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National Institutes of Health
Department of Health and Human Services

Novel Approaches to Elicit Broadly Neutralizing Antibodies to Influenza

National Vaccine Advisory Committee

June 10, 2014

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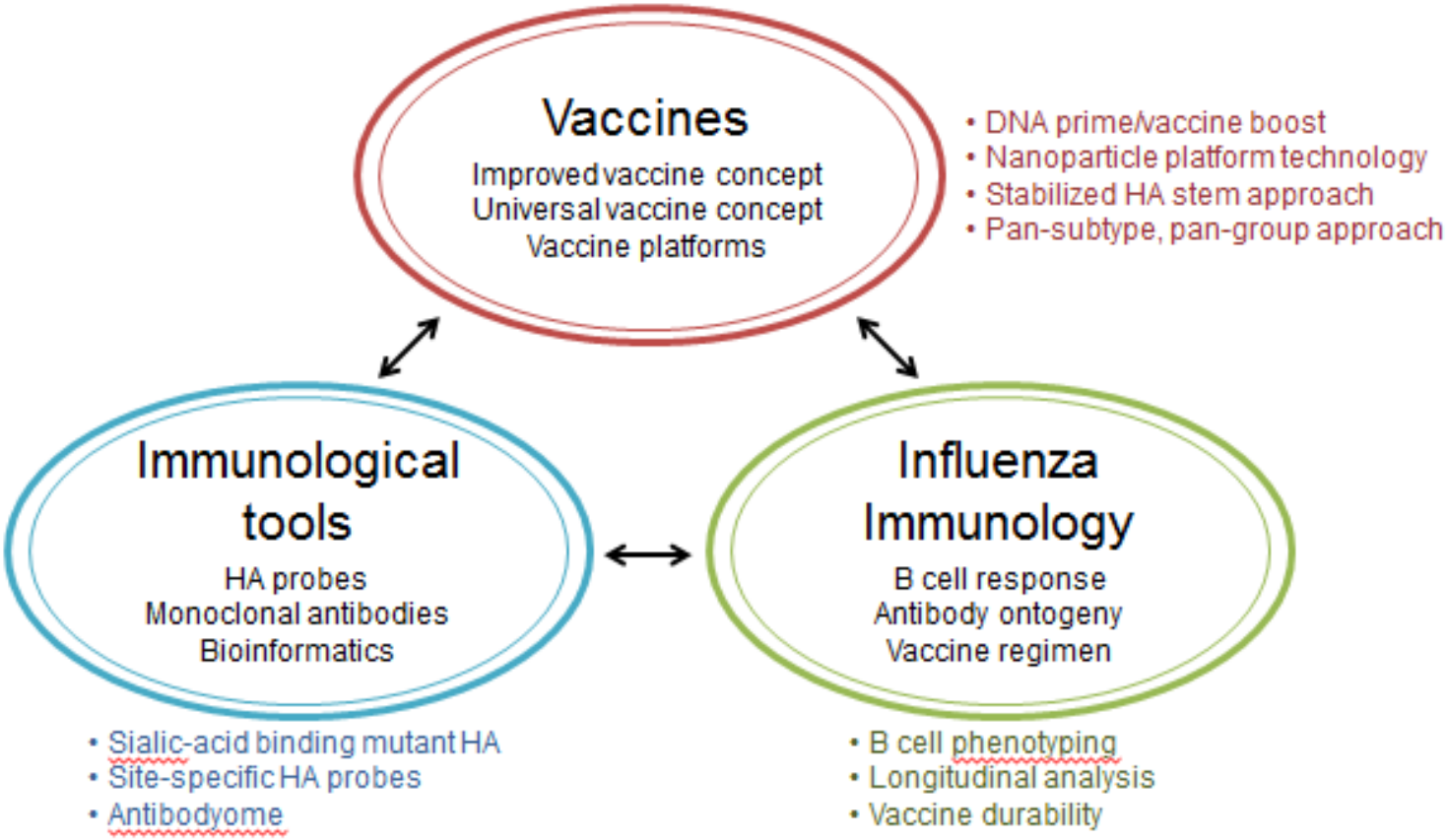
Viral Pathogenesis Laboratory, Viral Pathogenesis Translational Science Core

Vaccine Research Center

NIAID, National Institutes of Health

Basic and Clinical Research at the VRC

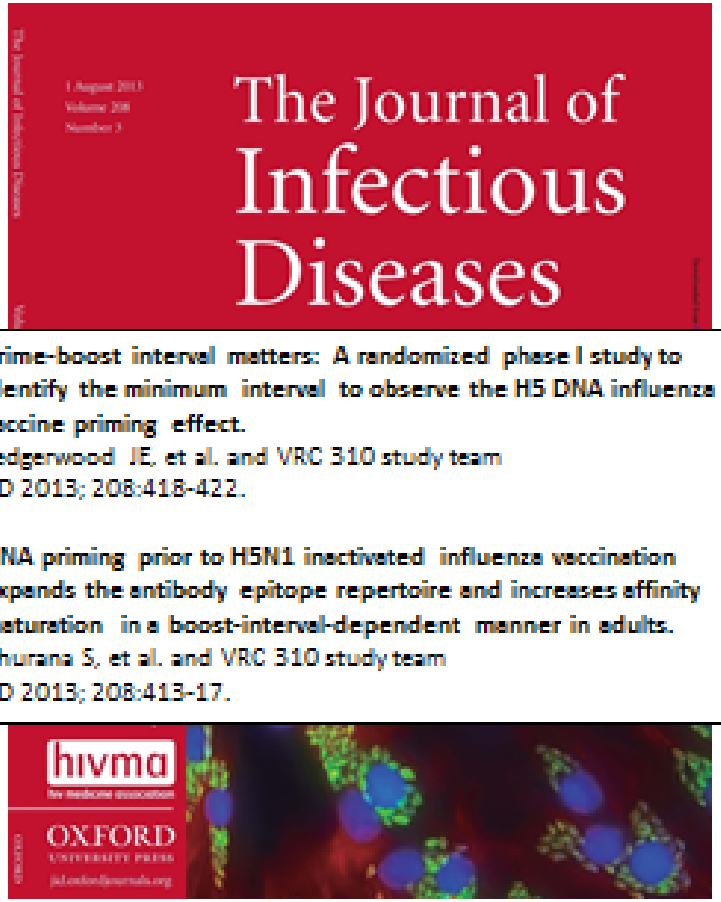


Outline

1. **Vaccine concepts**
   - DNA priming
   - HA-ferritin nanoparticle technology
   - Pre-emptive pan-Group 1 vaccine concept
   - HA stem-based universal vaccine concept

2. **Engineered HA as a novel immunological tool**

Influenza Vaccine Clinical Trials



Prime-boost interval matters: A randomized phase I study to identify the minimum interval to observe the H5 DNA influenza vaccine priming effect.
Ledgerwood JE, et al. and VRC 310 study team
JID 2013; 208:418-422.

