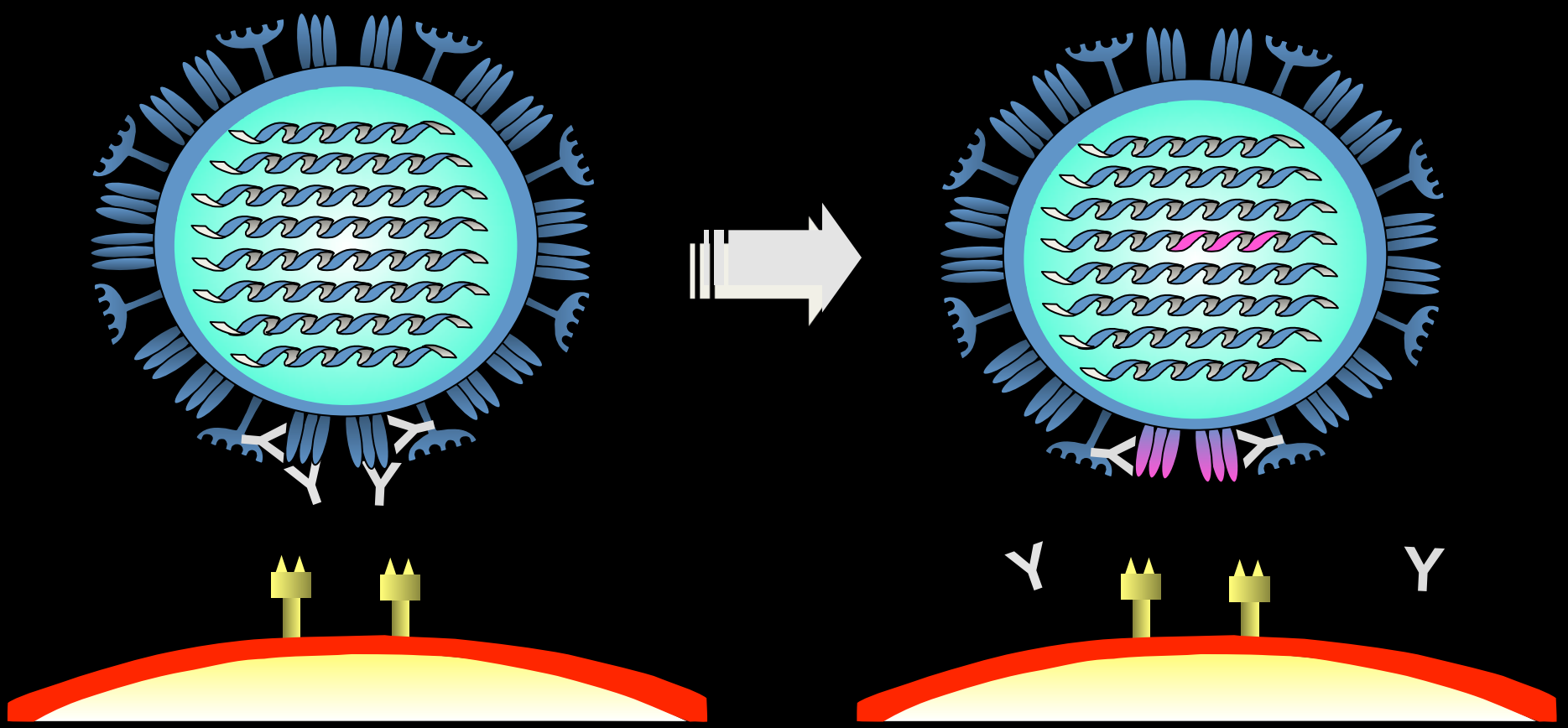
St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

