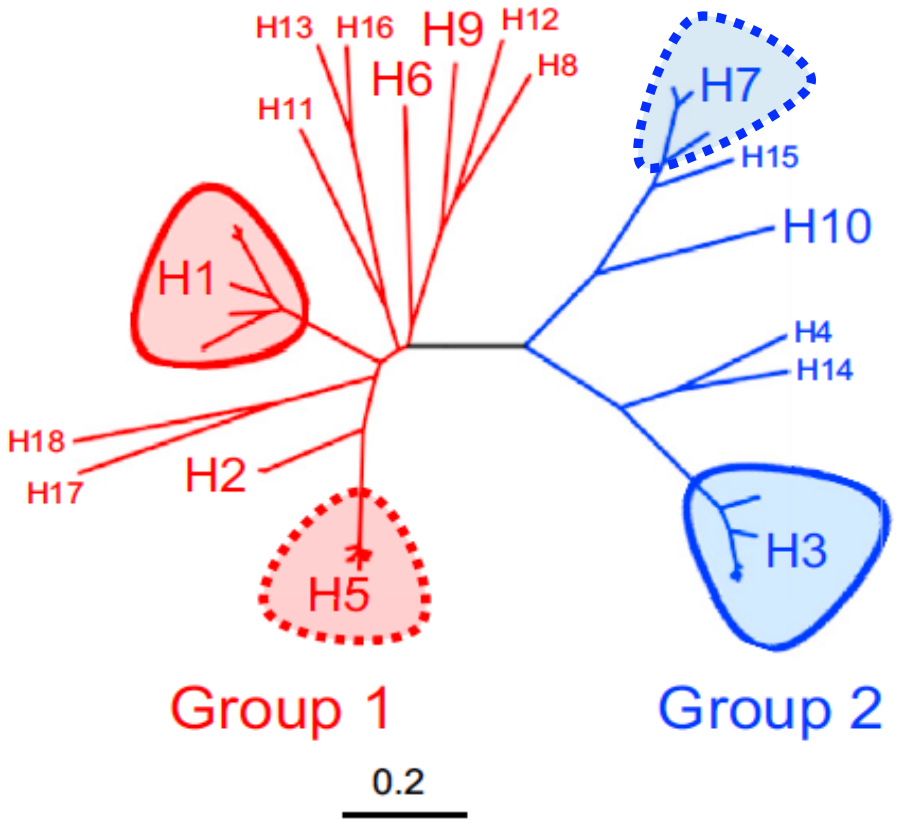
National Institute of Allergy and Infectious Diseases

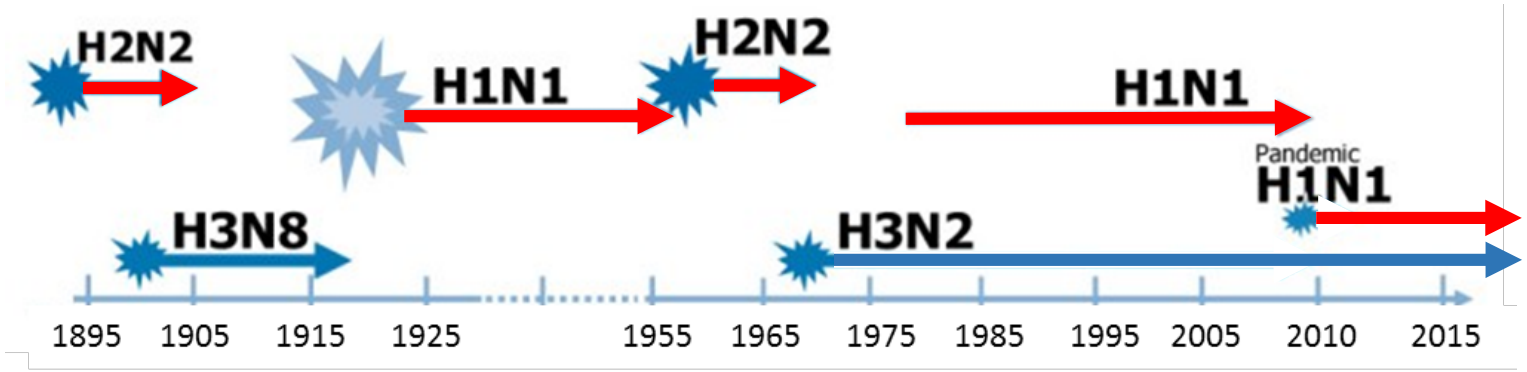
UNIVERSAL INFLUENZA VACCINES

WHO PDVAC meeting
26 June 2019

Barney S. Graham, MD, PhD
Deputy Director
Vaccine Research Center, NIAID, NIH

Influenza A has been the cause of prior pandemics





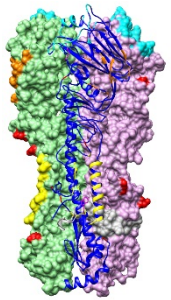
Need For a Universal Influenza Vaccine

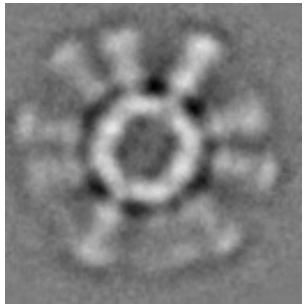
Current Influenza Vaccines:

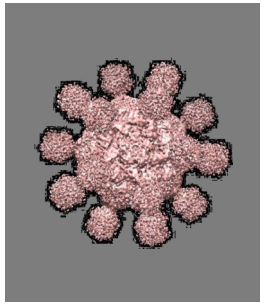
- Use 1940's technology - inactivated virus grown in chicken eggs
- Only 50-60% effective in good years
- Need to be reformulated every year to match circulating influenza strains
- Not effective against new pandemic strains and response is too late

Future Influenza Vaccines:

- Will use mammalian and insect cell manufacturing of recombinant proteins
- Apply new technologies and endpoints