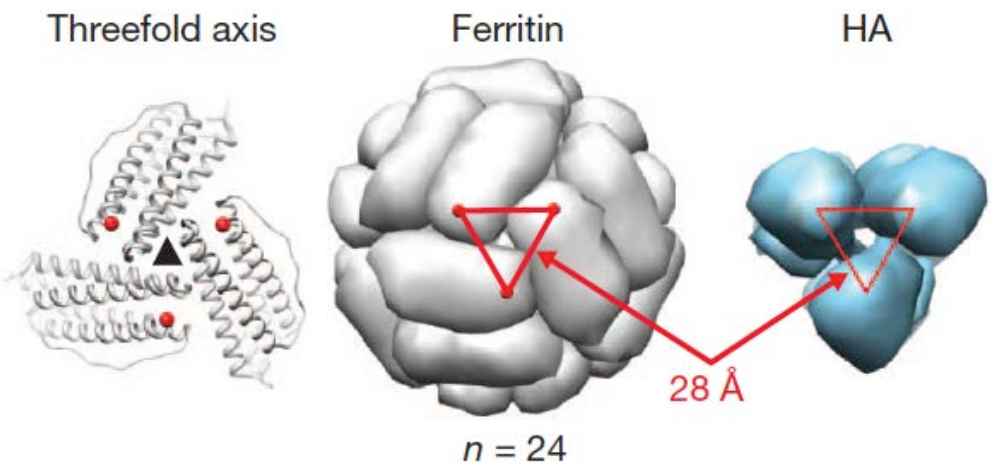
DNA priming prior to H5N1 inactivated influenza vaccination expands the antibody epitope repertoire and increases affinity maturation in a boost-interval-dependent manner in adults.
Khurana S, et al. and VRC 310 study team
JID 2013; 208:413-17.

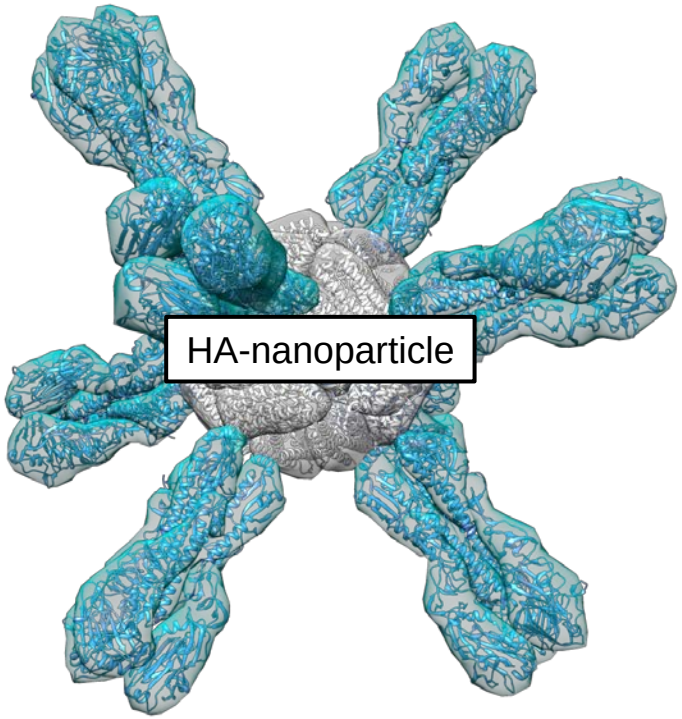
HA-Ferritin Nanoparticle Technology

LETTER

doi:10.1038/nature12202

Self-assembling influenza nanoparticle vaccines elicit broadly neutralizing H1N1 antibodies





Kanekiyo, M. et al. (2013)

Improved Neutralization Breadth and Potency

Neutralization titers

Mice Immunization - IC 50 HA Strain

Number	HA-trim	TIV	HA-np
1918 SC	n.d.	<SO	<50
1934 PRB	<so	<1100	2010
1986 Sing	n.d.	<100	210
1995 Beijing	-	1,654	>6,400
1995 NC	956	4, 215	323,390
2006 SI	n.d.	677	>3200
2007 Birs	n.d.	311	4,286

- BALB/c mice (n=5)
- 0.17 µg of H1 HA equiv.
- SAS (Ribi) adjuvant
- Injected twice at weeks 0 and 3
- Intramuscular route

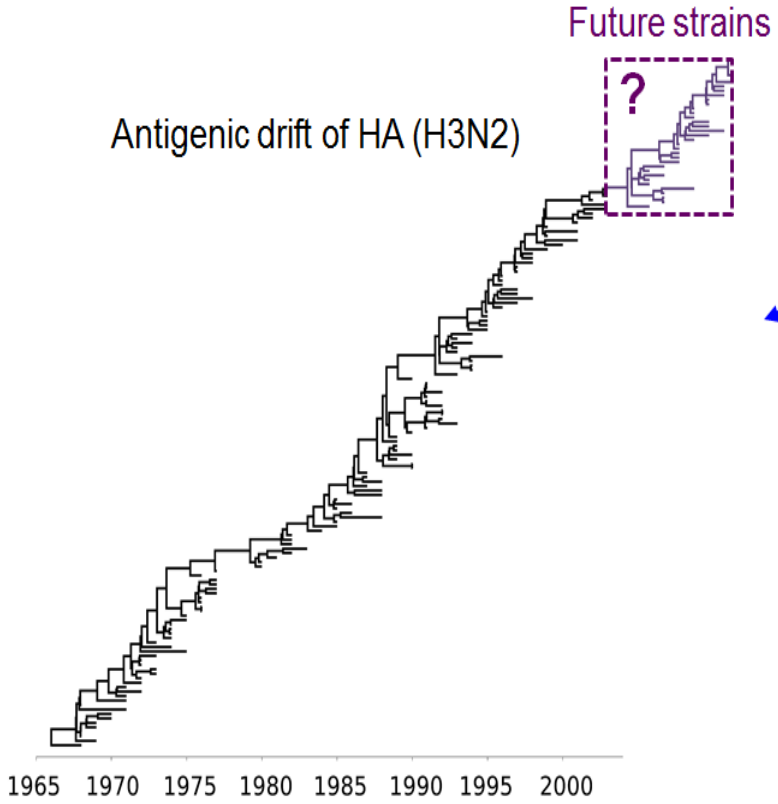
Ferrets Immunization - IC 50 HA Strain

Number	Control	TIV	HA-np
1918 SC	<50	<50	73
1986 Sing	<200	397	2,491
1995 Beijing	<50	623	>3,200
1999 NC	<200	2, 042	12,800
2006 SI	<50	77	>3,200
2007 Birs	<200	<200	4,286

