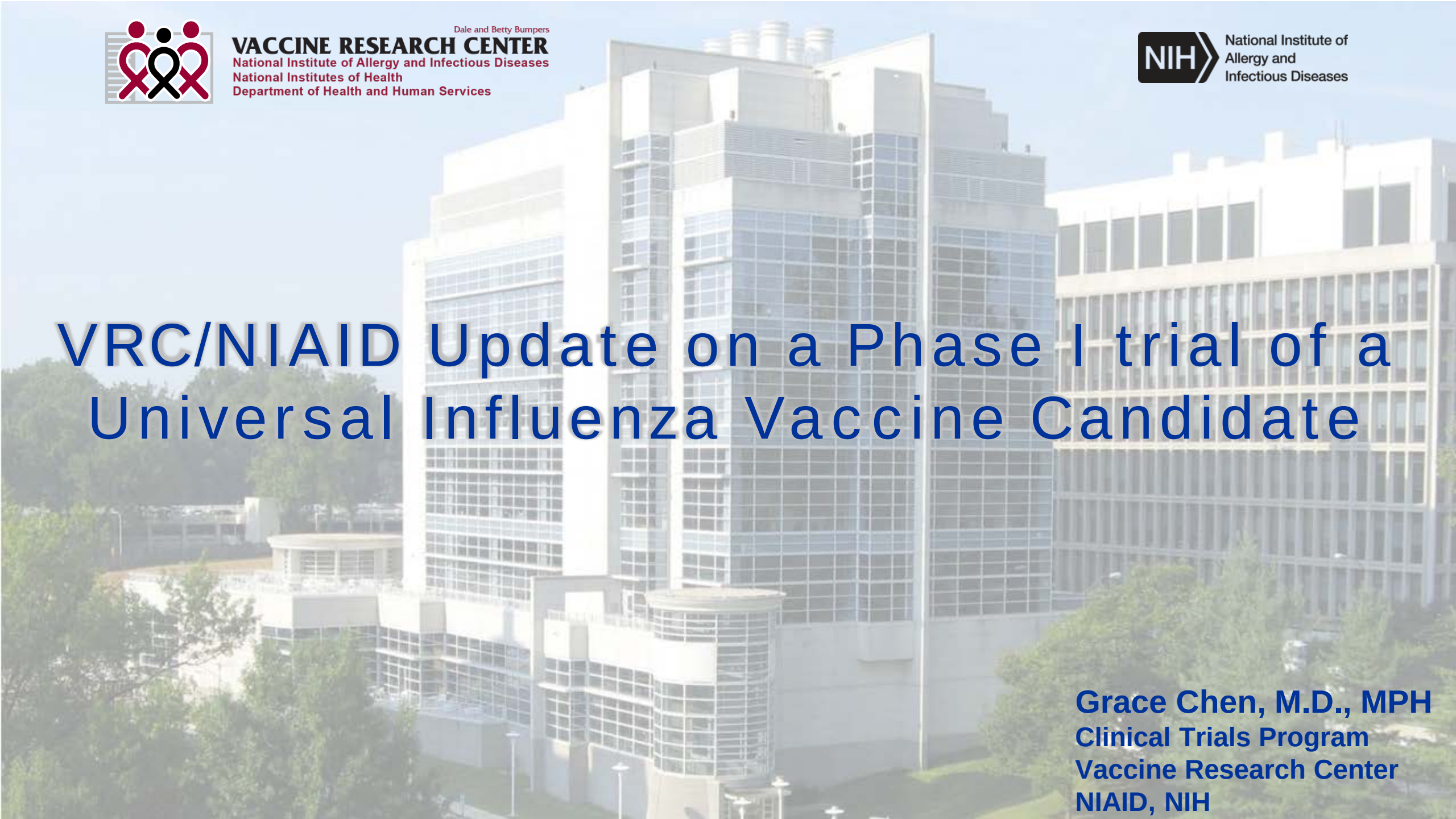

Dale and Betty Bumpers
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National Institute of Allergy and Infectious Diseases
National Institutes of Health
Department of Health and Human Services

NIH National Institute of Allergy and Infectious Diseases

VRC/NIAID Update on a Phase I trial of a Universal Influenza Vaccine Candidate

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Vaccine Research Center
NIAID, NIH

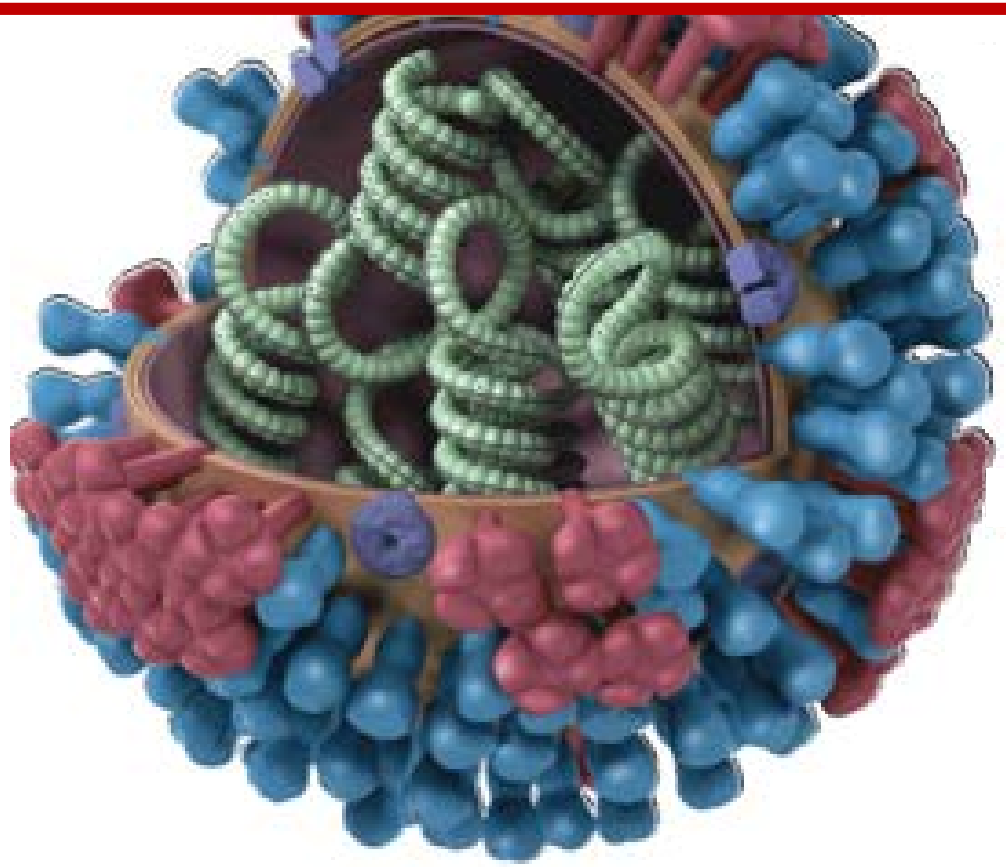
Thank you to the Committee for the invitation to present an update from the Vaccine Research Center at NIAID/NIH on the phase I trial of a universal influenza vaccine candidate.

