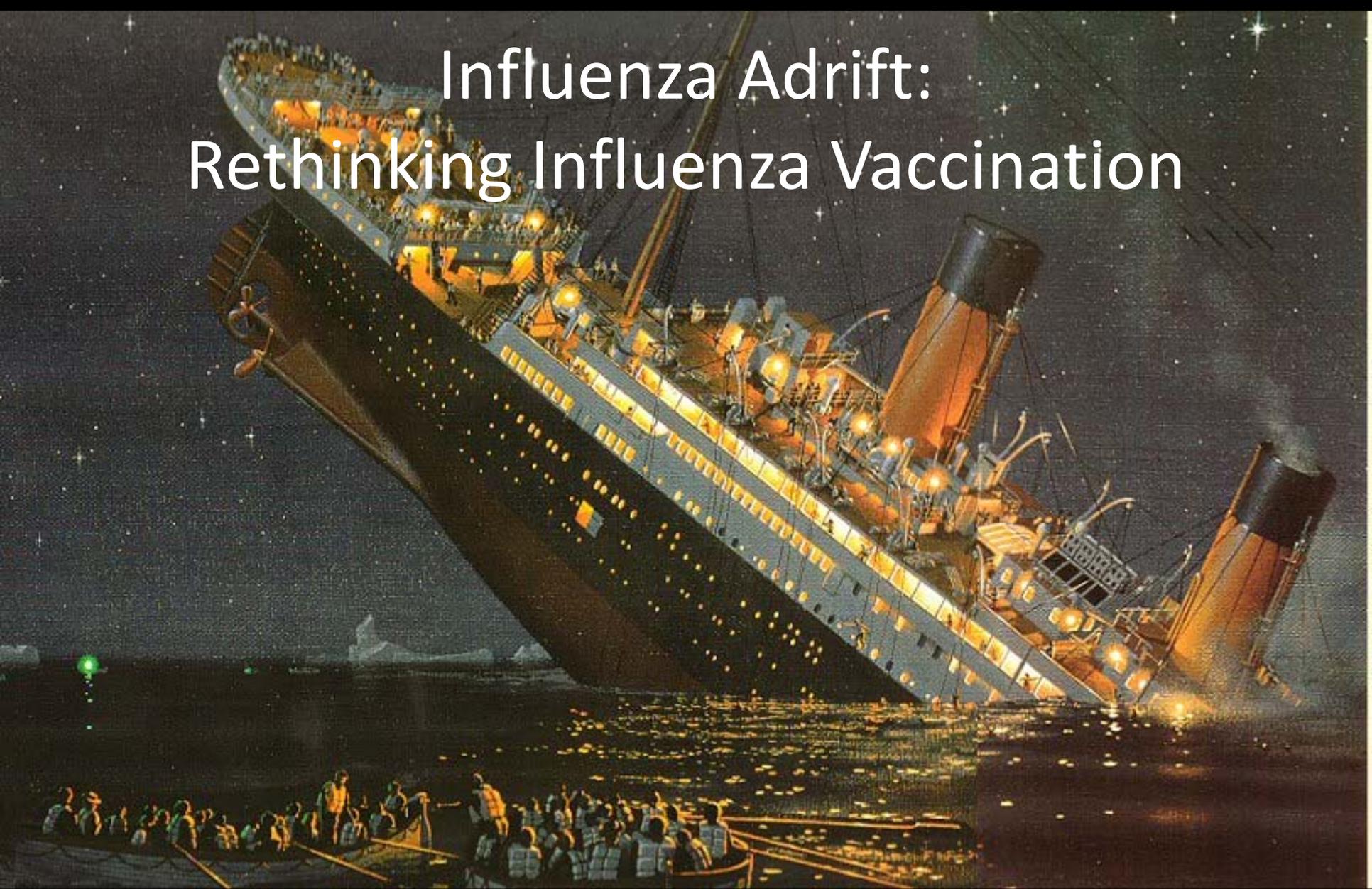


Influenza Adrift: Rethinking Influenza Vaccination

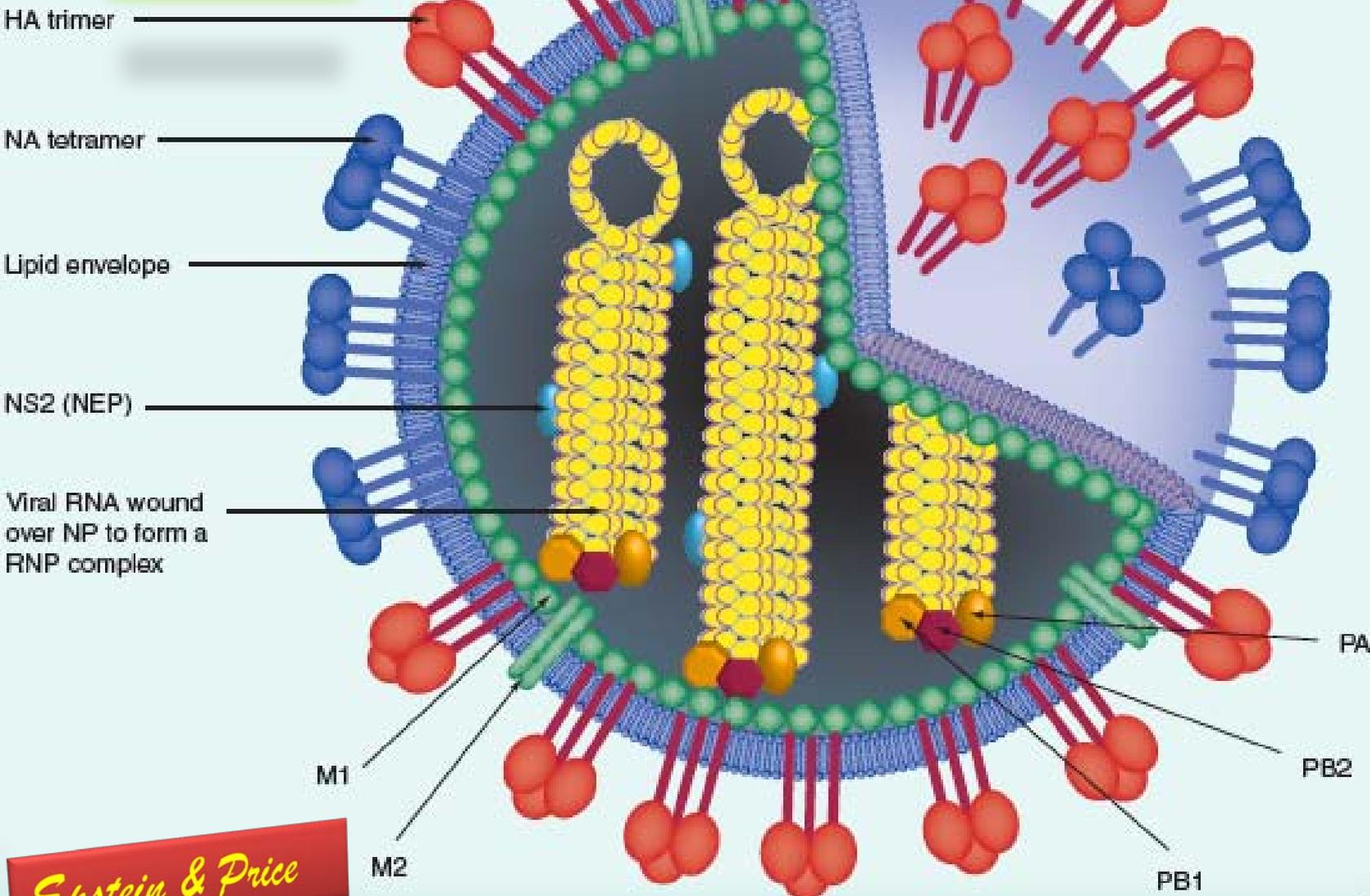


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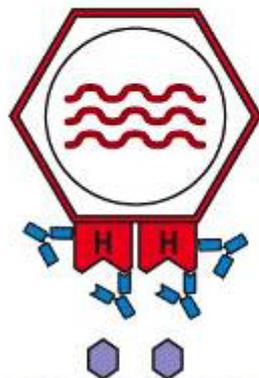
IAV



Epstein & Price

Antigenic drift

Neutralizing antibodies against hemagglutinin block binding to cells



Nightmare scenario: Antigenic shift with high path strain



1918: Iowa State gymnasium, converted into hospital

But antigenic drift isn't chopped liver.....



Translation for NNYs (non-New Yorkers)
Antigenic drift is important!.....



Drift...