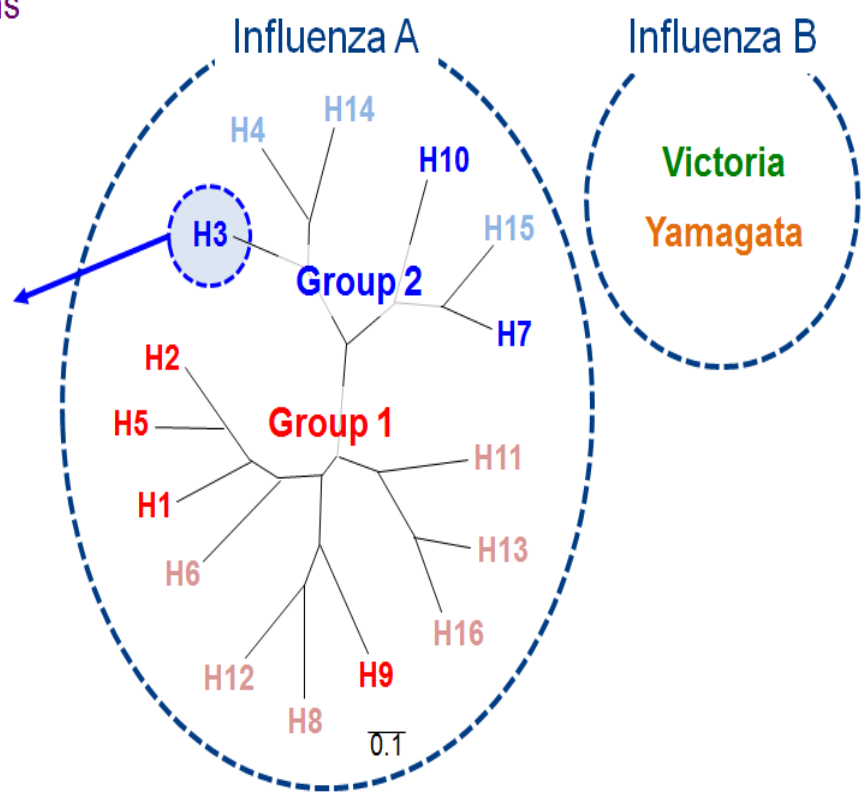
- 2.5 µg of H1 HA equiv.
- Ferrets (n=6)
- SAS (Ribi) adjuvant
- Injected twice at weeks 0 and 4
- Intramuscular route

Kanekiyo, M. et al. (2013)

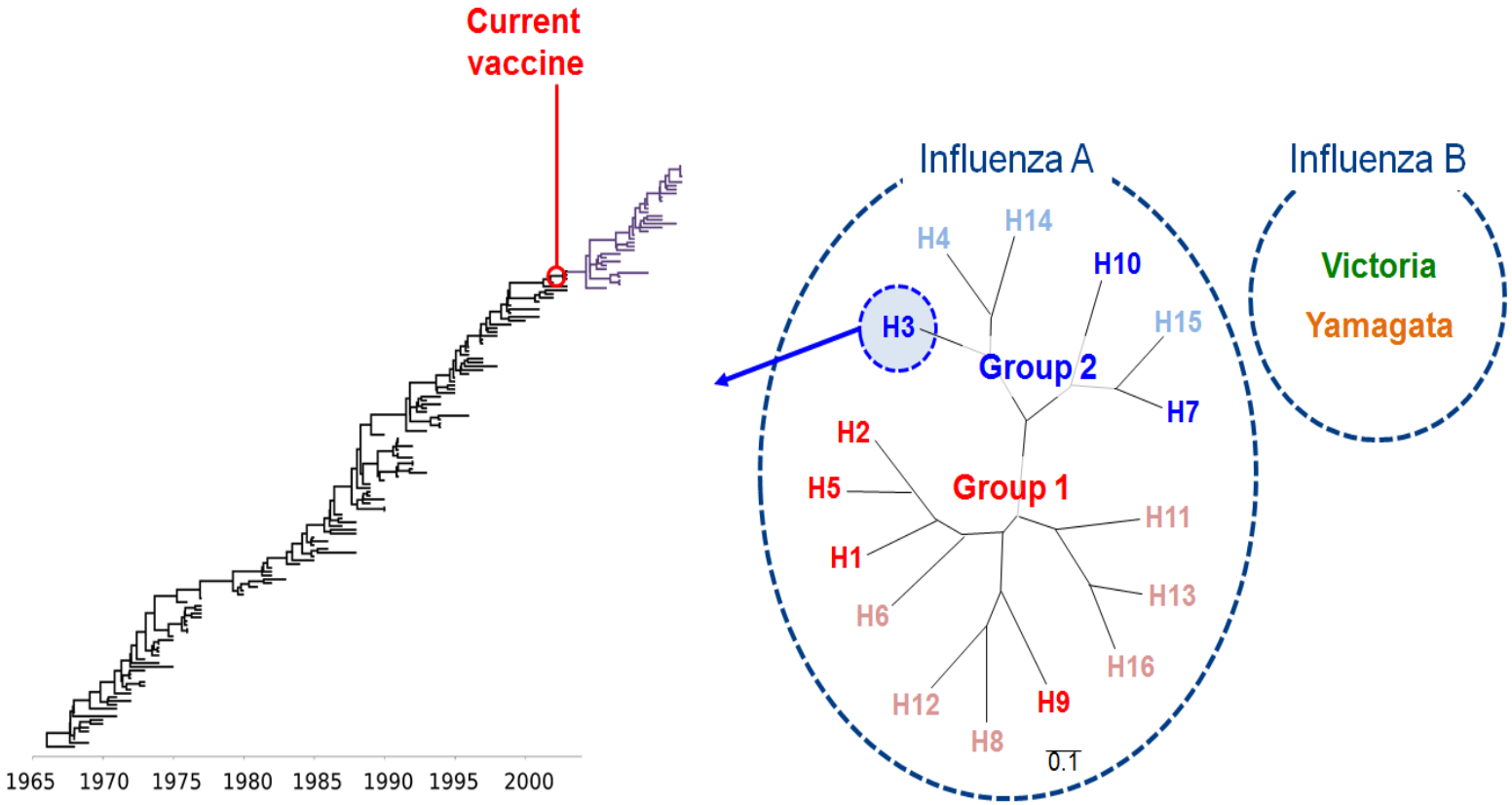
Influenza HA Diversity



Adapted from Volz, E.M. et al. (2013)