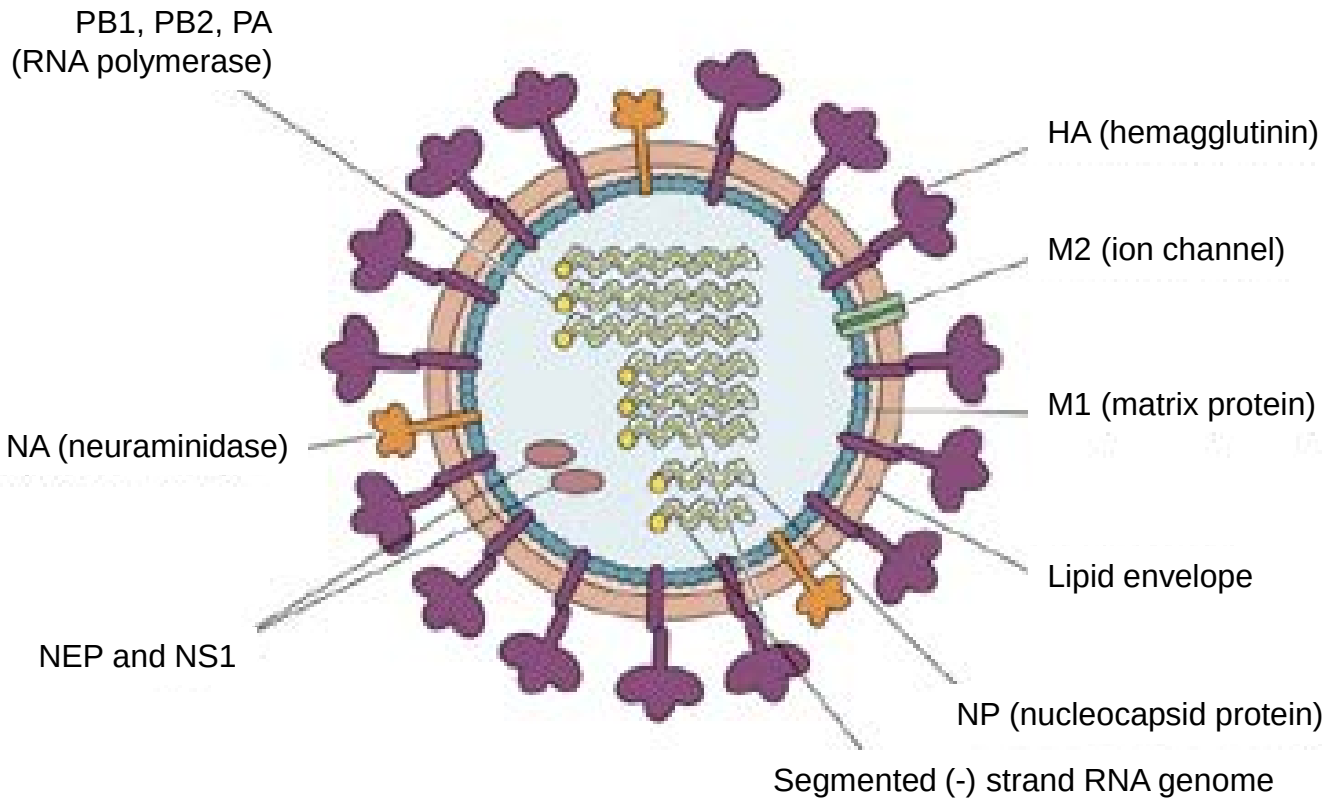
Outline

- Burden and Challenges of Influenza
- VRC Influenza Vaccine Development
- VRC Universal Influenza Vaccine candidate platform
- VRC Phase I Clinical Trial Updates on Universal Influenza Vaccine Candidate

To provide some context to the trial- I will talk a bit first about the VRC influenza vaccine program and then more specifically about the platform used in our phase I trials.

Influenza Genome and Proteins



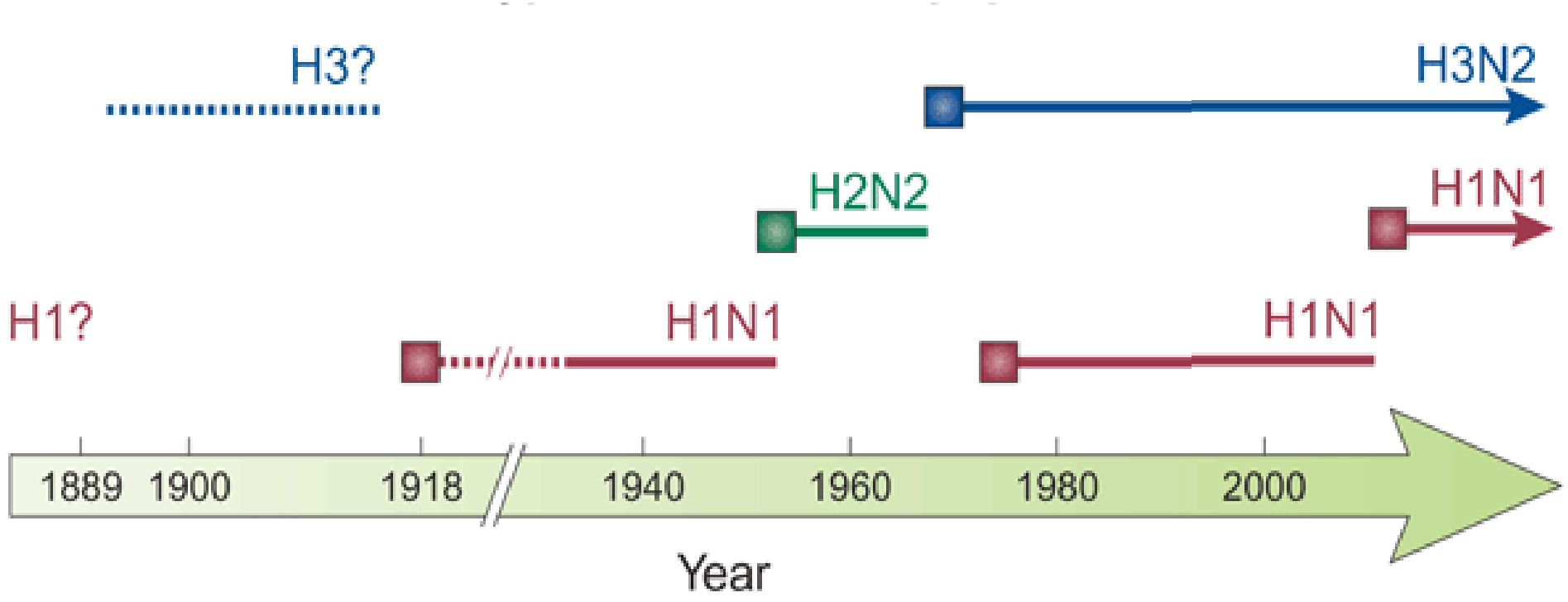


- Orthomyxovirus with segmented, negative-sense, single-stranded RNA genome
- 8 gene segments encoding 11 proteins
- Sialic acid receptor-dependent tropism

Influenza remains a significant public health burden accounting for 3-5 million deaths and 300-500K hospitalizations due to serious illness in the worldwide.