- necessitates modifying vaccines on a yearly basis
- In USA alone causes ten of thousands deaths and \$50+ billion of economic losses
- Deaths ~ 30,000 per year
- Vaccine is by far the most cost effective option
- Is wise to invest in basic and translational research to improve vaccines
- This is why we have governments



Human Influenza A Viruses

- Most important antigen is HA
- 3 IAVs known to extensively circulate in humans and cause disease
- H1N1 1918-1957
- H2N2 1957-1968
- H3N2 1968-today
- Oops...H1N1 1977-today
- H1N1 2009 (Swine origin)



Complacency is the enemy of better

- Familiarity breeds complacency: Flu has been around for a long time
- Standard flu vaccines haven't changed much in 60 years
- Need to re-examine current practices and assumptions



Are Current Vaccines Effective?



Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis

Michael T Osterholm, Nicholas S Kelley, Alfred Sommer, Edward A Belongia

*Lancet Infect Dis 2012;
12: 36-44*

Interpretation Influenza vaccines can provide moderate protection against virologically confirmed influenza, but such protection is greatly reduced or absent in some seasons. Evidence for protection in adults aged 65 years or older is lacking. LAIVs consistently show highest efficacy in young children (aged 6 months to 7 years). New vaccines with improved clinical efficacy and effectiveness are needed to further reduce influenza-related morbidity and mortality.



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Optimism is essential

- Optimism is warranted!



- Have been enormous increases in understanding the host immune response to flu and how to manipulate it



Can we make a better flu vaccine?

- Very probably
- Don't immediately need a "universal vaccine"
- Subtype specific would be a huge advance
- Even retarding drift is enough
- Many approaches



T cell responses

- T cell cross-reactivity across subtypes known for 35 years
- Most T cells recognize conserved peptides in conserved internal proteins
- CD4 T cells against conserved peptide help B cell (antibody responses)
- CD8 T cells kill flu-infected cells &/or secrete useful anti-viral cytokines





If T cell vaccines could work, why is drift a problem: best immunity comes from natural infection...right?



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T cell responses

- Protect mice, monkey, and chickens
 - “monkeys mislead....
 -mice lie...
 -chickens.....”
- Despite skepticism of animal models, T cells might confer protection in humans...
- Remarkably, are no compelling large scale studies correlating T cell memory and influenza outcome



Can We Measure T cell responses?