Degrees of Universality for Influenza Vaccine Concepts



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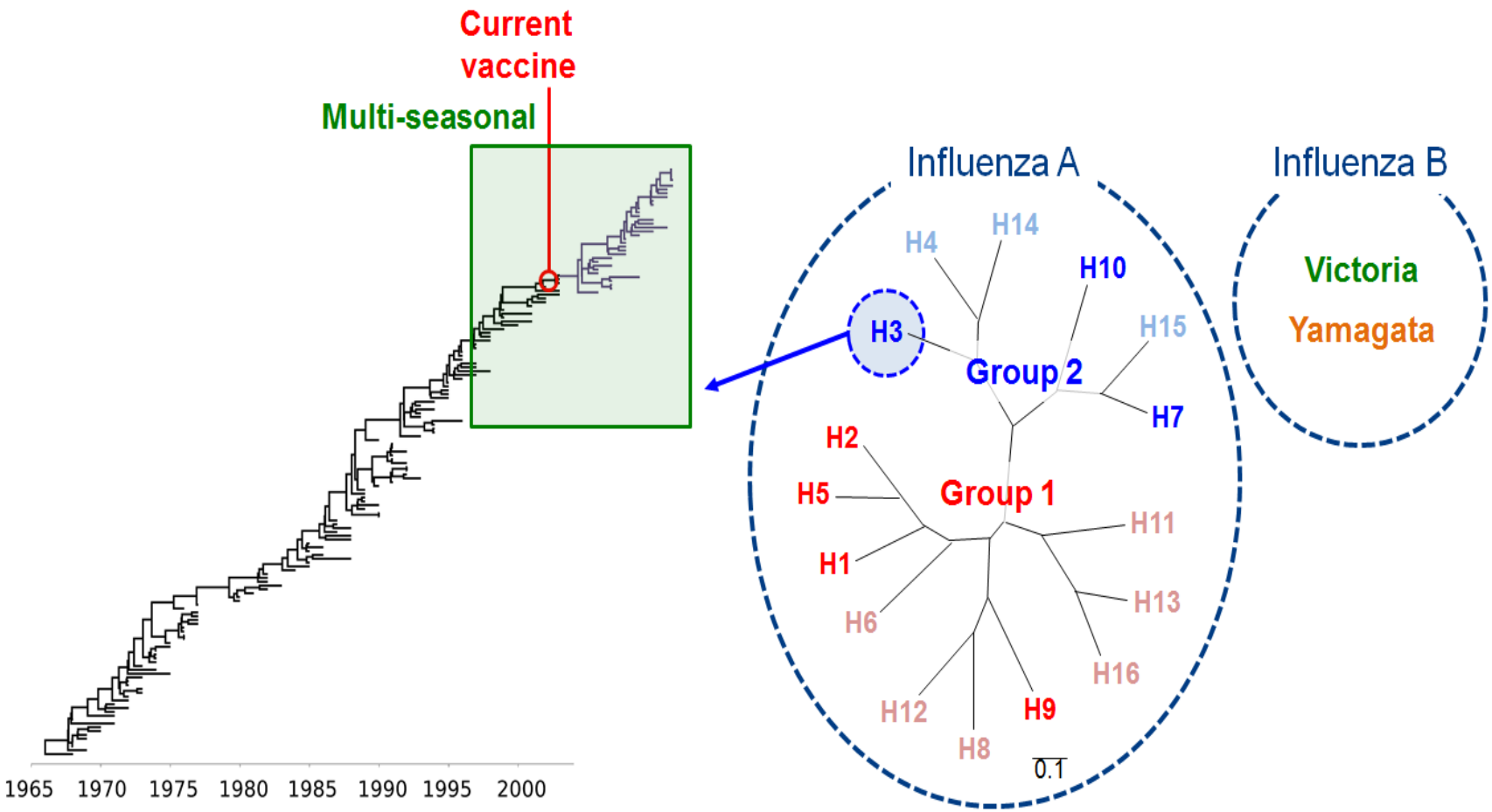