Shown here is the influenza virion. This virus has some unique virologic characteristics including the capacity for antigenic drift and shift. Antigenic drift leads to the periodic seasonal epidemics with can lead to significant morbidity and mortality.

Historical Influenza Pandemics



Adapted from Palese, et al. Nat Med, 2004

Antigenic shifts give rise to potential for pandemics which can have even more significant impact (with estimates of mortality in 1918 pandemic ranging from 40-100 million) underscoring need for more universal influenza vaccine platform.

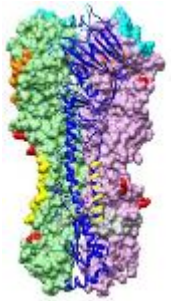
Need for a Universal Influenza Vaccine

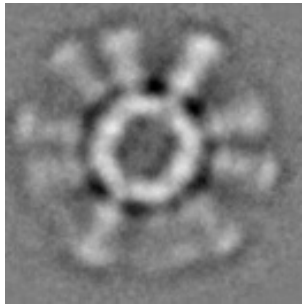
Current Influenza Vaccines:

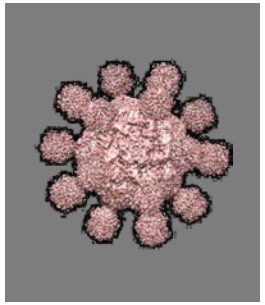
- Use 1940's technology - inactivated virus grown in chicken eggs
- Only 50-60% effective in good years
- Need to be reformulated every year to match circulating influenza strains
- Not effective against new pandemic strains and response is too late

Future Influenza Vaccines:

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







Current licensed influenza vaccines have limitations– including a manufacturing process that is reliant on eggs and thus may not be agile in response to a pandemic as well as being subject to egg adapted mutations. Effectiveness of the vaccine is highly variable depending on the match between the vaccine strains and circulating strains and are only in the range of 50-60% effective in good years. Current Influenza vaccines need to be reformulated and administered with each flu season and are also not likely to be effective against new pandemic strains.

Given these limitations- there is room for improvement for influenza vaccine development and technology.

Public Health Burden of Emerging & Re-emerging Viruses

Vaccine Challenges

- Vaccines for unmet needs
- Emerging viruses
- Improving licensed vaccines

Traditional Approaches

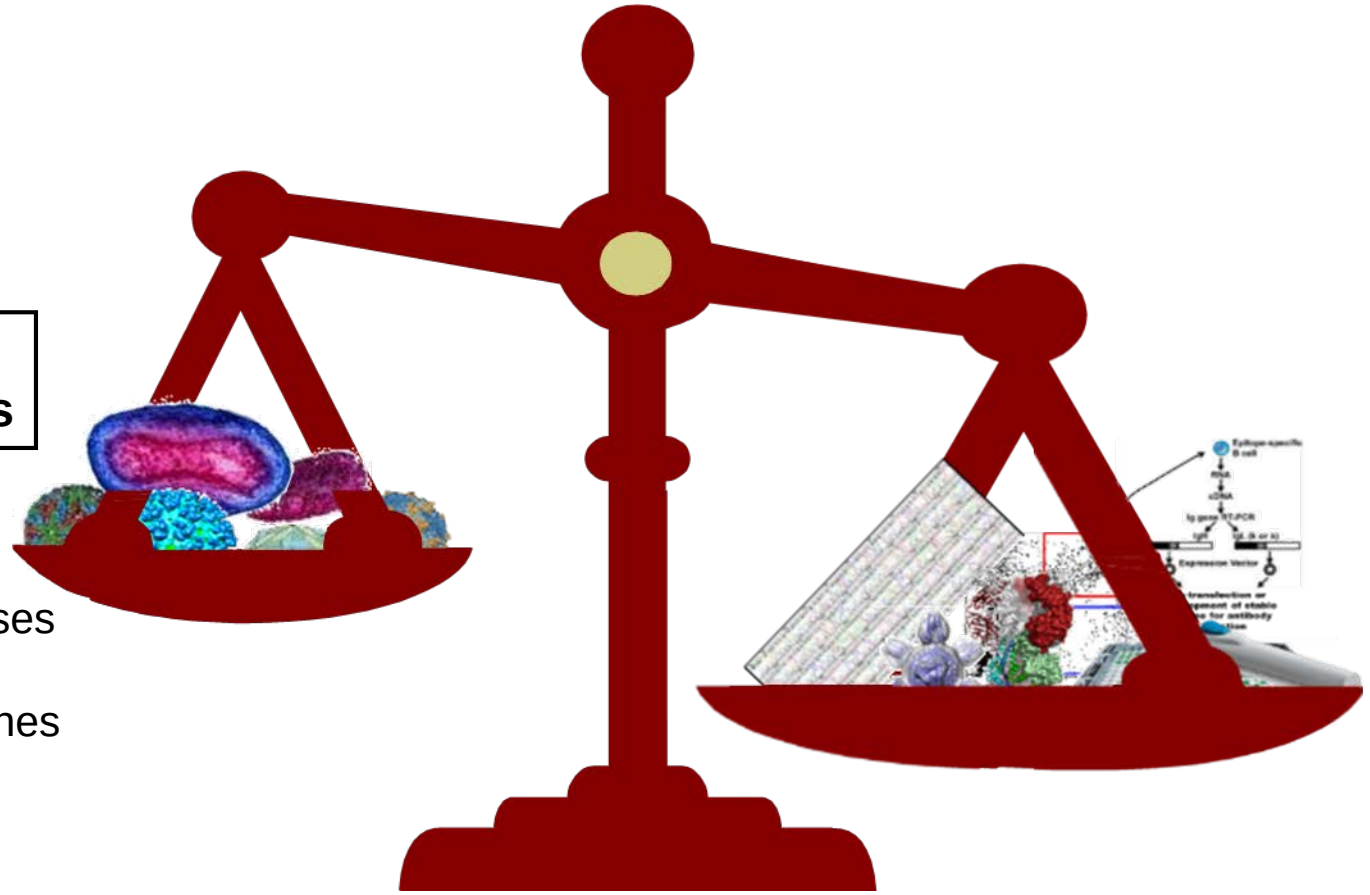
- Licensed vaccines/antibiotics
- Passive surveillance
- Contact tracing
- Quarantine

I'll only quickly highlight in this slide that as seen with influenza- the challenges to vaccine development have really not been well met by traditional approaches that are currently being utilized.