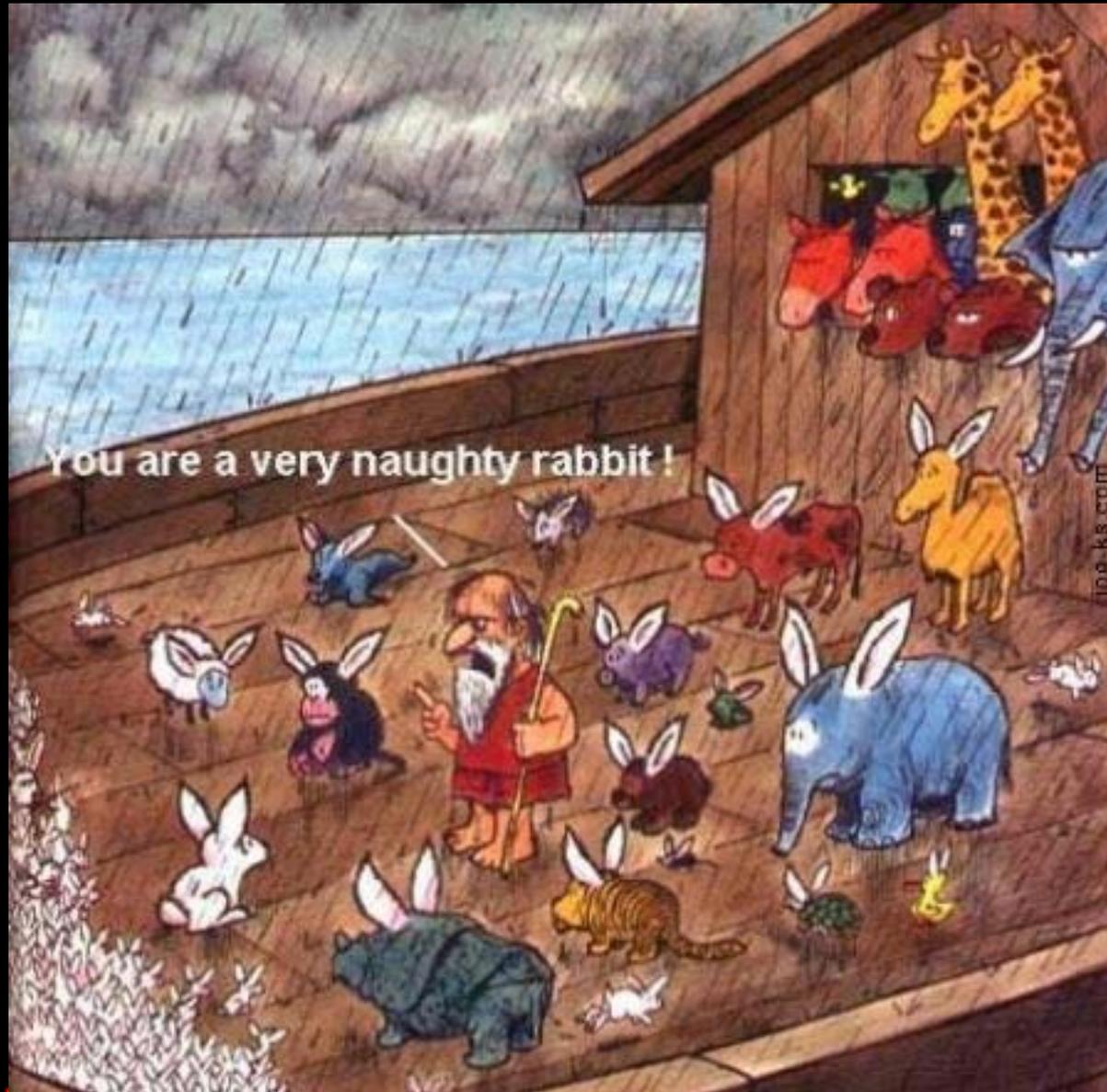


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Are There T cell Vaccines?



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T cell vaccinologists have been naughty

- Recombinant
 - DNA
 - Viral vectors (Ad, Vac, VSV, etc)
 - Bacterial vectors
- Non-recombinant
 - Irradiated virus
 - Virus like particles
 - Proteins
 - Peptides