Prospects for improved and more readily available vaccines

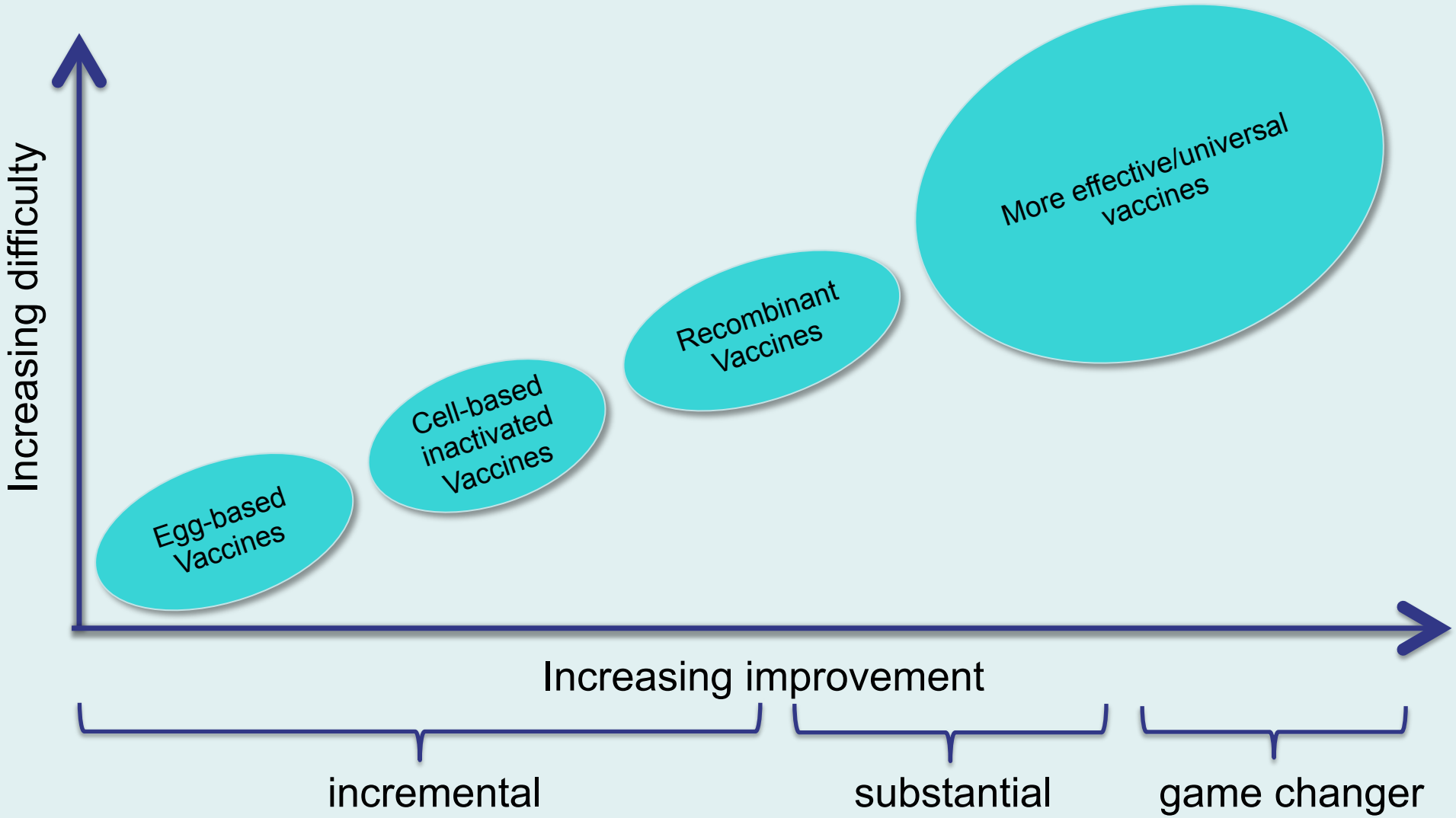
Richard Webby
ISG 2018

Webby takes stage #its going to be huge. Close to a million people turned up to listen; way bigger crowd than Doherty #little T cell man.