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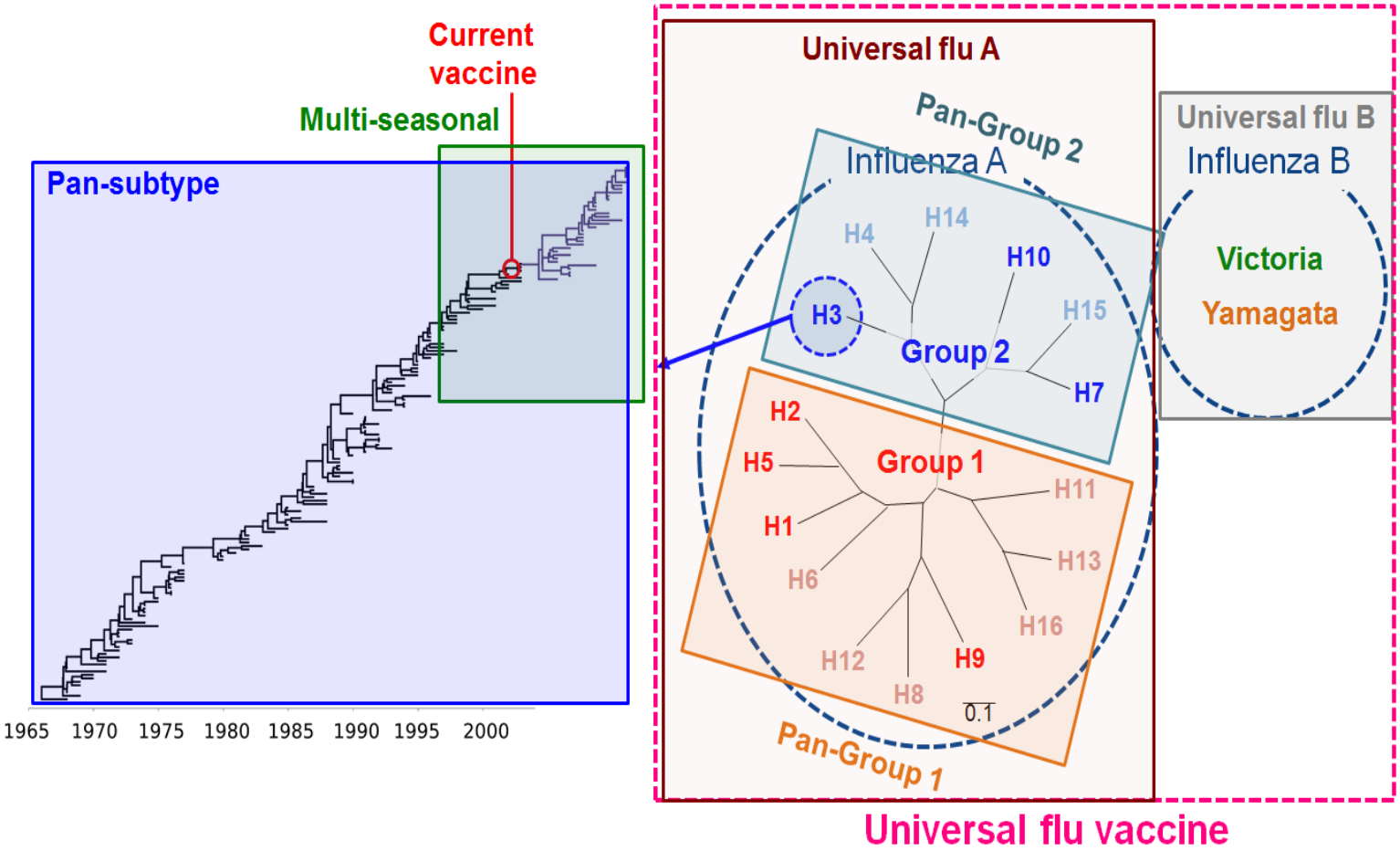
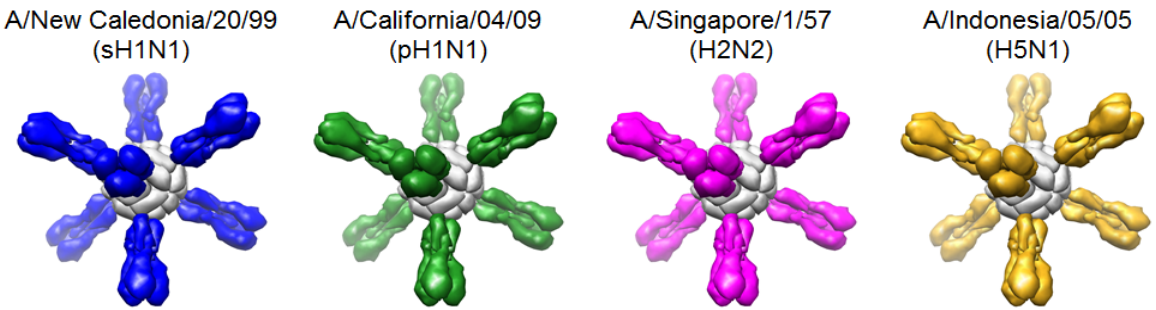
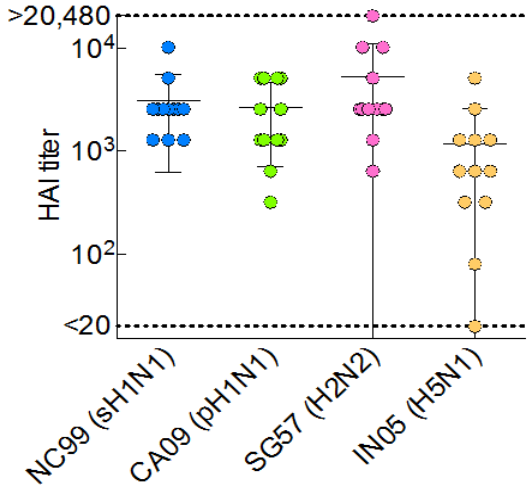