New Technologies Facilitate an Engineering Approach

Vaccine Challenges

- Vaccines for unmet needs
- Emerging viruses
- Improving licensed vaccines



New Technologies

- Structural biology
- Protein engineering
- Single cell sorting and analysis
- High throughput sequencing
- Rapid isolation of human mAbs
- Antibody lineage analysis
- Rapid diagnostic tools
- Systems biology

However, the landscape is changing. New technologies available in the last 10 years provide new options for pandemic preparedness and response. This applies to therapeutics and diagnostics as well as vaccines

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

Erbelding et al. J Infect Dis. 2018

These new capabilities have reinvigorated the efforts to develop a universal influenza vaccine which can really include a breadth of goals. The VRC's goals (consistent with the 2018 NIAID strategic plan for development of a universal influenza vaccine) include developing a vaccine with improved and consistent efficacy >75% and a product that would not require annual revision and would ideally provide durable immunity for greater than 1 year.

J Infect Dis. 2018 Jul 2;218(3):347-354. doi: 10.1093/infdis/jiy103.

Biological Challenges for a 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

Beyond the challenges already discussed-additional challenges exist for a universal influenza vaccine including a trememdous amount of antigenic variation in flu viruses as well as the still unclearly defined impact of pre-existing immunity due to the …

Technology Focus of VRC Influenza Vaccine Development Program

- **Design** - Structure-guided approach for antigens and probes
- **Display** – Natural and designer nanoparticles
- **Delivery** – Protein or nucleic acid
- **Detection**-- Specific immunological endpoints

In order to overcome some of these challenges- VRC is utilizing leveraging technological advances in structure guided approach to design antigens including natural and designer nanoparticles as well as different delivery techniques to develop vaccine platforms. In addition, the VRC influenza vaccine program is also focusing on making advancements in the assessment of the immune response to vaccination.

Detection of specific immunological endpoints

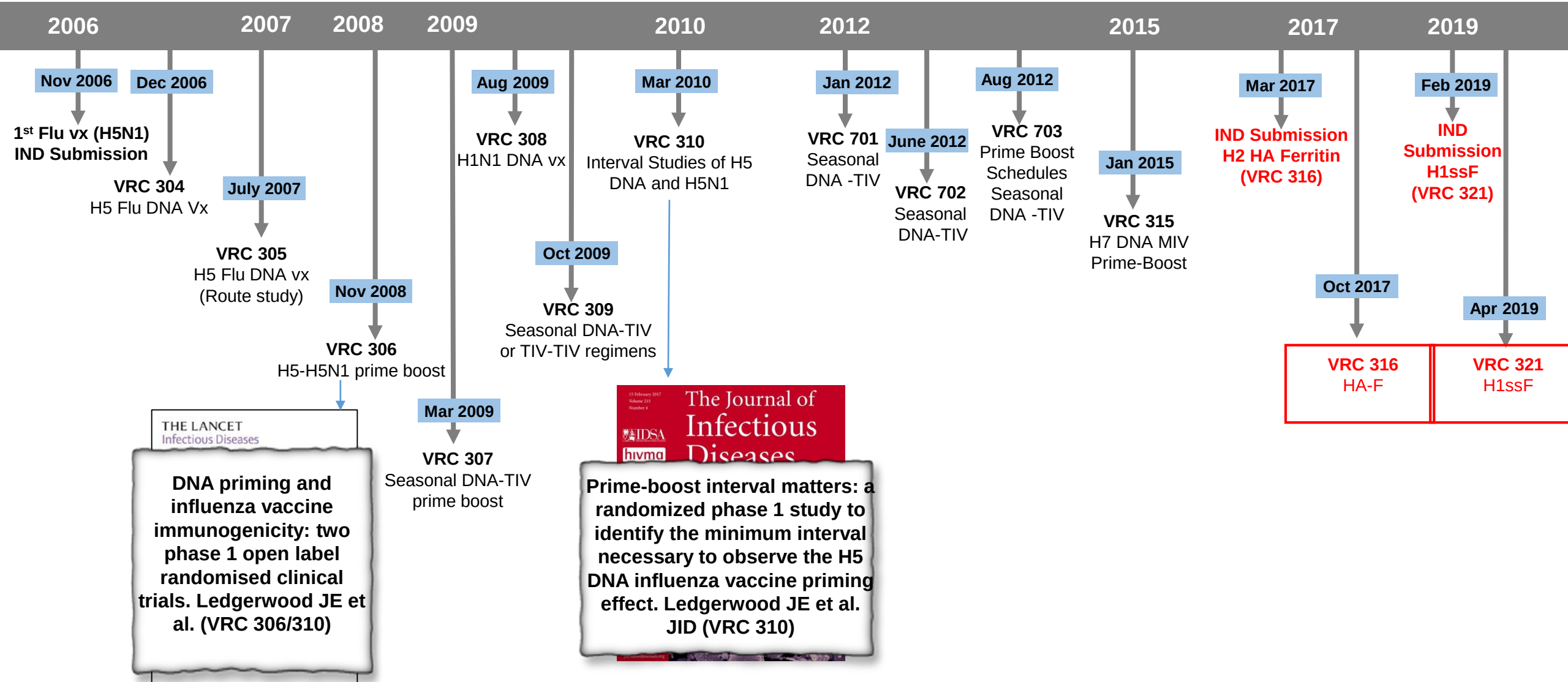
Define and target specific antibody lineages with cross-neutralizing activity