The problem



Improving influenza vaccines



Defining a universal influenza vaccine

- A vaccine that provides safe, more effective and long-lasting immunity against a broad spectrum of divergent influenza viruses in all ages and people in high risk groups
- Prime for emergence of a pandemic influenza virus
- Improve vaccine effectiveness
- Reduce the need for annual vaccination

Landscape of Next Generation Influenza Vaccine (NGIV) Candidates

BIOMEDICAL ADVANCED RESEARCH AND DEVELOPMENT AUTHORITY — BARDA

Pre Clinical

- Janssen — Mini-HA
- H5 Immunity Management
- SAM rna — Seqirus — A CSL Company
- MEDIGEN, INC. — VLP
- Avatar Medical, LLC — Headless HA
- Nanoparticles – HA stem, NP, TLR/CD40 — Indiana University
- 4xM2e HA LAIV — Georgia State University
- Chimeric HAs — Icahn School of Medicine at Mount Sinai
- DNA prime/ subunit boost — Protectus
- Centralized HA/NA inactivated vaccine — University of Nebraska-Lincoln
- H1N1 & H3N2 stem trimers — VaxiV
- M2e-HA stem — Georgia State University
- Ad5-vectored HA, NP, M — Etubics
- M2e CpG gold nanoparticles — Texas Tech University
- Surface antigen/adjuvant vaccine engineering (SAAVE) — University of Georgia
- HA nanoparticles + free HA & NP
- M2e-TLR5 fusion protein — Georgia State University
- Germline-targeted HA stem — The Scripps Research Institute
- TLR5, TLR7/8 adjuvants — Wake Forest University
- Laser vaccine adjuvant — Massachusetts General Hospital
- Microneedle adjuvant GIFT4/IFN-lambda 2 — Emory University
- Nanoparticle adjuvant TNF, IL-12 — Columbia University
- Nematode-secreted rASP-1 adjuvant — New York Blood Center

Phase 1

- NanoBio — IN HA nanoemulsion
- HA Stablized Stalk — NIH NIAID
- ΔM2 LAIV — FluGen
- MVA prime and Ad5 Boost Vectors with M1 NP — vaccitech
- CodaGenix Inc. — SeraBio LAIV
- ANS1 LAIV — Vivaldi Biosciences
- GSK — Chimeric HA
- Sanofi — M2e - hepB core fusion
- valera — RNA
- DNA — inovio Pharmaceuticals