Development of Pan-Group 1 (H1, H2 and H5) HA-np

Quadrivalent pan-Group 1 HA-nanoparticles

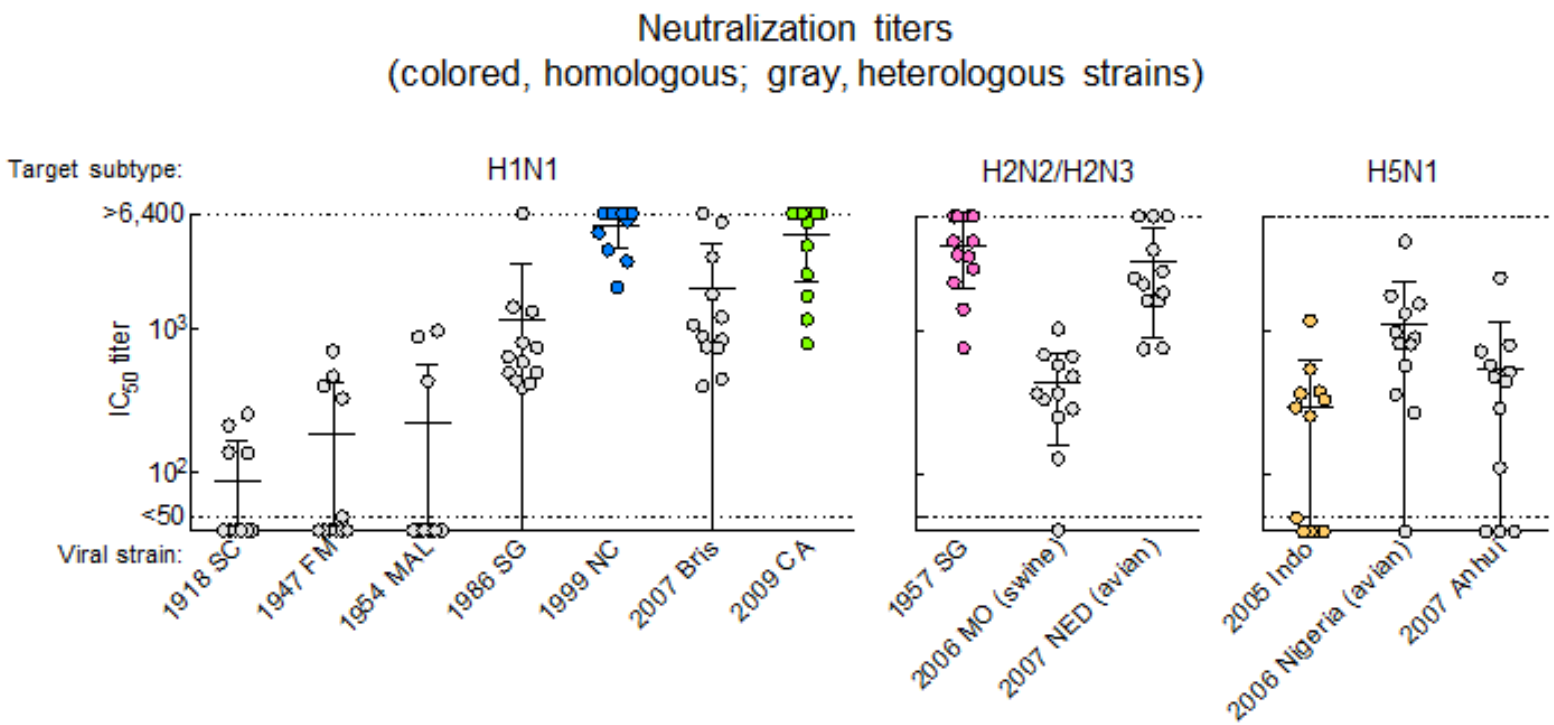


Hemagglutination inhibition (HAI) titers
(homologous strains)



- Ferrets (n=12)
- 10 µg of HA (total)
- SAS (Ribi) adjuvant
- Injected twice at weeks 0 and 4
- Intramuscular route

Neutralization Titers Against Panel of H1, H2 and H5 Viruses



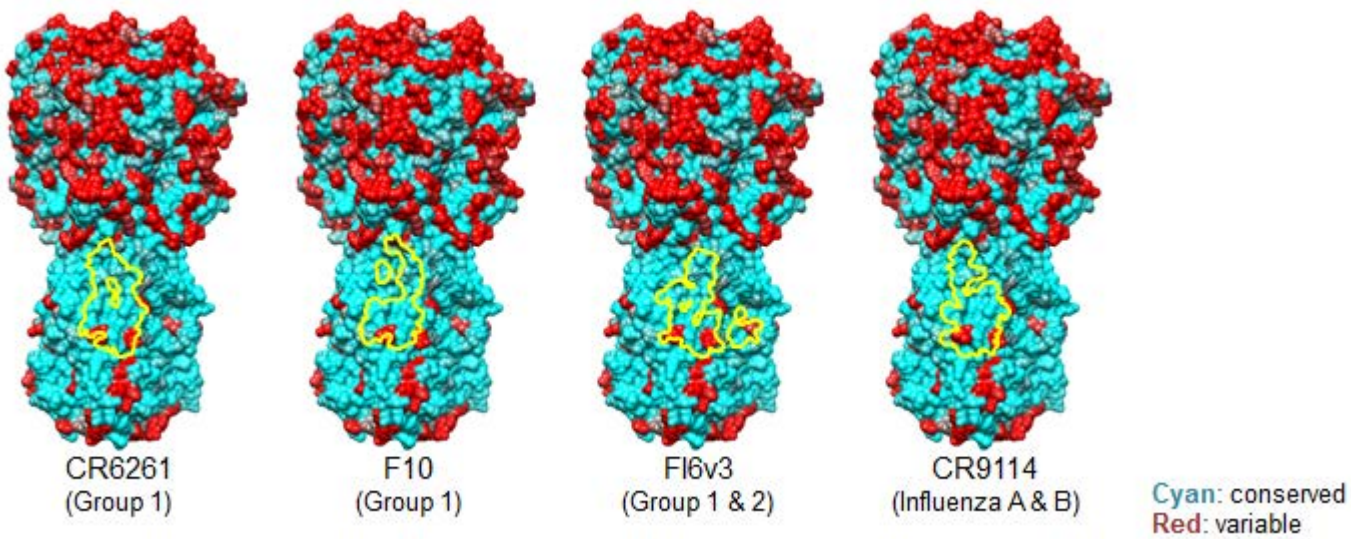
- Ferrets (n=12)
- 10 µg of HA (total)
- SAS (Ribi) adjuvant
- Injected twice at weeks 0 and 4
- Intramuscular route