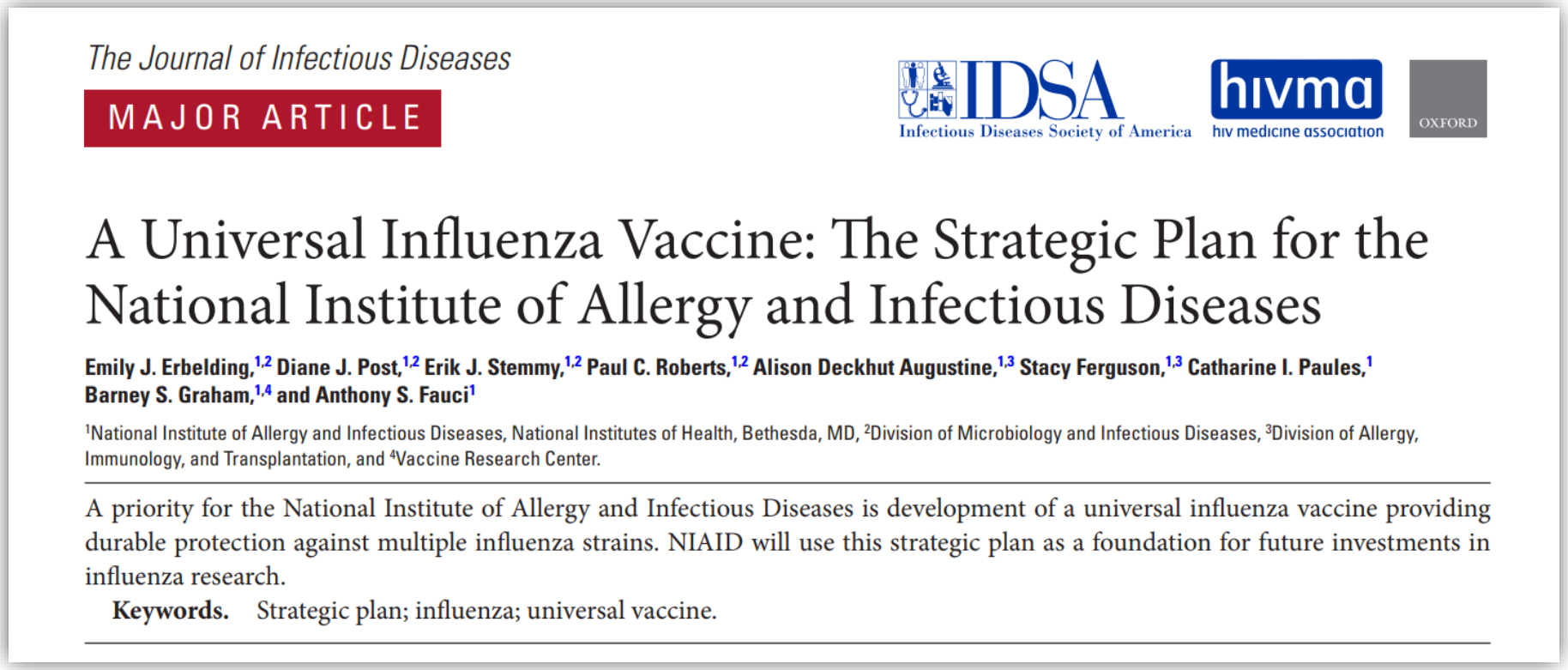
Major Biological Challenges for Universal Influenza Vaccine

- **Antigenic variation and genetic plasticity**
  - Extensive zoonotic reservoir, reassortment, adaptive mutations
- **Pre-existing immunity**
  - Immunodominance of serotype-specific epitopes
  - Immunodominance of antibody lineages with limited breadth
  - Influence on B cell phenotypes

Influenza Vaccine Strategies

	Strategy	Phase	Theoretical Mechanism
Leading universal vaccine concepts	HA stem or head-stem chimera	Phase I	Broad NAb (no HAI) and ADCC
	HA head chimera (COBRA)	Pre-clinical	Broad NAb (with HAI)
Additional concepts	M2 ectodomain	I/II	Broad cross-reactive Ab; ADCC (no NT)
	Co-assembled HA on NP	Pre-clinical	Favors cross-reactive B cells
Improved seasonal vaccines	HA rosettes, individual full-length HA nanoparticles, VLP	I/II	Potency from particle display, breadth from multiple strains mixed or sequential delivery
	Add neuraminidase antigen	Pre-clinical	Additional antigen for NT breadth/potency
	Live-attenuated or single-round virus or gene-based delivery	Phase I	Additional antigens, T cell responses, and mucosal immunity
	Mammalian cells, high-dose, adjuvants, LAIV or DNA prime	Post-marketing	Improved manufacturing or immunogenicity of conventional vaccine

NIAID Universal Influenza Vaccine Strategic Plan



The Journal of Infectious Diseases

MAJOR ARTICLE

A Universal Influenza Vaccine: The Strategic Plan for the National Institute of Allergy and Infectious Diseases

Emily J. Erbelding,[1,2] Diane J. Post,[1,2] Erik J. Stemmy,[1,2] Paul C. Roberts,[1,2] Alison Deckhut Augustine,[1,3] Stacy Ferguson,[1,3] Catharine I. Paules,[1] Barney S. Graham,[1,4] and Anthony S. Fauci[1]

[1]National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, [2]Division of Microbiology and Infectious Diseases, [3]Division of Allergy, Immunology, and Transplantation, and [4]Vaccine Research Center.

A priority for the National Institute of Allergy and Infectious Diseases is development of a universal influenza vaccine providing durable protection against multiple influenza strains. NIAID will use this strategic plan as a foundation for future investments in influenza research.

Keywords. Strategic plan; influenza; universal vaccine.