Phase 2

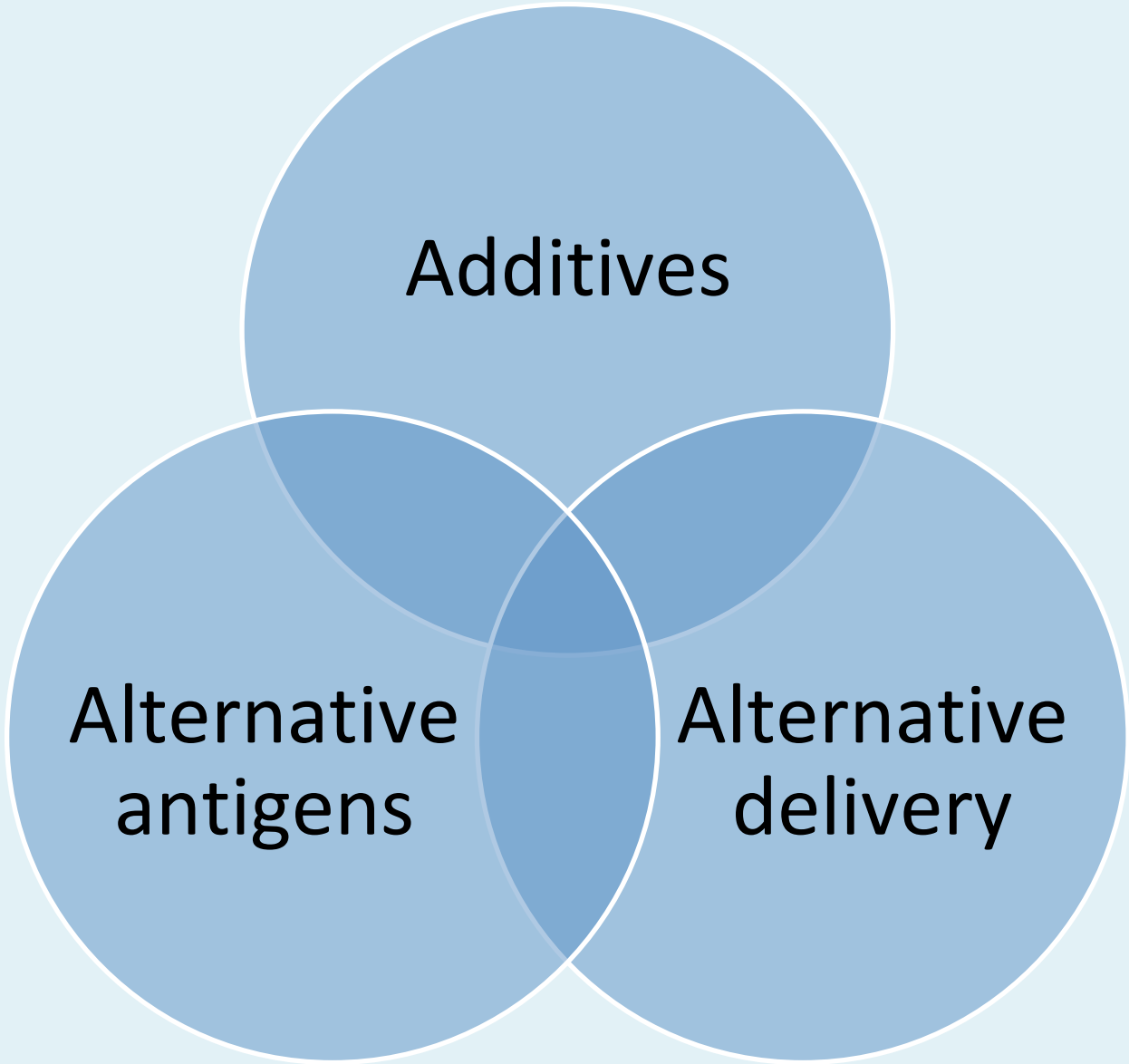
- VLP from tobacco plants — medicago
- MVA — MVA Vector NP M1 +TIV — vaccitech
- Replication deficient hAd5 HA/TRL 3 agonist — VAXART
- Ad5 — NasoVax — altimmune
- Conserved epitopes from HA + NP + M1 — BiondVax
- NPA + NPB + M1 + M2 polypeptides — SEEK

NIAID supported

BARDA supported

Version 2-2-2018

How?



Additives

- Adjuvants
- Reduce antigen requirements
- Stimulate different components of immune response
- Increase breadth of neutralizing response
- Many have poorly defined mechanisms

Alternative Delivery

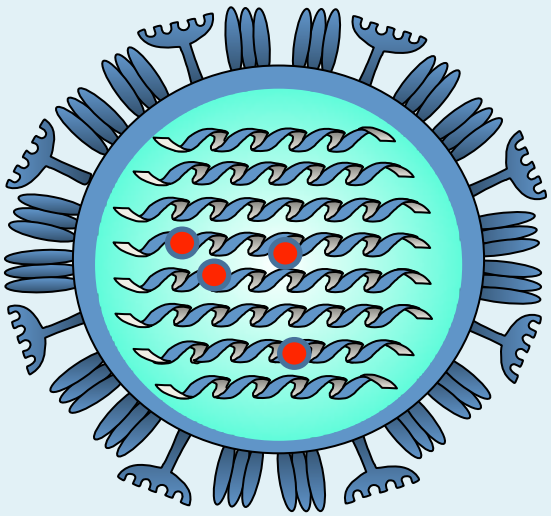
- Viral vectored- adeno, MVA
- Nucleic acid- DNA, RNA
- Peptides
- Nanocarriers
- VLP
- Prime boost strategies