So there is no reason not to know
whether T cells are useful



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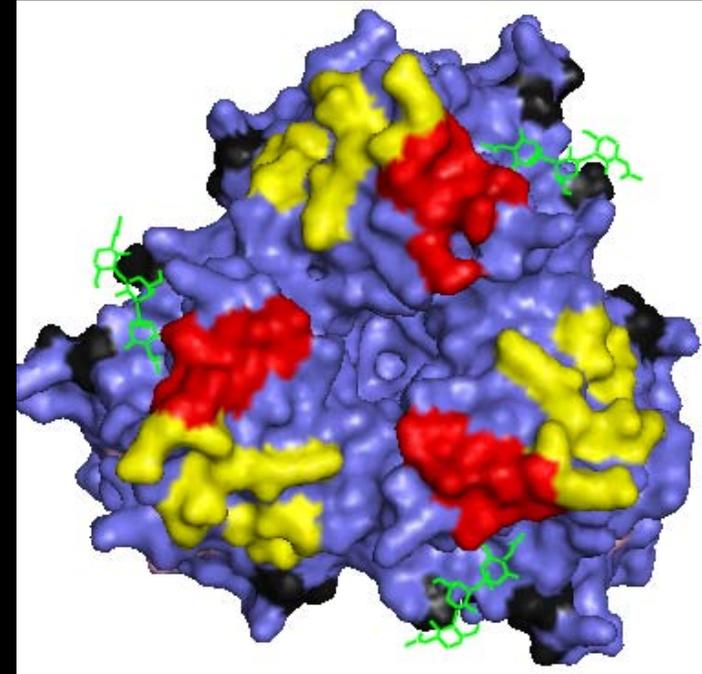
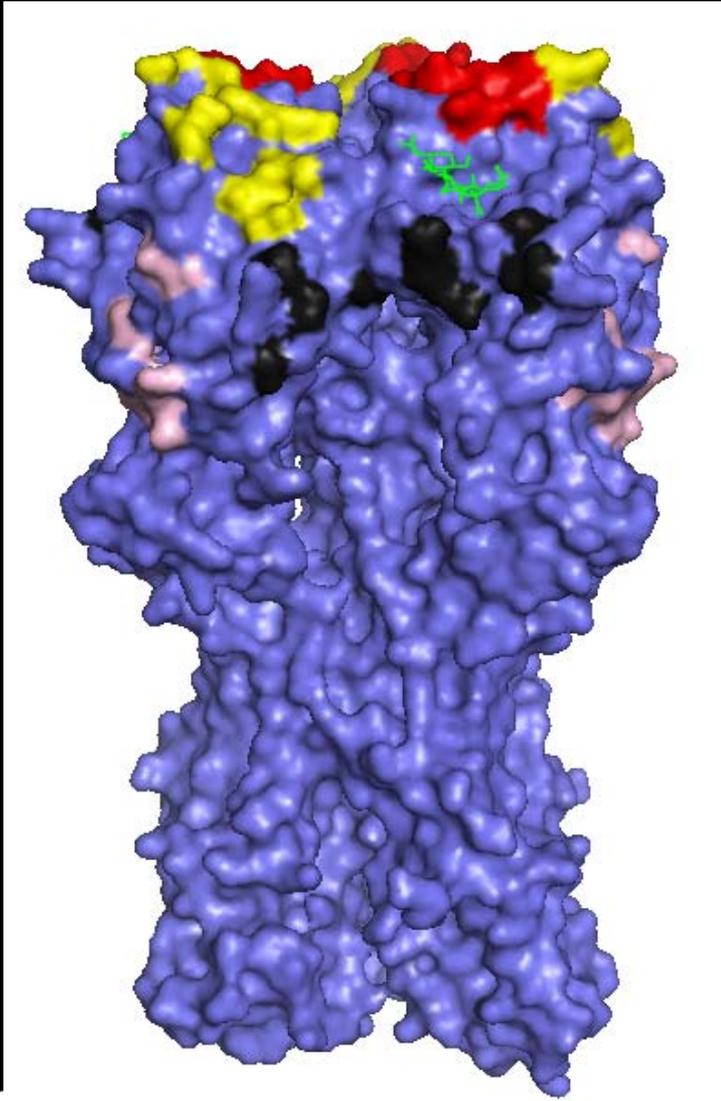
B cell vaccinologists...even naughtier

- Potential targets (in inverse order of promise*)
 - NP
 - Known to be on surface of infected cells for 35 years
 - Abs presumably work by complement or antibody-dependent cellular cytotoxicity (ADCC)
 - M2
 - 23-residue extracellular domain abundantly expressed on cell surface, few copies on virions
 - Abs potentially work by direct action, virion phagocytosis or ADCC
 - Target of several commercial vaccine trials
 - NA
 - Long known to confer protection against flu
 - Antibodies prevent virion release from cell surface and other ligands
 - We don't even measure how much NA is in vaccine preps !
 - HA
 - Extremely promising new findings