- NIAID priority to develop a universal influenza vaccine that provides durable protection against multiple influenza strains
- Foundation for future investments in influenza research (CIVIC grants)

National Institute of Allergy and Infectious Diseases

Goals for a Universal Influenza Vaccine

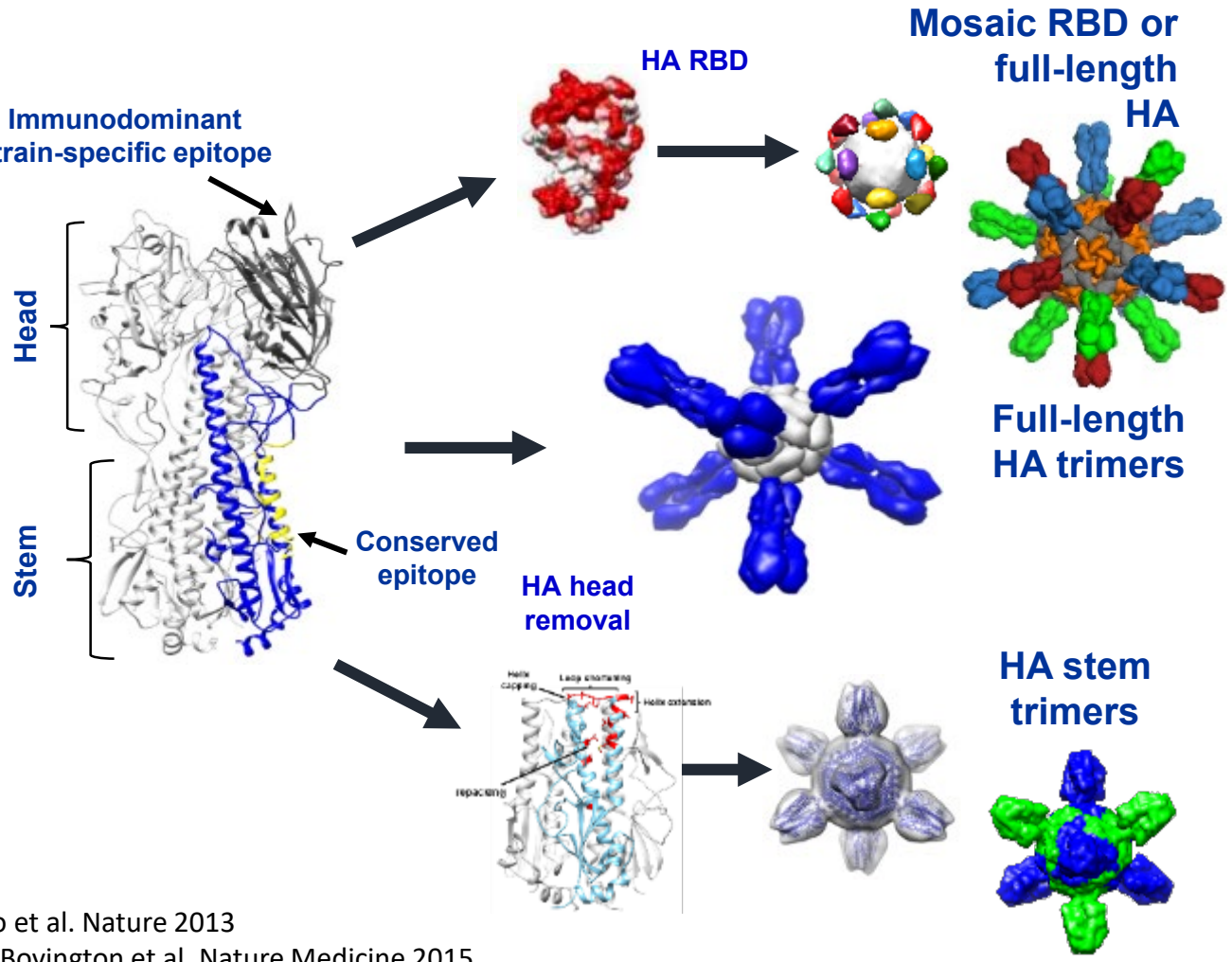
- Consistent efficacy >75% against medically-attended illness caused by seasonal and pandemic strains of influenza
- Single product that does not require annual revision
- Durable immunity for greater than 1 year

New Technologies Have Changed the Options for Universal Influenza Vaccine Development

- **Design** - Structure-guided approach for antigens and probes
- **Display** – Natural and designer nanoparticles
- **Delivery** – Proteins, nucleic acid, vectors
- **Detection** of specific immunological endpoints
  - Define and target specific antibody lineages with cross-neutralizing activity
  - Analysis of B cell phenotype and repertoire at single-cell level
  - Development of high-throughput functional serological assays

VRC Universal Influenza Vaccine Development

HA is primary antigenic target | **Structure-guided antigen design** | **Nanoparticle display** | **Strategy for achieving protective antibodies against future drifted and pandemic strains**