Wei, Yassine

Conserved HA Stem-Based Universal Vaccine Concept

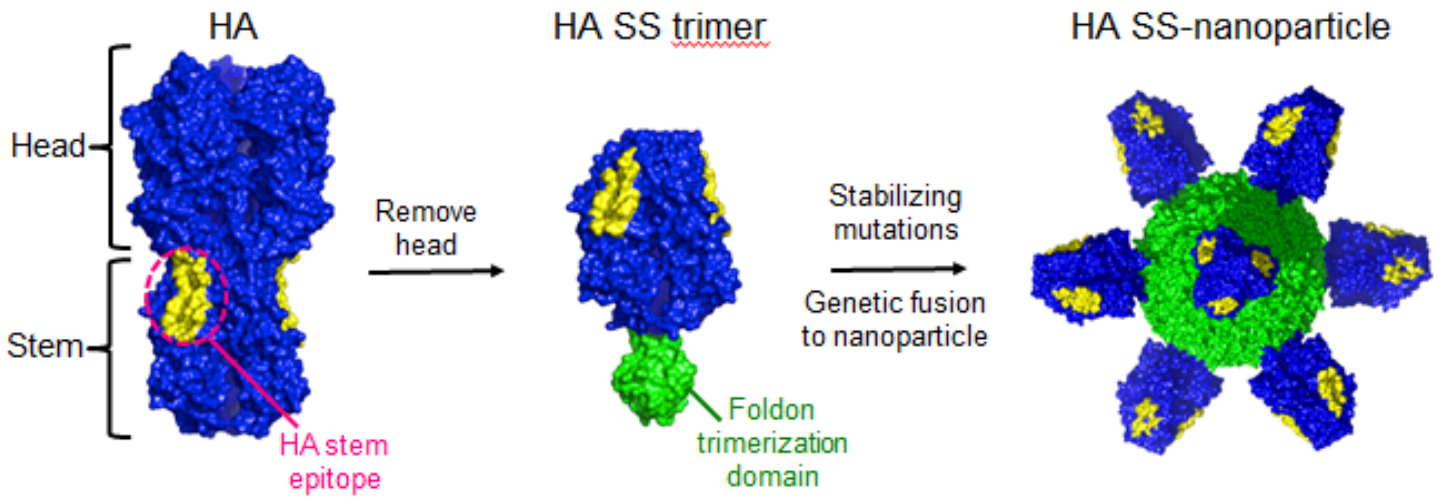
Yassine, Boyington

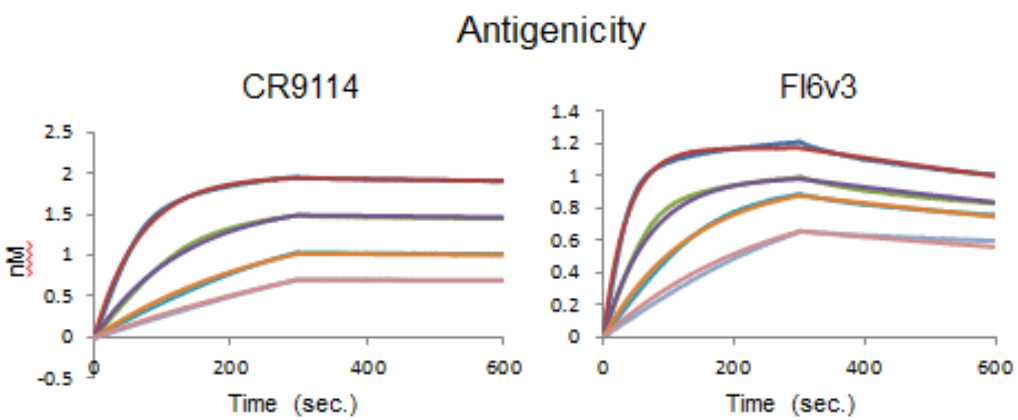
- Unlike HA globular head, stem domain is highly conserved among strains, subtypes or even between influenza A and B
- Humans can induce broadly neutralizing stem-directed antibodies through natural infections and/or vaccinations
- Immunogens that can predominantly or exclusively elicit the stem-directed neutralizing antibodies might provide protection against unforeseen influenza viruses

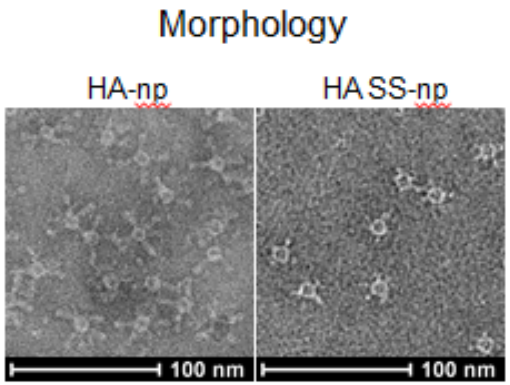


HA Stabilized Stem (SS)-Nanoparticles

Yassine, Boyington, Joyce

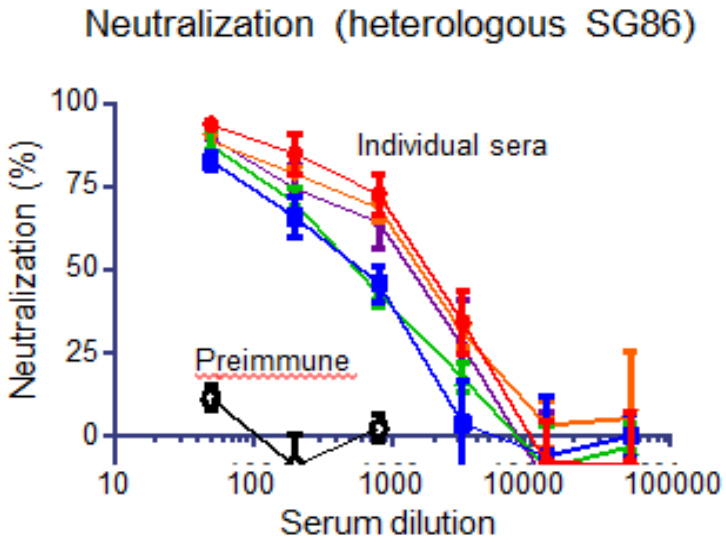


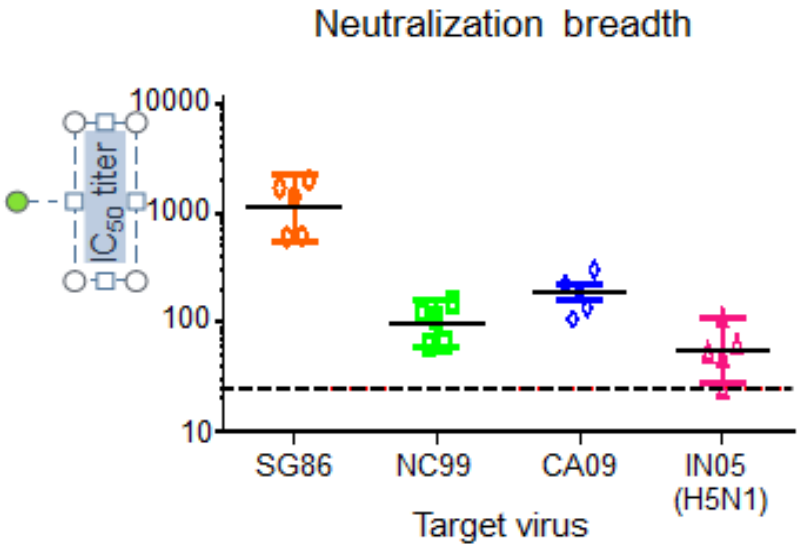




HA Stem-Directed Heterosubtypic Neutralization

Yassine, Boyington





There are no detectable HAI titers against either NC99 or SG86 virus (<1:20)

- BALB/c mice (n=5)
- 2 µg (NC99-based)
- SAS (Ribi) adjuvant
- Injected twice at weeks 0 and 4
- Intramuscular route