Alternative Antigen

- LAIV
- M, NP T cell epitopes
- M2e
- HA stalk

Live attenuated vaccines

- Stimulate natural immunity
- Induce humoral and cellular immunity
- Correlates of immunity unclear
- Likely variably attenuated across ages



Temperatur
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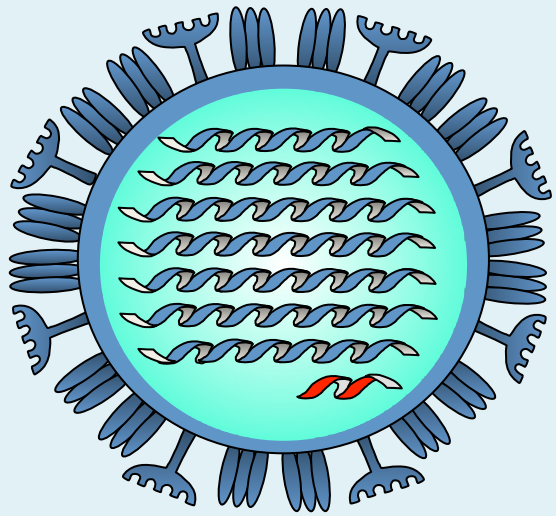
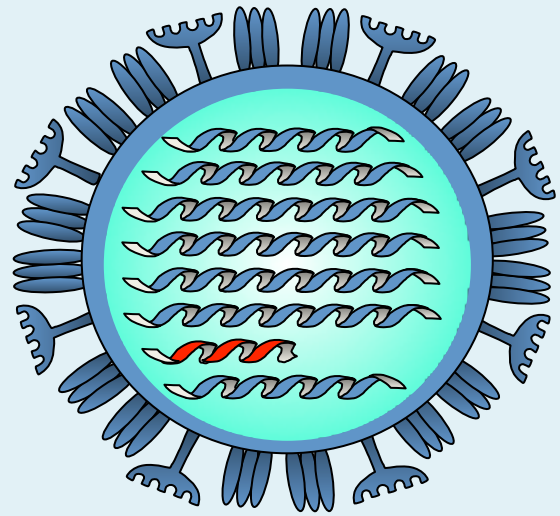
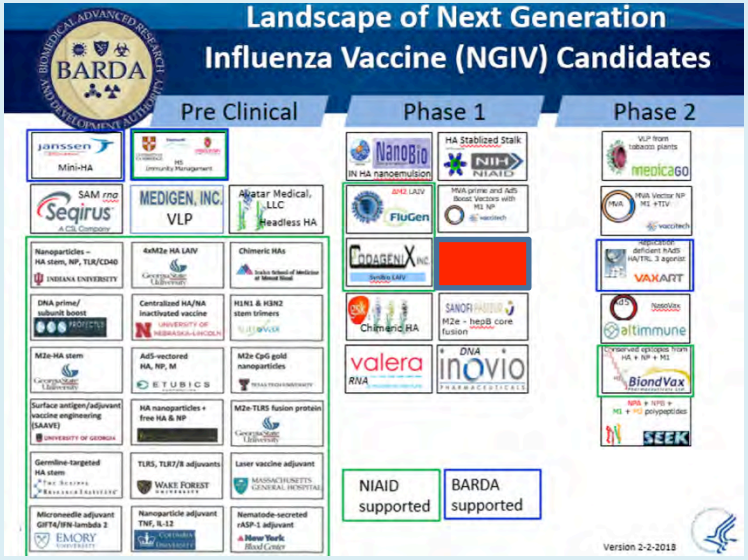