Avoiding immunodominance

Mosaic full-length HA on custom nanoparticles

Accumulation of breadth

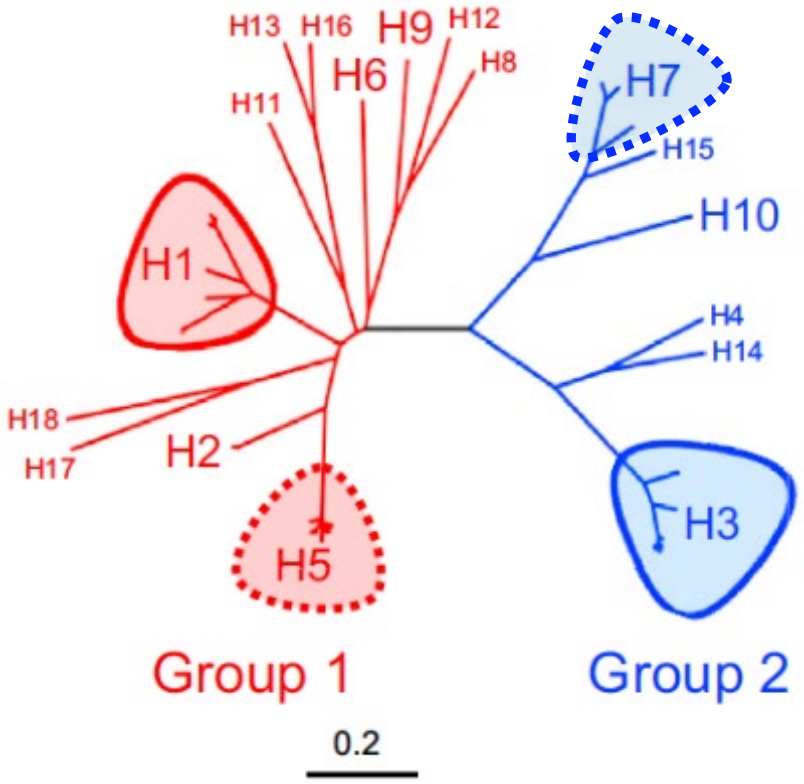
Targeting conserved sites

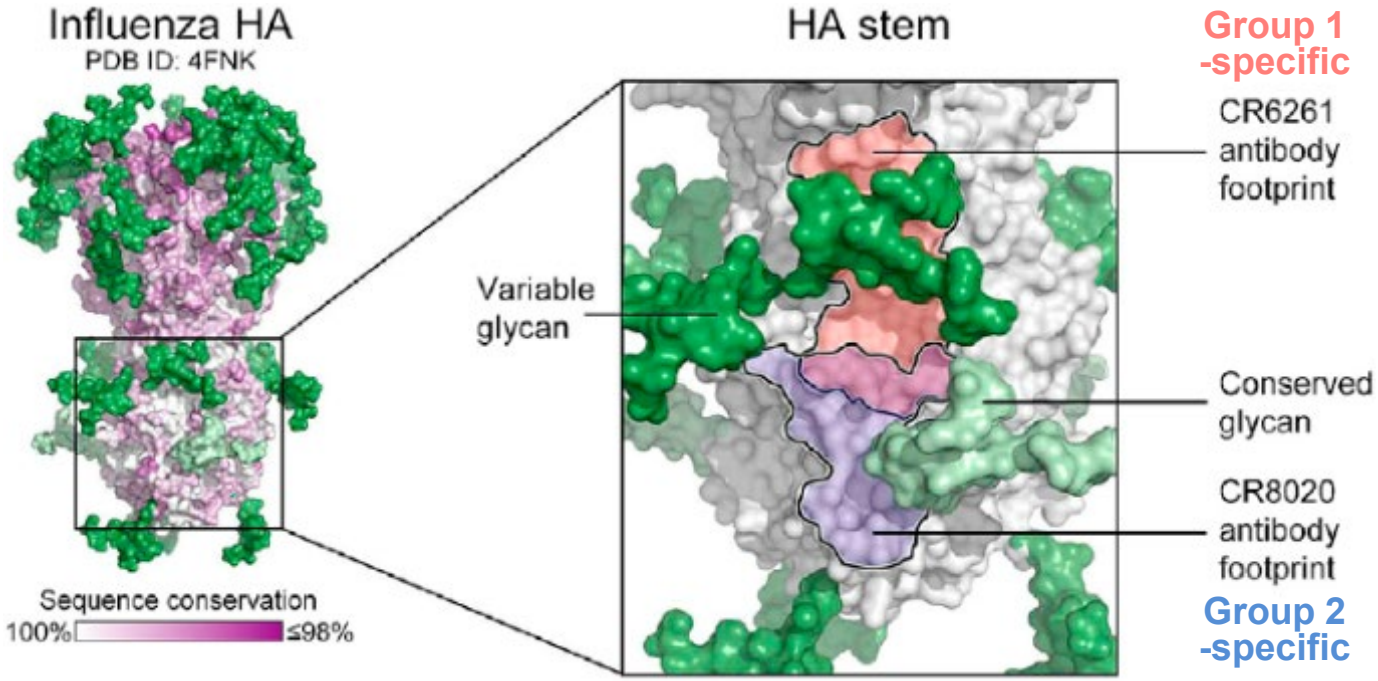
Group 1 & 2 on insect ferritin

Kanekiyo et al. Nature 2013
Yassine, Boyington et al. Nature Medicine 2015
Kanekiyo et al. Nature Immunology 2019