Analysis of B cell phenotype and repertoire at single-cell level

Development of high-throughput functional serological assays

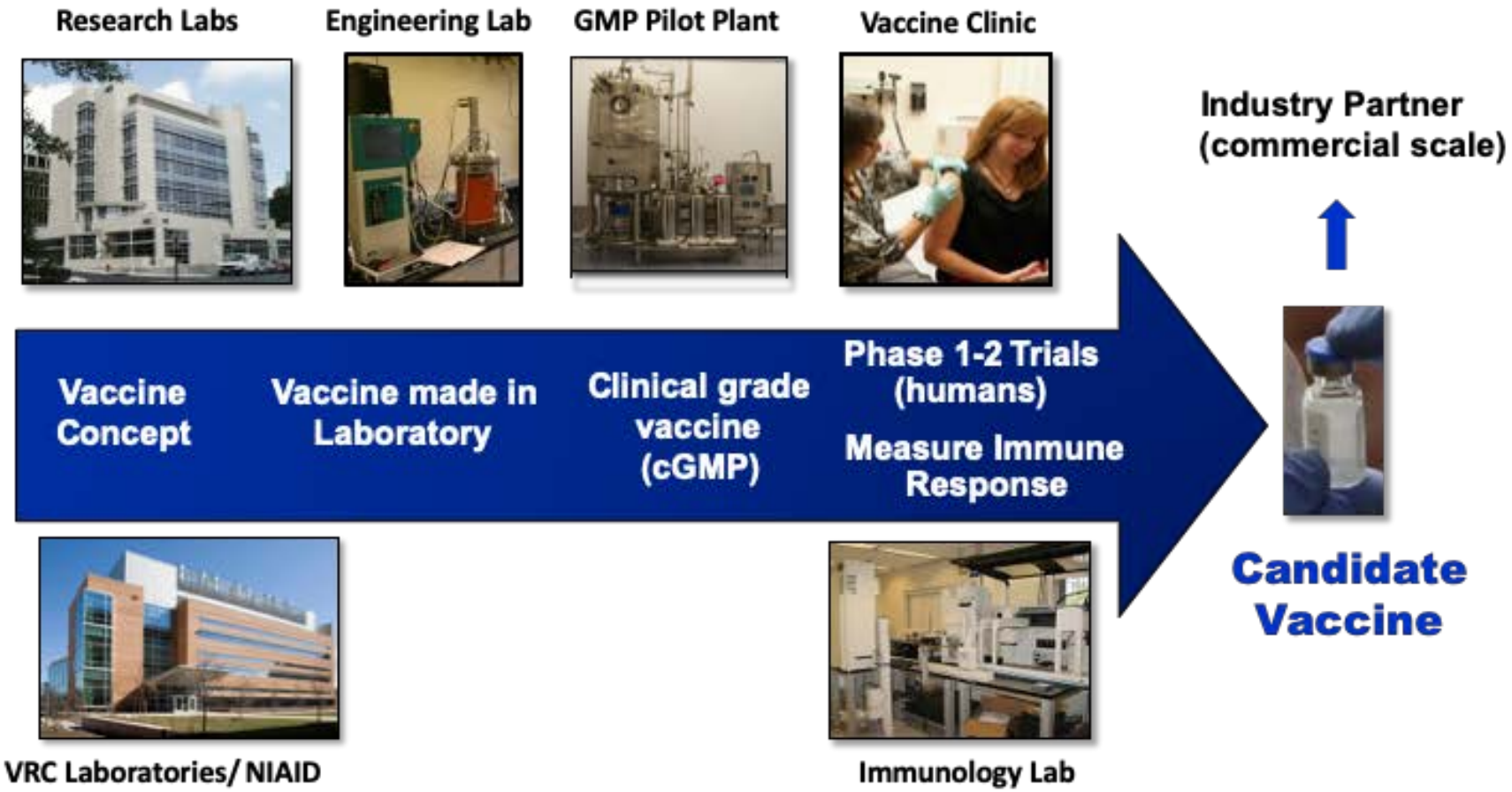
Influenza Vaccine Clinical Development at VRC

Universal Flu vaccine platform



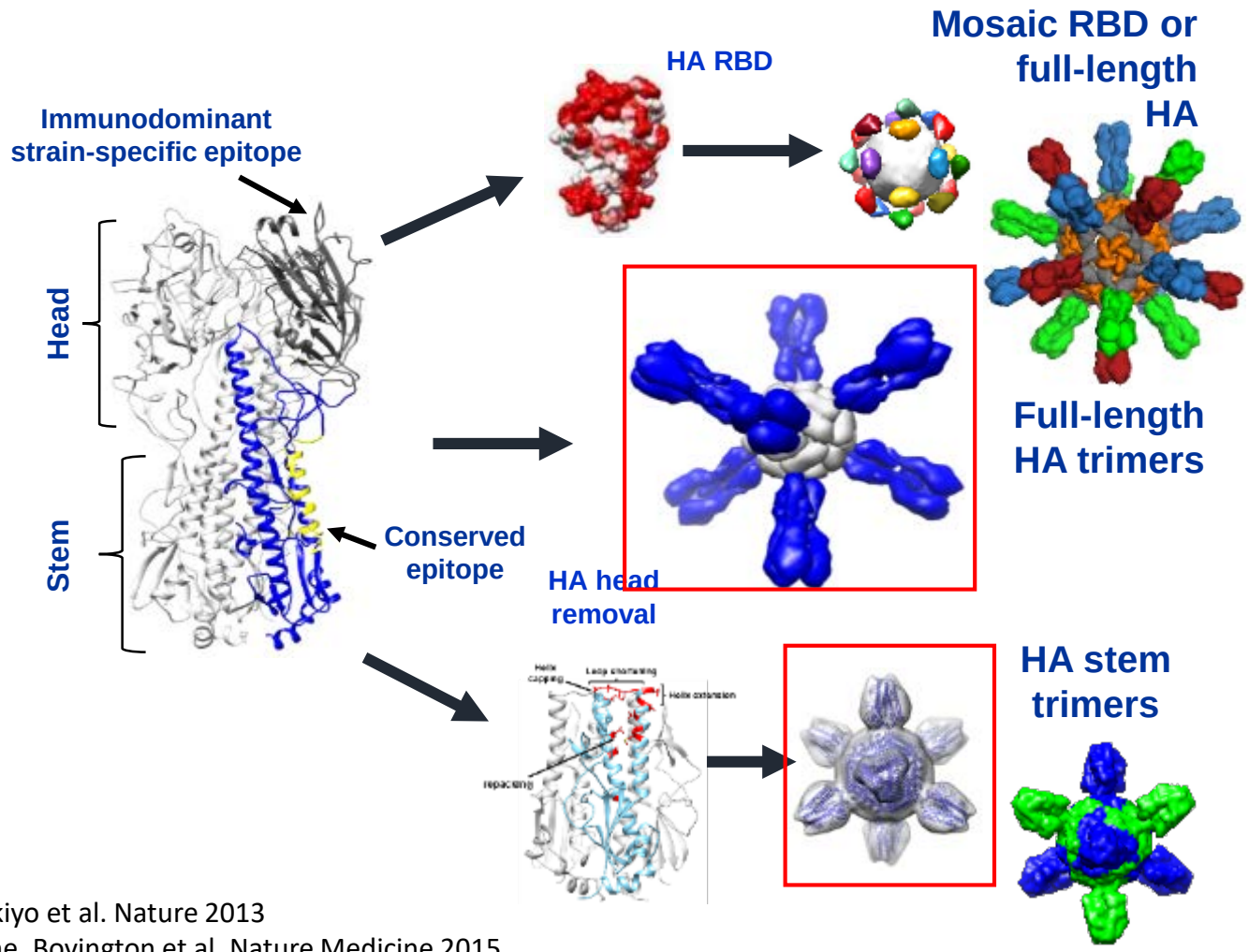
Influenza vaccine clinical development at the VRC has been ongoing since 2006. However, in the last few years- we have flu vaccine development efforts have been focused more on the development of a universal influenza vaccine candidate and began with a proof of concept testing in a platform that was first tested in 2017-2018 and has continued in development as the platform being used in the VRC universal vaccine candidate first in human trial- called VRC 321.

VRC Vaccine Development Pathway



I will just highlight here that the VRC vaccine development pathway is unique in many ways- including the ability to advance promising vaccine candidates that were developed by scientists on the NIH campus into phase I clinical testing.