*** According to me**



H1 HA has 5 Classical Antigenic Sites Defined by mouse mAbs



Antigenic sites

Sa

Sb

Ca1 and Ca2

Cb

Receptor

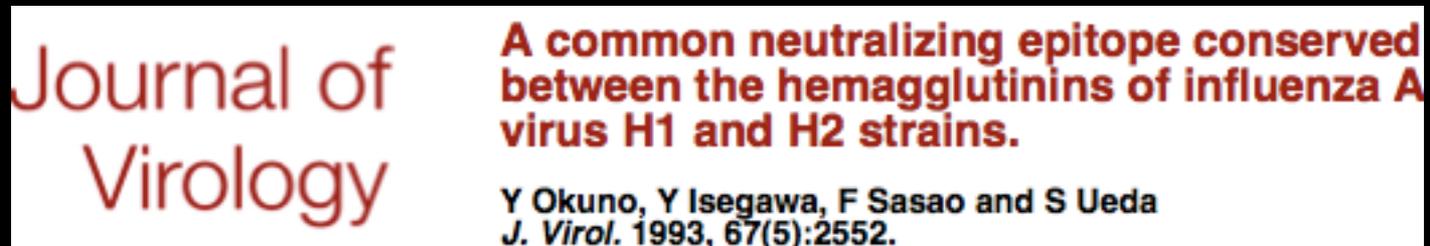
Sialic Acid



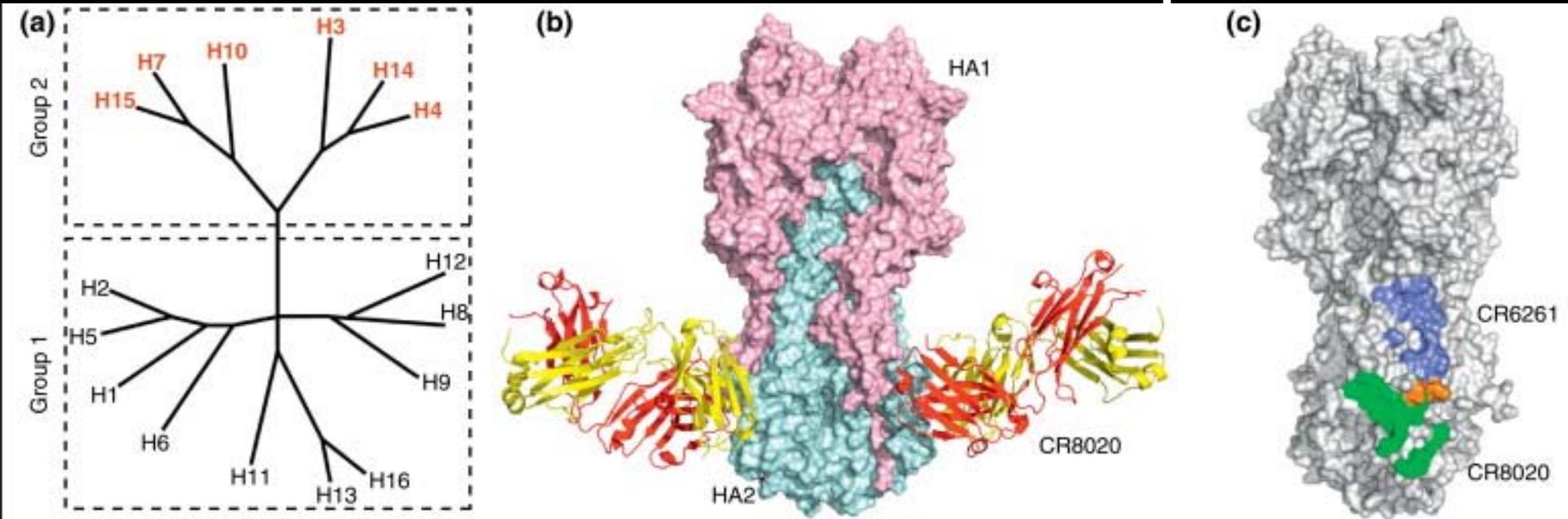
Viva la revolución: rethinking influenza A virus antigenic drift