Influenza virus HA – sites of vulnerability

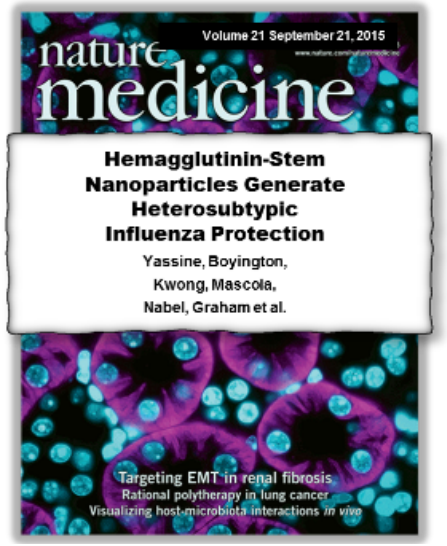
Diversity of influenza A hemagglutinins

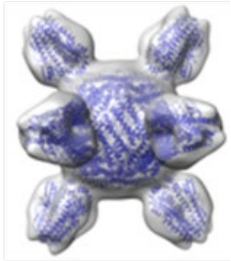


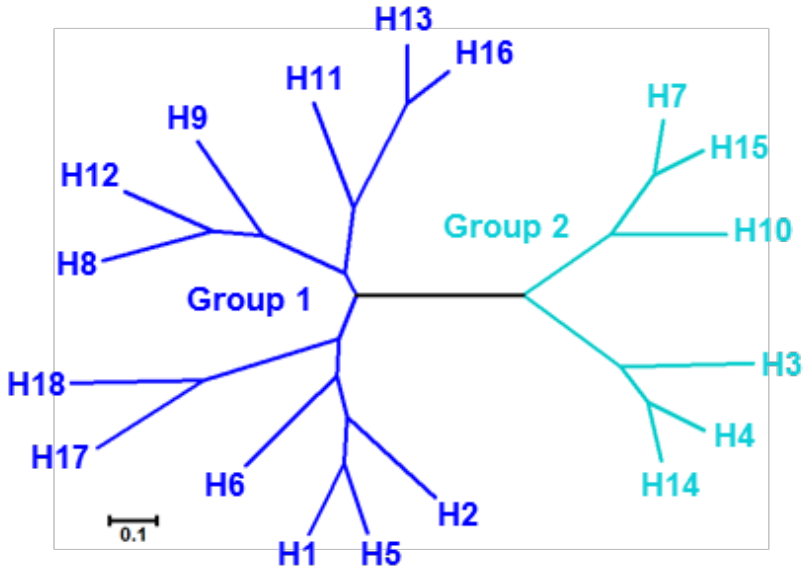


Joyce et al. *Cell* (2016)

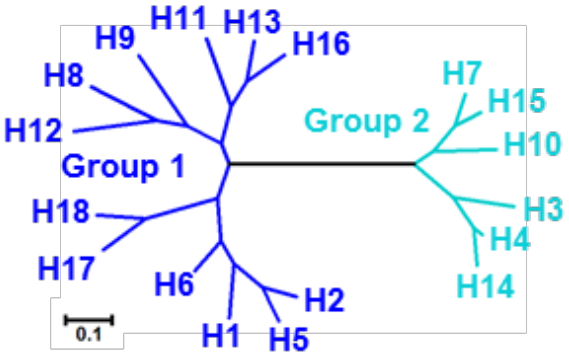
Headless HA-stem antigens achieve heterosubtypic protection and induce multi-donor cross-neutralizing antibody lineages



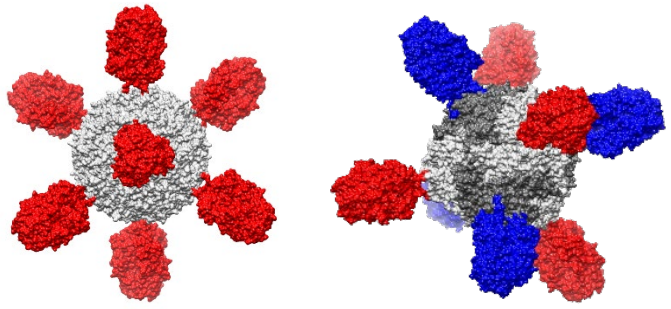




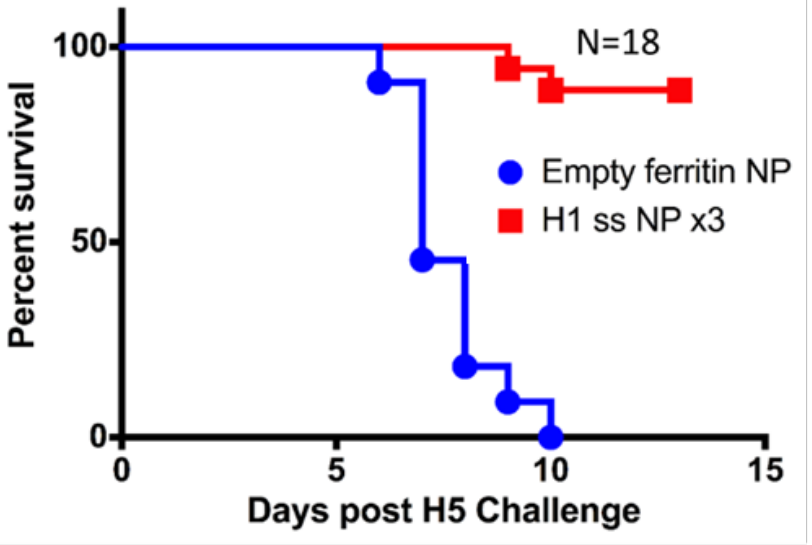
Full length HA

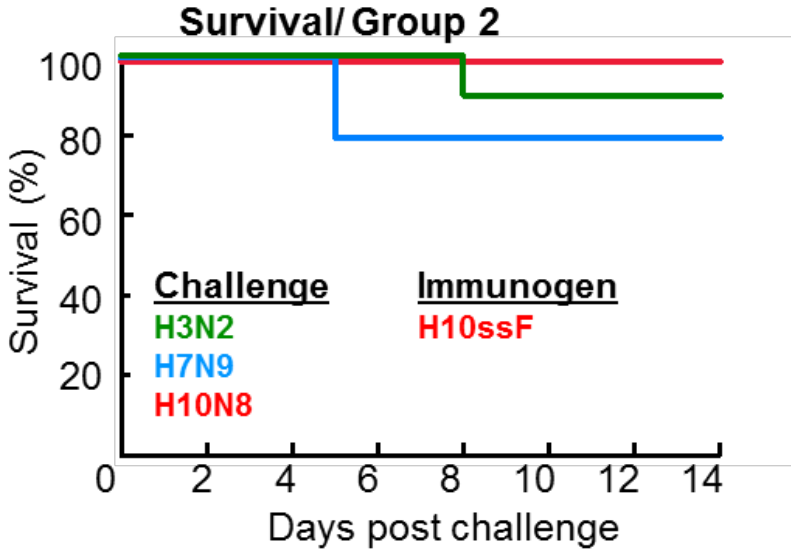


HA stem


H. pylori ferritin

Insect ferritin





Yassine, Boyington, et al. Nature Medicine 2015

Corbett, Moin et al. mBio 2019

Evolution and Development of Self-Assembling Proteinaceous Nanoparticle-based Vaccines