Outline

1. **Vaccine concepts**
   - DNA priming
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   - Preemptive pan-group 1 vaccine concept
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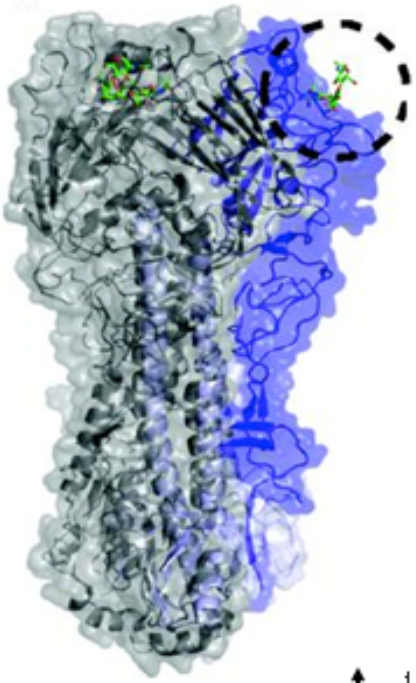
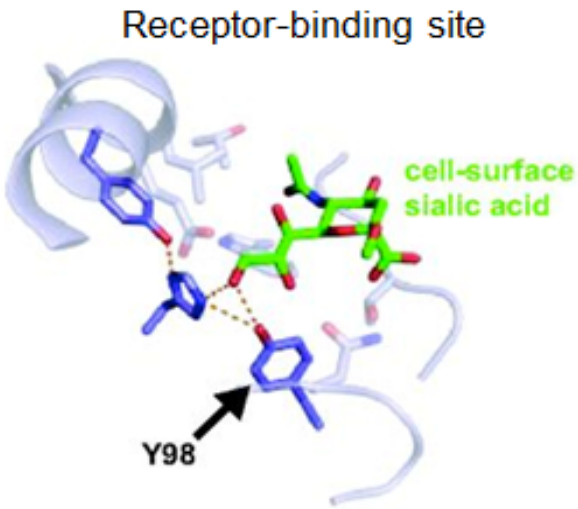
1. **Engineered HA as a novel immunological tool**

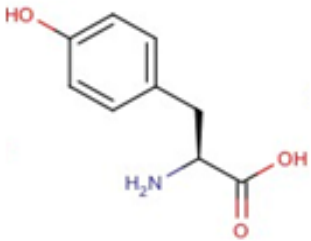
Development of Fine-Tuned HA Probes

Whittle, Wheatley, McDermott

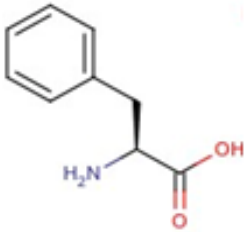


HA

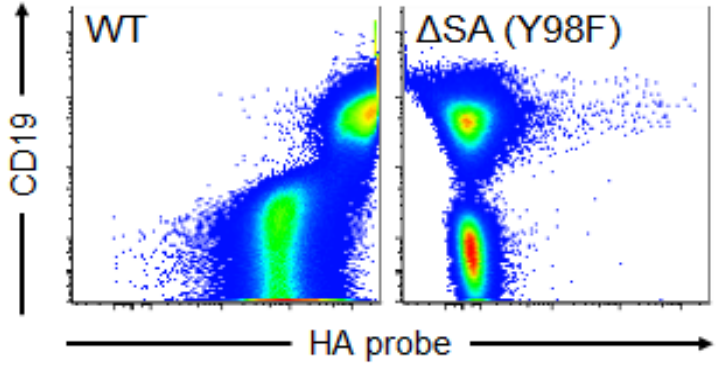




Tyrosine



Phenylalanine

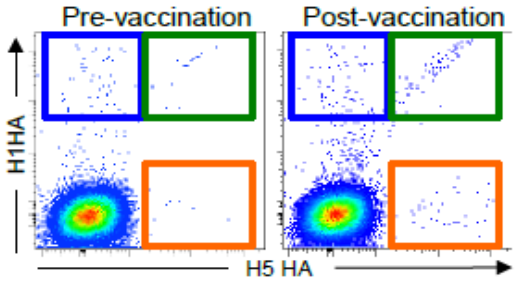


Whittle, J.R.R. et al. (2014)

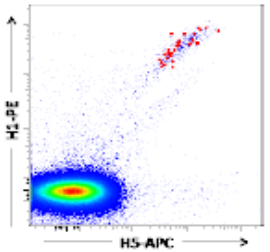
Applications of ΔSA HA Probes

Wheatley, McDermott

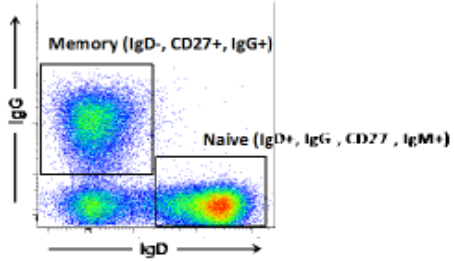
HA-specific B cell selection



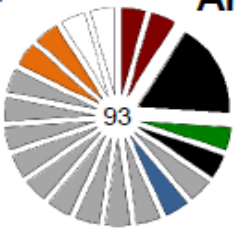
mAb isolation



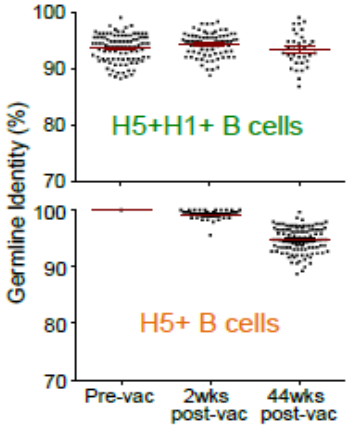
B cell phenotype



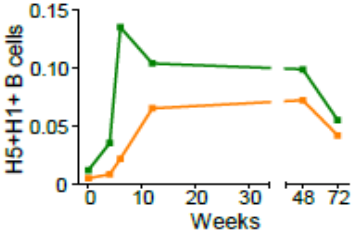
Antibody sequence analysis



Affinity maturation and ontogeny



B cell kinetics



Summary

- DNA priming improves conventional vaccines
- Preemptive pan-Group 1 HA-nanoparticles using H1, H2 and H5 have been produced
  - Elicit robust HAI titers against vaccine strains
  - Immune sera neutralized heterologous strains including avian- and swine-origin H2N2, H2N3 and H5N1
- HA-stabilized stem-nanoparticles have been rationally designed
  - Possess desired antigenicity
  - H1 HA stem-induced neutralizing antibody weakly neutralizes H5N1 virus
- HAs lacking sialic-acid binding property have been developed as probes
  - Enables analysis and selection of HA-specific B cells by flow cytometry

Future Directions

- Vaccines
  - HA-ferritin clinical trial
  - HA stem-nanoparticles clinical trial
  - Novel approaches to achieve breadth

- Immunological tools
  - Antigenic site-specific HA probes
  - Characterization of mAbs to map NT and non-NT cross-reactive antigenic sites

- Influenza Immunology
  - B cell analysis of human samples
  - Isolation of new human mAbs
  - Antibodyome analysis

Acknowledgements

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Peter Kwong
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Clinical Trials Program

Julie Ledgerwood
Team

Vaccine Translational Research Program

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