VRC Universal Influenza Vaccine Development

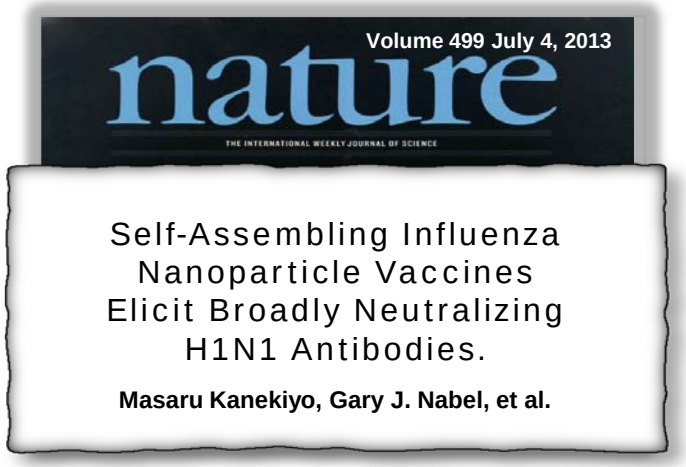


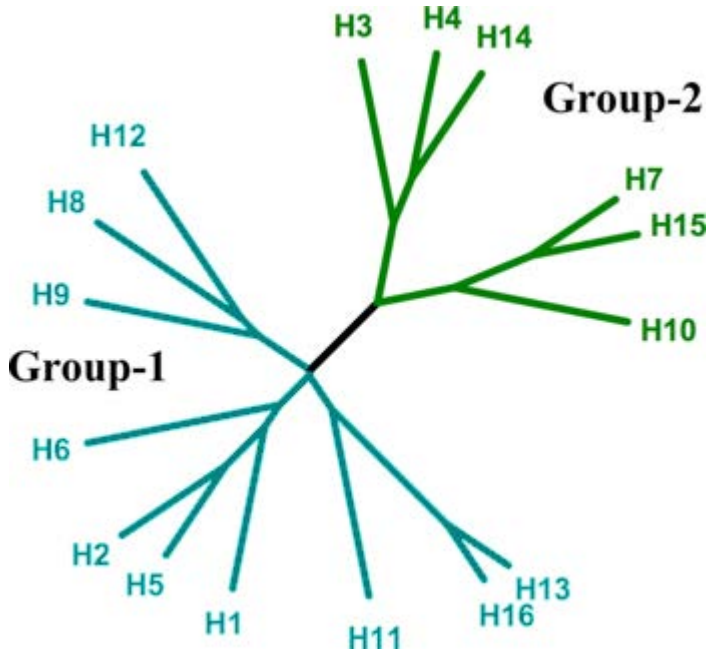
Kanekiyo et al. Nature 2013
Yassine, Boyington et al. Nature Medicine 2015
Kanekiyo et al. Nature Immunology 2019

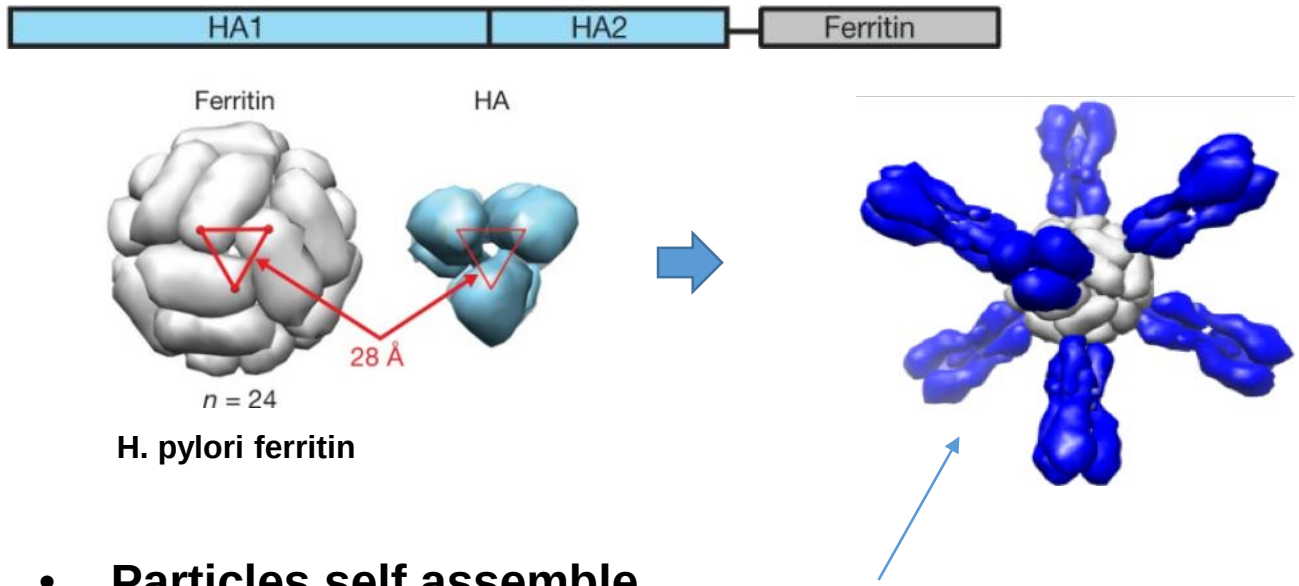
Shown here is the universal influenza vaccine candidate that we tested in VRC 321- composed of an H1 HA virus stem (which has more conserved epitopes) fused to an H. pylori ferritin platform. Prior to testing this universal influenza vaccine candidate- we had previously tested the ferritin platform with an H2 influenza HA head and I will discuss both these trials in brief detail.

Because of its highly divergent sequence from mammalian ferritins, we chose ferritin from Helicobacter pylori.

Influenza Full-Length HA Ferritin Nanoparticle







H. pylori ferritin

- **Particles self assemble**
- **HA is displayed in antigenically-authentic trimeric conformation**
- **Immunogenic in ferrets and NHP – elicits neutralizing antibodies**

We first tested the H pylori ferritin platform with an H2 influenza HA head in clinical trials following preclinical studies demonstrating safety and immunogenicity in animal models.

Utilizing an H2 influenza conferred several advantages- first, although H2 has not circulated in humans since 1968, H2 influenza still circulates in avian reservoirs and thus represents a pandemic pathogen. In addition- as you will see in the next slide of the trial design- we were able to assess the impact on naïve vs experienced individuals utilizing an H2 influenza vaccine.