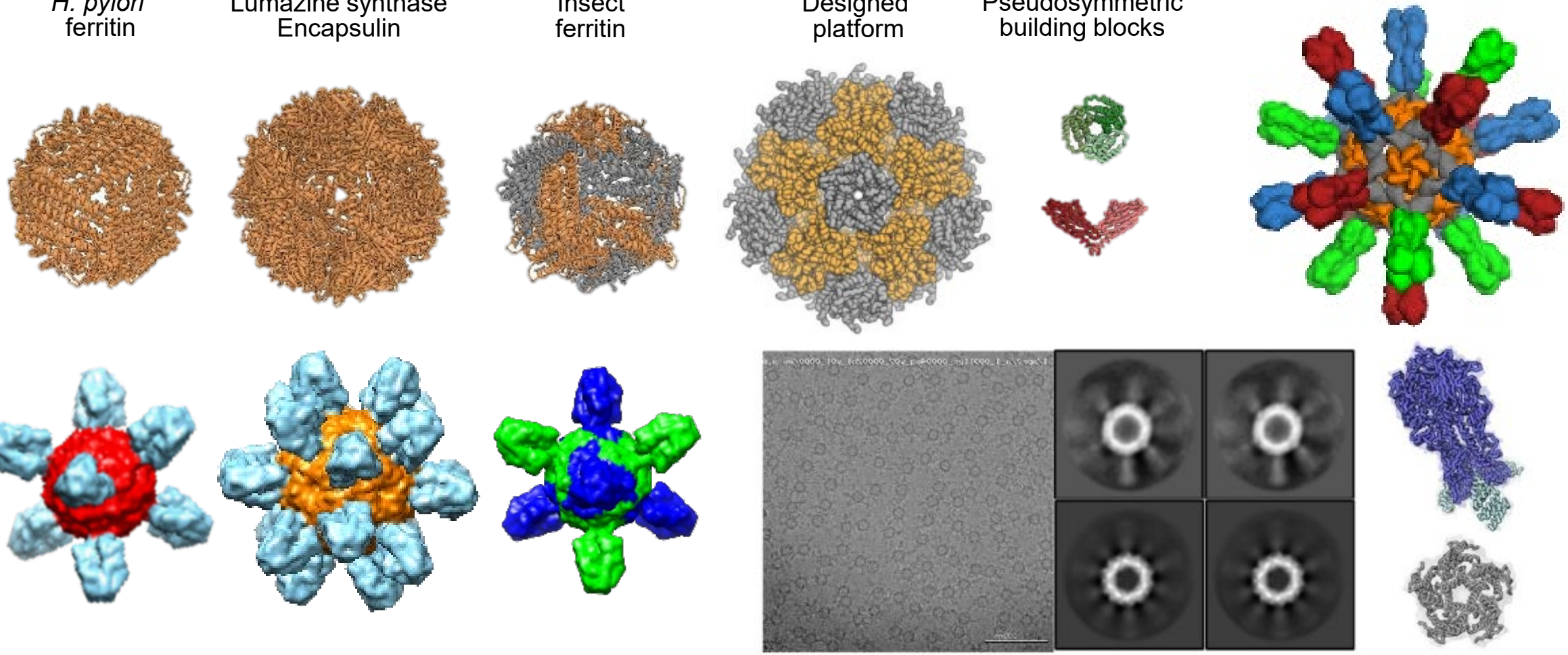
v1.0 — *H. pylori* ferritin

v1.1 — Lumazine synthase Encapsulin

v2.0 — Insect ferritin

v3.0 — Designed platform

Pseudosymmetric building blocks



Neil King, Daniel Ellis – UWash Institute for Protein Design

Co-display of heterotypic antigens in mosaic arrays

Mosaic antigen concept

Homogeneous antigens
(viruses, vaccines, etc.)

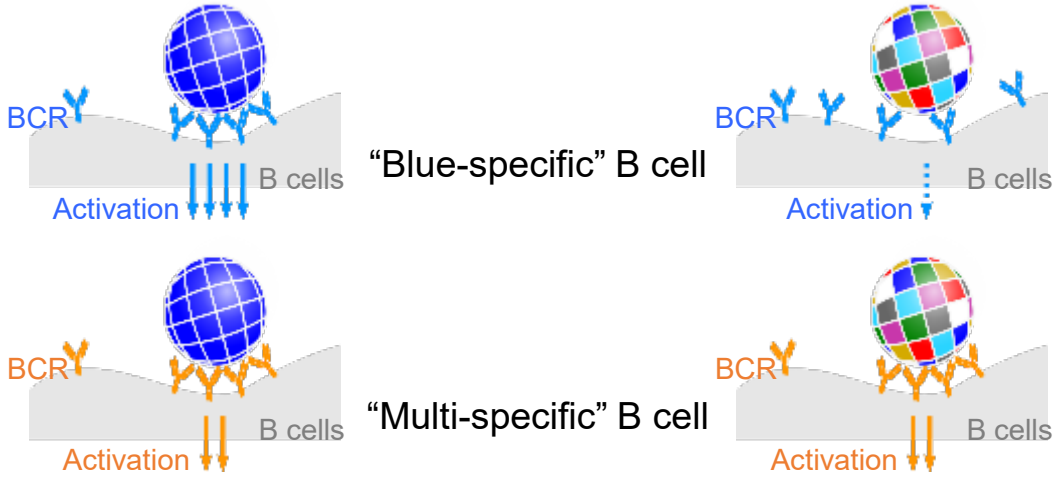
Building blocks

Particulate Ag

Heterogeneous antigens
(non-natural array)