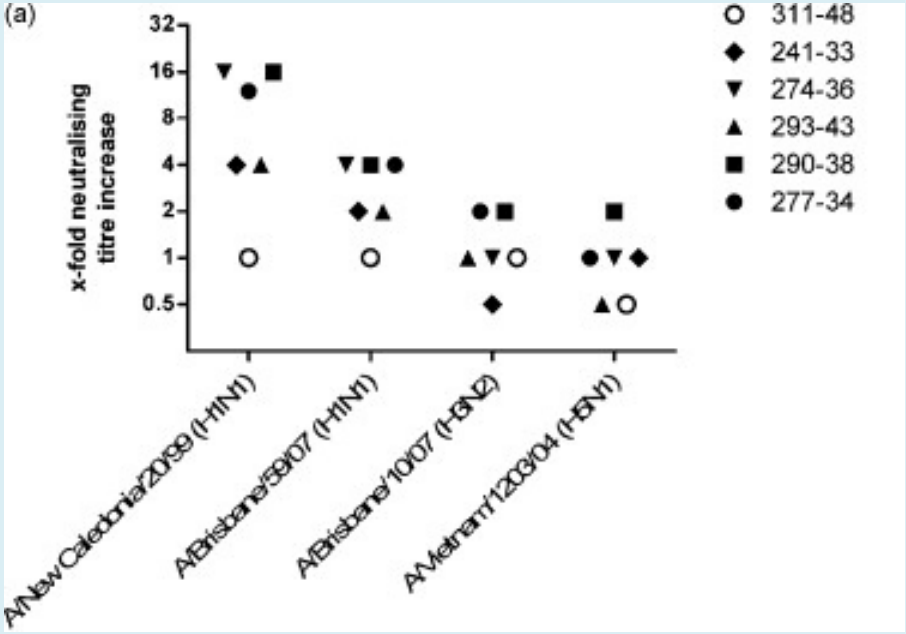
NS1 deletion;
Phase II,
veterinary
licensed