Influenza HA Ferritin Phase 1 Trial

VRC 316

Phase I Influenza H2 HA Ferritin Vaccine (unadjuvanted) Alone or in a Prime-Boost Regimen with an Influenza DNA Vaccine

Subjects: Healthy adults, 18 – 70 years old

Enrollment: 50

Safe and well tolerated

VRC 316 Schema

Part I: Dose Escalation of HA-F A/Sing

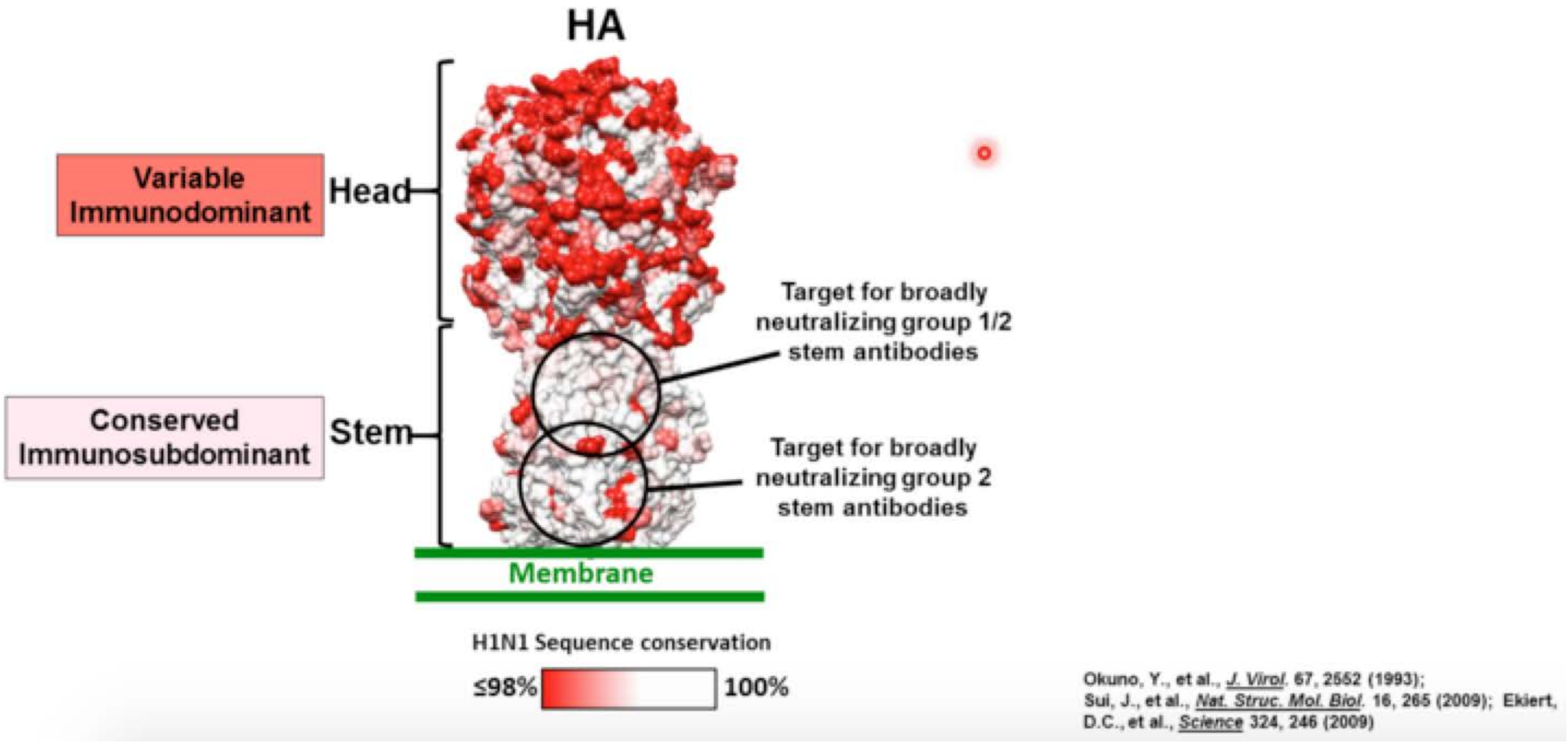
Group	Dose Level	Age Cohorts	Subjects	Day 0 Prime	Week 16 (±4 weeks) Boost
1	Low	18 - 47	5/5	HA-F A/Sing 20 mcg	
2	High	18 - 47	5/5	HA-F A/Sing 60 mcg	HA-F A/Sing 60 mcg
		Total	**10** *(HA-F A/Sing injections are administered IM by needle and syringe.)*		

Part II: Evaluation of HA-F A/Sing and DNA A/Sing in Prime-Boost Regimens

Group	Regimen	Age Cohorts	Subjects	Day 0 Prime	Week 16 (±4 weeks) Boost
3	DNA A/Sing HA-F A/Sing	Group 3A 18 - 47	10/10	DNA A/Sing 4mg	HA-F A/Sing 60 mcg
		Group 3B 52 - 70	10/10		
4	HA-F A/Sing HA-F A/Sing	Group 4A 18 - 47	10/10	HA-F A/Sing 60 mcg	HA-F A/Sing 60 mcg
		Group 4B 52-70	10/10		
		Total	**40** *(DNA A/Sing injections are administered IM by Pharmajet.)*		

Here is the study design of the first clinical trial evaluating the H pylori ferritin platform- this is not the universal influenza vaccine candidate trial but rather the clinical trial that we first tested the VRC H pylori ferritin platform using an H2. Our preliminary results showed that this vaccine platform was safe and well tolerated as well as immunogenic and we therefore utilized this platform for our first universal influenza vaccine candidate.