Building blocks

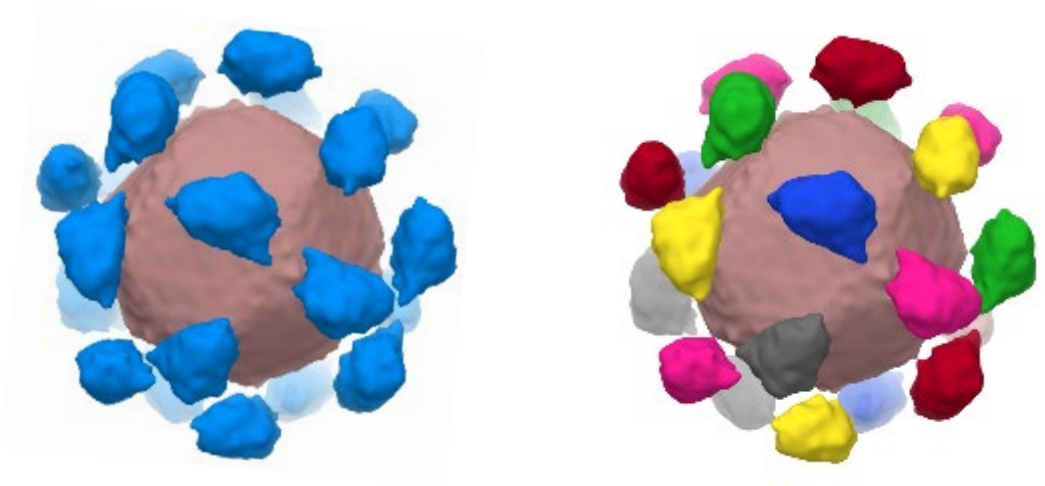
Particulate Ag



Experimental approach

Monotypic display

Mosaic display



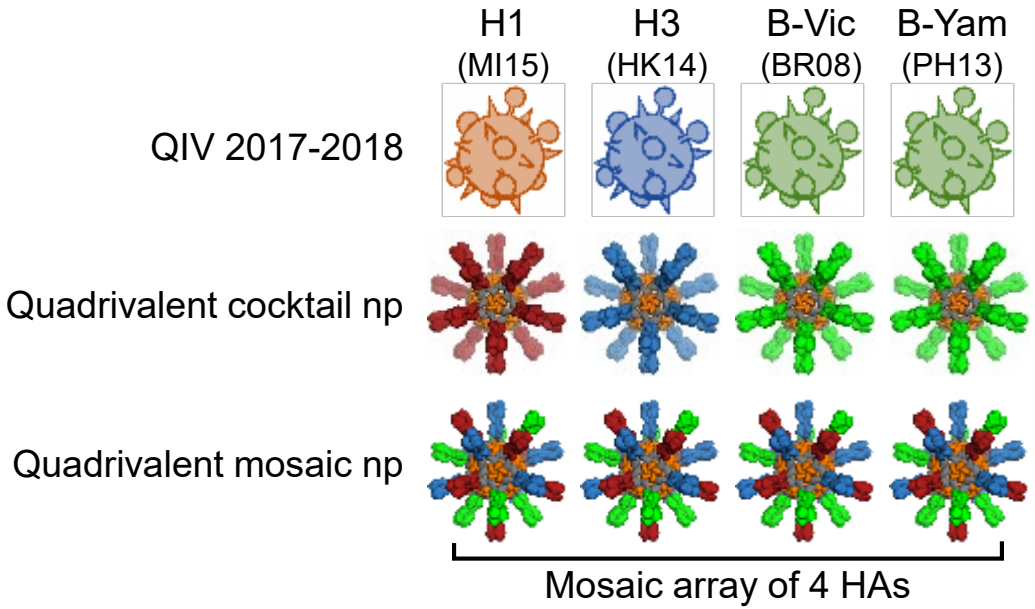
Per-particle antigen density of blue

Antigen heterogeneity

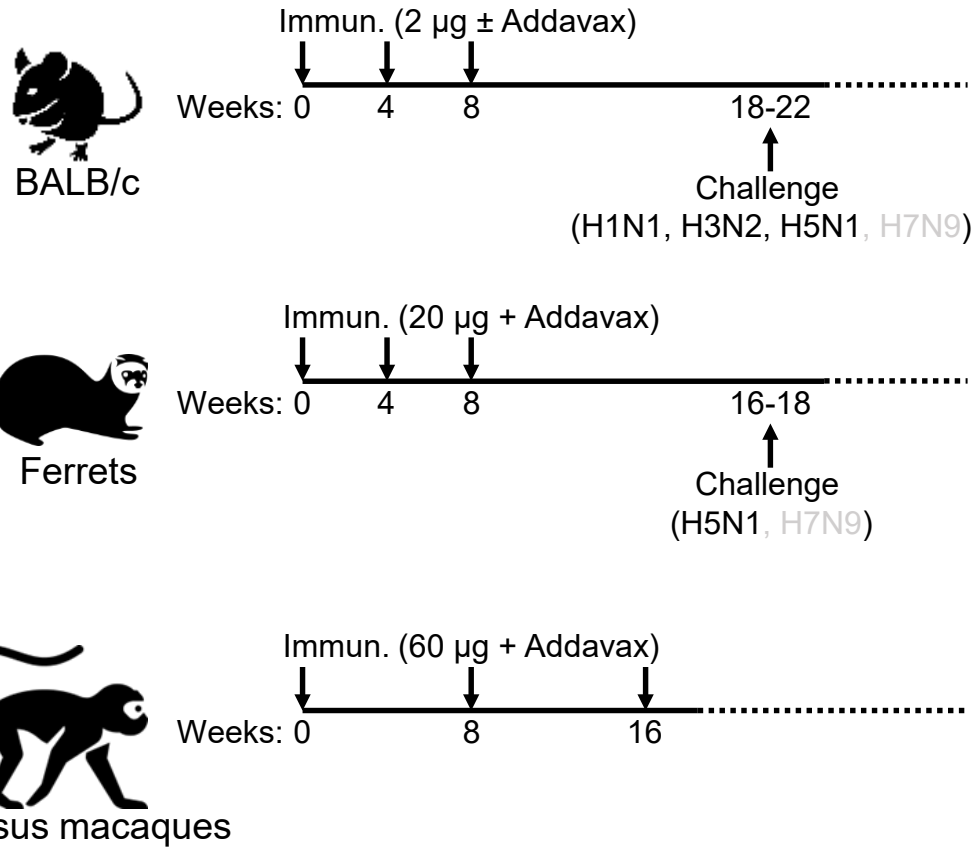
Kanekiyo et al., Nat Immunol (2019)