Jonathan W Yewdell

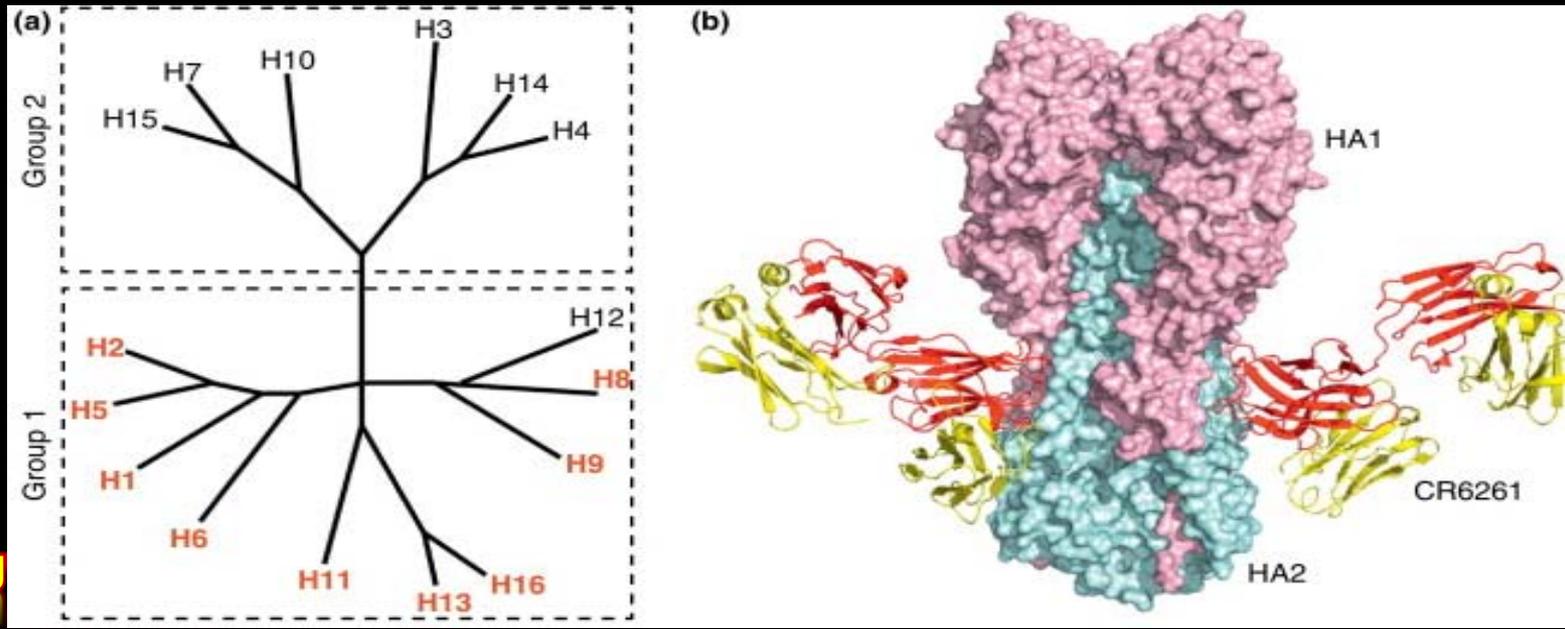
- La revolución: human monoclonal Abs
- Based on generation of drift/shift resistant neutralizing Abs specific for conserved regions in HA stem and receptor binding site (RBS)
- But mice didn't lie