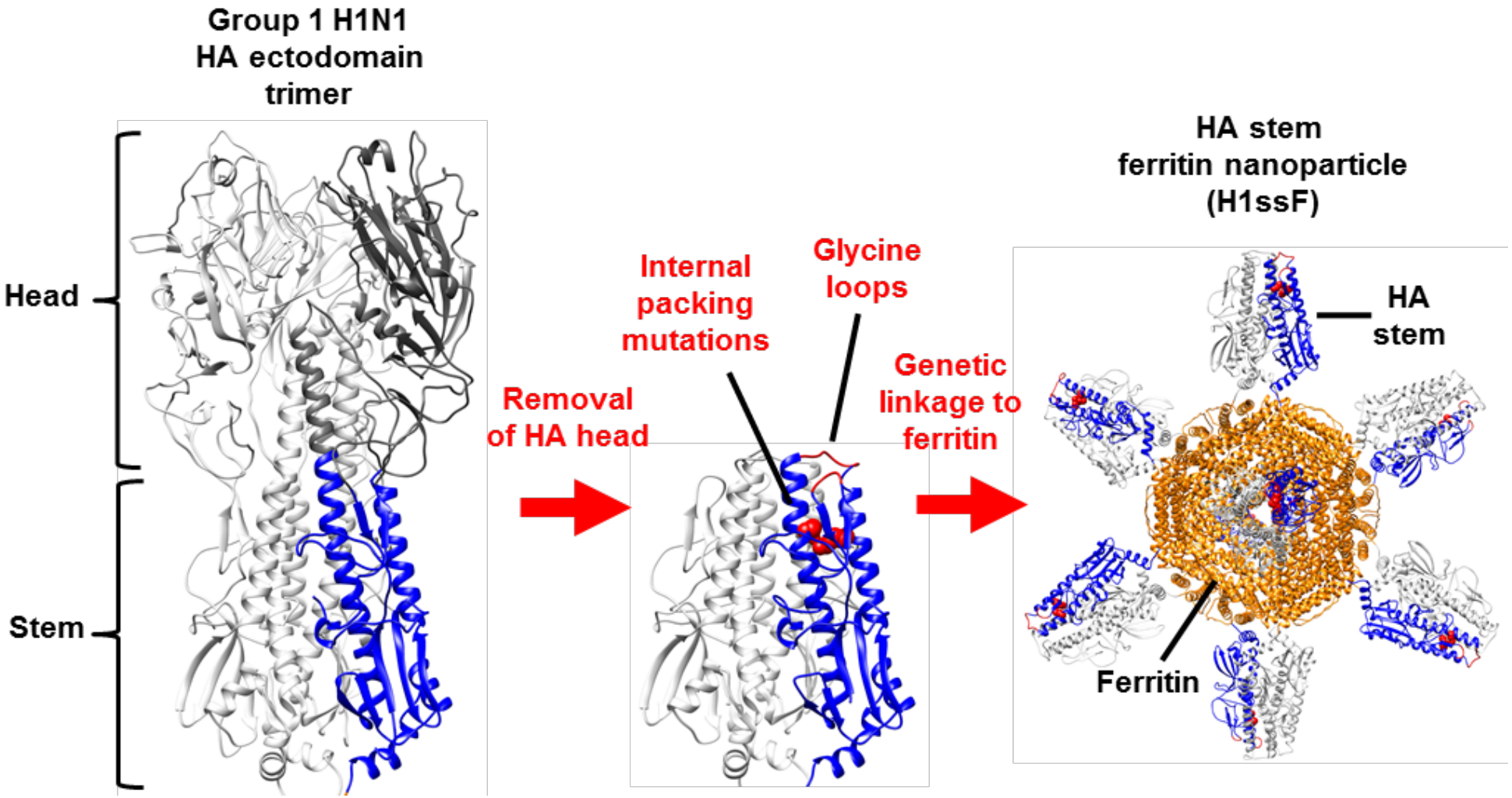
Conserved HA Stem as a Vaccine Target



Okuno, et al. *J Virol.* 1993; 67 (5): 2552-8.
Sui, et al. *Nat Struct Mol Biol.* 2009; 16(3): 256-73.
Ekiert, et al. *Science.* 2009; 32 (5924): 246-51.

The vaccine used in the trial utilized an H1 influenza HA stem (which as you can see represented here) has more conserved immunosubdominant epitopes- fused to an H pylori ferritin.

Group 1 HA Stem Antigen Design

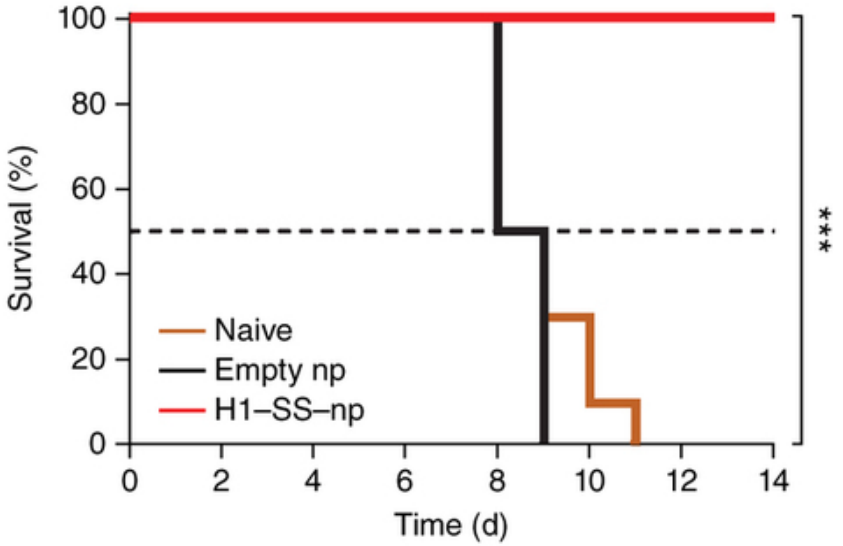


Yassine, Boyington, et al. Nature Medicine 2015

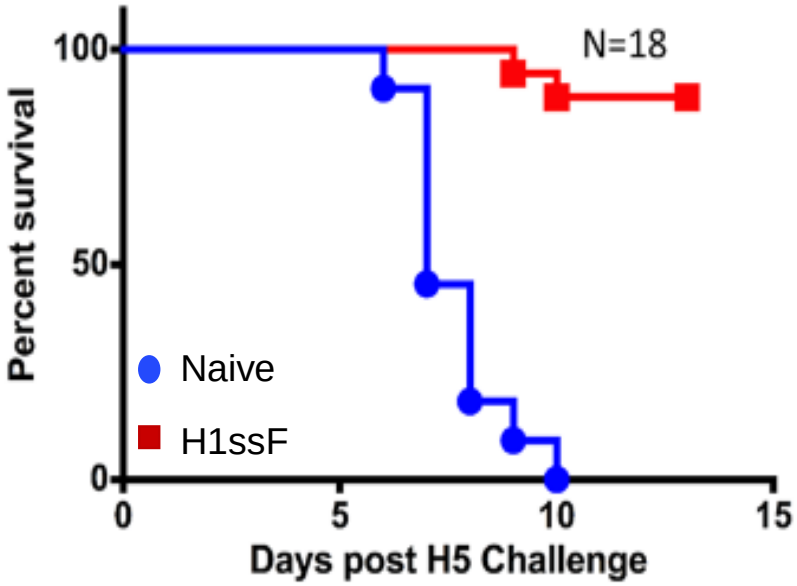
This is just a visual representation again of the vaccine- starting with the HA and then removing the immunodominant HA head and then linking the HA stem to ferritin thus creating the vaccine.

Group 1 HA Stem Preclinical Data

Mice



Ferrets



- H1ssF protects animals from heterologous H5N1 lethal challenge
- Headless HA-stem antigens achieve heterosubtypic protection and induce multi-donor cross-neutralizing antibody lineages

Yassine, Boyington, et al. Nature Medicine 2015

Influenza HA Stem Ferritin Phase 1 Trial

VRC 321
Phase I Influenza H1ssF (unadjuvanted)

Subjects: Healthy adults, 18 – 70 years old

Enrollment goal: 53

VRC 321 Schema				
Group	**Age Cohort**	**Subjects**	**Day 0**	**Week 16**
1	18 - 40	5	20 mcg	
2A	18 - 40	12	60 mcg	60 mcg
2B	41- 49	12	60 mcg	60 mcg
2C	50 - 59	12	60 mcg	60 mcg
2D	60 - 70	12	60 mcg	60 mcg
Total		***53***		

And here is the study design that was developed to assess this vaccine candidate. Our goal will be to recruit just over 50 volunteers age 18-70 and we will evaluate safety, tolerability and immunogenicity. We began vaccinations in April and hope to complete enrollment by the end of the year and have preliminary data by mid-2020.

Summary

- Recent advances in vaccine technologies have allowed for new platforms for potential universal influenza vaccine candidates
- Targeting HA stem epitopes may lead to an improved breadth of immune response
- VRC has tested a ferritin based platform in iterative phase I clinical trials (including a potential universal influenza vaccine candidate)

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