Full-length HA mosaic nanoparticle vaccine

Immunization groups

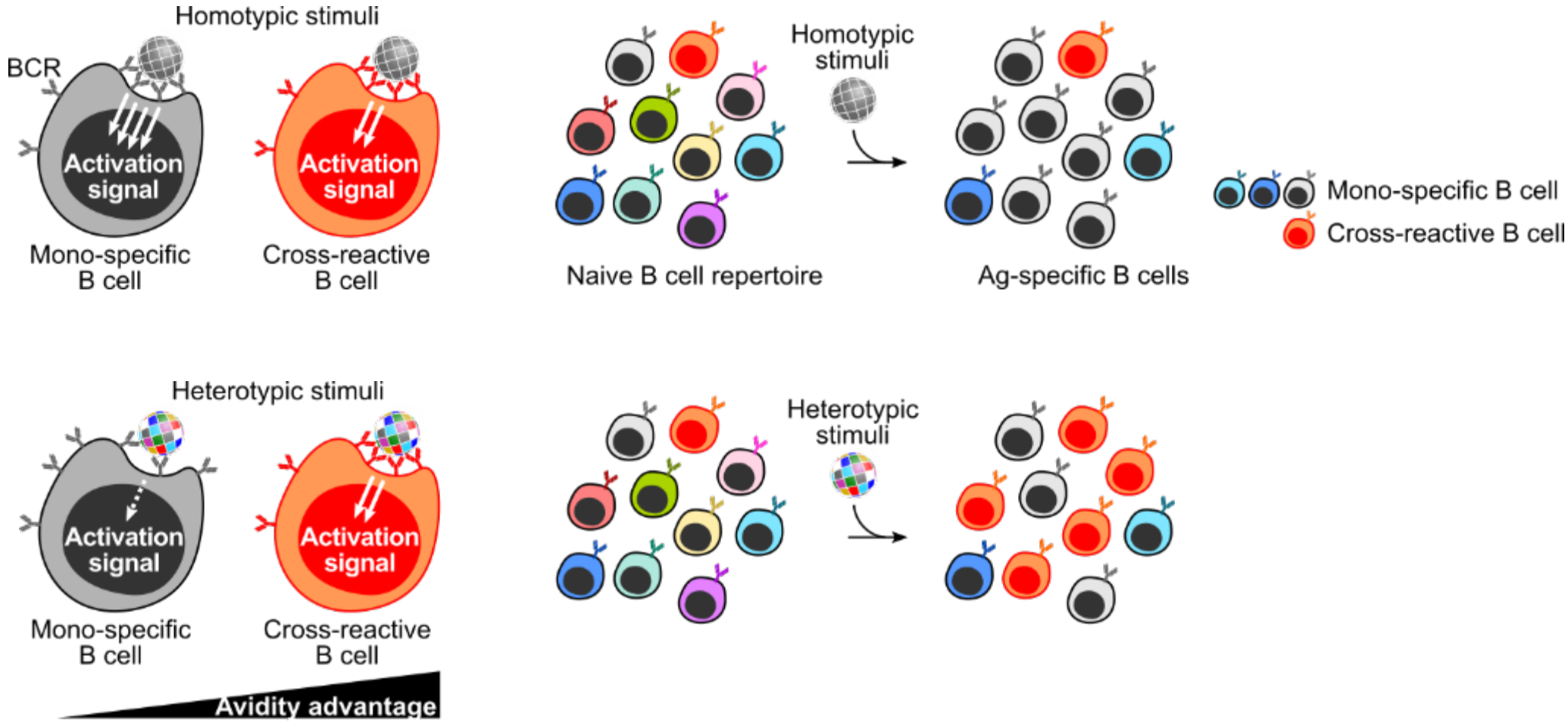


Animal models



Boyoglu-Barnum, Ellis et al., in preparation

Mosaic nanoparticle vaccine principle



Kanekiyo et al., Nat Immunol (2019)

Summary

- New technologies are transforming vaccinology providing solutions for long-standing problems and emerging viral diseases
- Targeting structurally-defined sites of vulnerability, defining specific antibody lineages, and advances in protein engineering have provided new options for influenza vaccines
- Mosaic antigen display may provide a way to overcome antigenic diversity and immunodominance
- In the short-term improved seasonal vaccines using cell-based manufacturing, dose-adjustments, adjuvants, and added neuraminidase, synthetic vaccinology for rapid manufacturing
- WHO PDVAC could help:
  - define and facilitate acceptable regulatory and logistical pathways to compare with conventional vaccines, e.g. new biomarkers and surrogate endpoints
  - Clarify pathway to replace current manufacturing technology
  - Define key target populations and priorities

NIAID Vaccine Research Center

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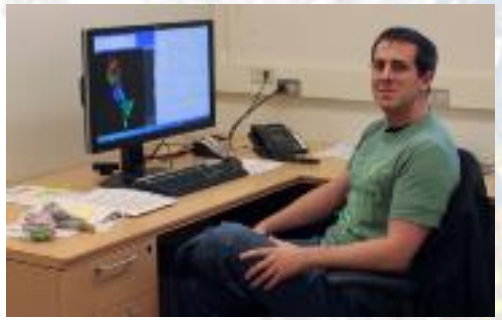

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