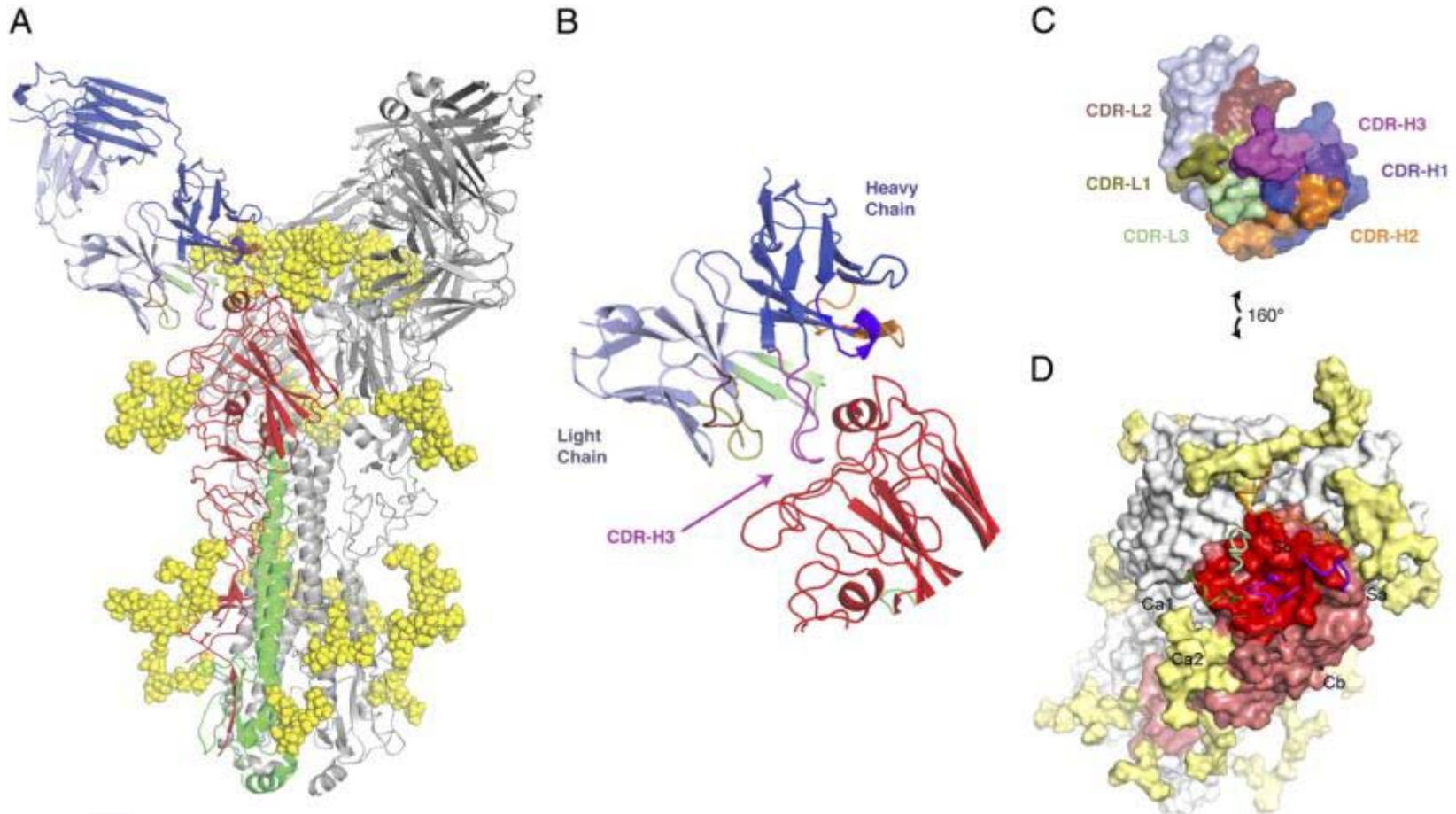
Most BN-Abs are Stem-Specific



Damian C Ekiert, Ian A Wilson *Current Opinion in Virology* 2012



But not all...



Broadly neutralizing human antibody that recognizes the receptor-binding pocket of influenza virus hemagglutinin

James R. R. Whittle^a, Ruijun Zhang^b, Surender Khurana^c, Lisa R. King^c, Jody Manischewitz^c, Hana Golding^c, Philip R. Dormitzer^d, Barton F. Haynes^{b,e,f}, Emmanuel B. Walter^{b,g}, M. Anthony Moody^{b,h}, Thomas B. Kepler^{b,h}, Hua-Xin Liao^{b,e}, and Stephen C. Harrison^{a,1}

^aLaboratory of Molecular Medicine, Children's Hospital, Harvard Medical School and Howard Hughes Medical Institute, Boston, MA 02115; ^bDuke Human Vaccine Institute and Departments of ^cMedicine, ^dImmunology, ^ePediatrics, and ^fBiostatistics and Bioinformatics, Duke University Medical Center, Durham, NC 27710; ^gDivision of Viral Products, Center for Biologics Evaluation and Research, Food and Drug Administration, Bethesda, MD 20892; and ^hNovartis Vaccines and Diagnostics, Cambridge, MA 02139

PNAS



JW



Basic Questions: Hemagglutininology

- Mechanisms of neutralization
 - Head vs. stem
 - Head vs. head and stem vs. stem!
 - Need to study in vivo
 - General question of contribution of avidity to neutralization
 - on vs. off rates may be important discriminators
 - Contribution of ADCC
 - Take advantage of insight into neutralization to generate small molecule therapeutics
- How do anti-stem Abs effect transmission?
- What will the virus do?
 - Escape?



Clinical Endpoints

- Can't use standard assays...like HAI
 - Was never very good
 - Is not relevant for stalk antibodies
- In vitro neutralization is probably the best compromise
 - But the devil is in the exact details of the assay



Moving forward

- Exploit enormous advances in immunology/genetics to characterize response to existing vaccines
 - Measure multiple immune parameters
 - Including anti-stem antibodies and also responses to individual antigen sites
 - Be careful not to oversimplify interpretation
 - Anti-stems Abs are not not all equal!!
 - Why??
 - Genotype individuals
 - Correlate outcomes (including failure) with genotype (including Ig repertoire) and phenotype of immune response
 - Information could be immediately useful in explaining vaccine efficacy
 - Essential for advances in systems biology analysis of immunity



Moving forward

- Set common standards for comparing vaccine efficiency
 - Make common reagents available



Perform small trials

- Importance of human challenge models for proof of principle
 - Need mechanisms for performing head to head studies with different adjuvants
- Encourage novel platforms
- Encourage diversity in approaches
 - M2 and T cell based approaches
 - Different routes of immunization
- Don't ignore age related differences in strategies and outcomes
- Importance of children as the major community vector
 - Best way to protect elderly is herd immunity