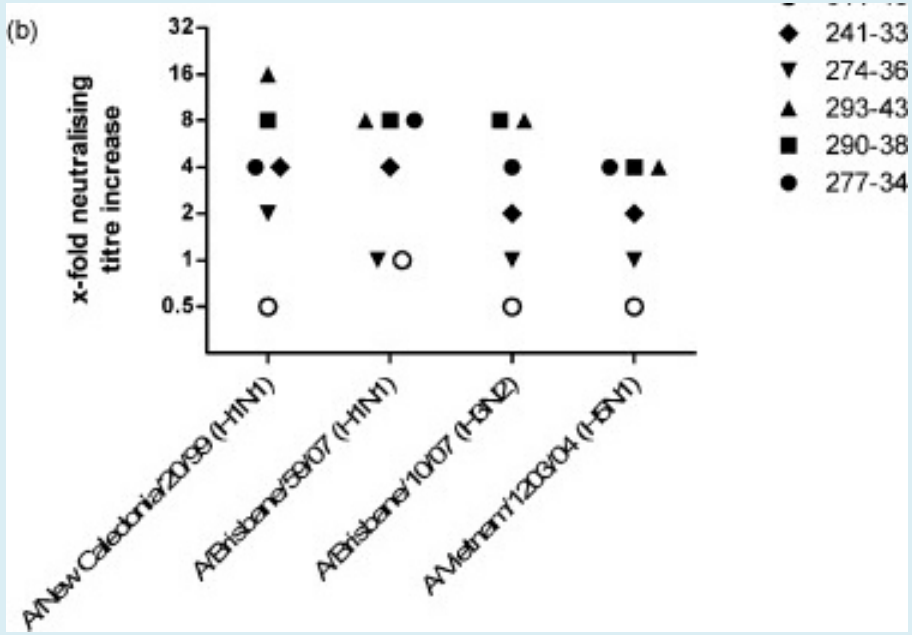


M2 deletion;
Phase II

NS1 deletion





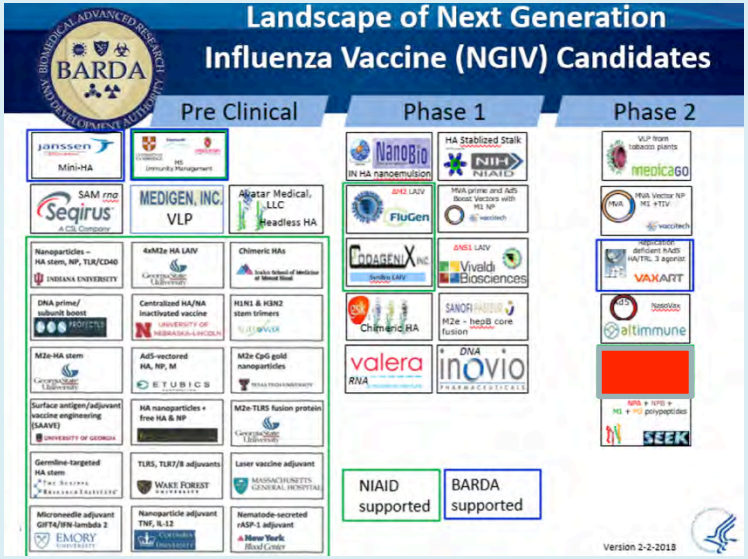


Morokutti et al 2014

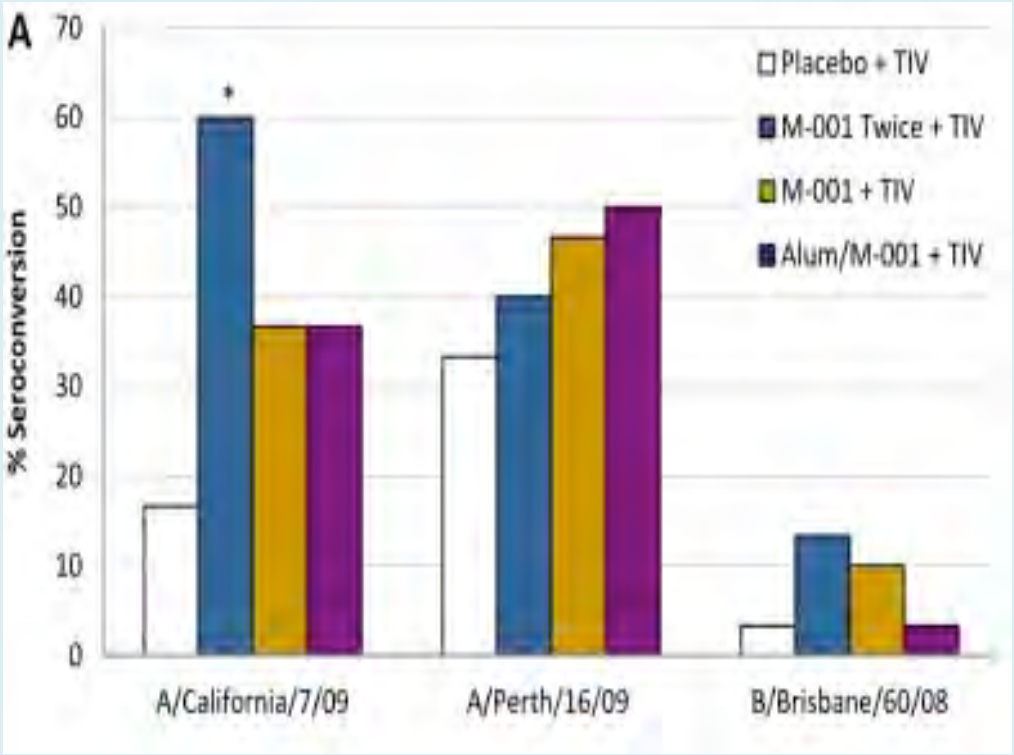
Epitope-based vaccine

- Target more conserved regions of viral genome, typically M and NP for T cells and M2e
- “add-on” to HA-based approaches- stand alone potency uncertain
- T cell epitope containing peptides poorly immunogenic on their own
- Use variety of presentation approaches

Synthetic polypeptide



Peptide	Amino Acids Sequence
Hemagglutinin (HA) epitope 1	PKYVKQNTLKLAT
Hemagglutinin (HA) epitope 2	SKAYSNCYPYDVPDYASL
Hemagglutinin (HA) epitope 3	WLTGKNGLYP
Hemagglutinin (HA) epitope 4	WTGVTQN
Hemagglutinin (HA) epitope 5	PAKLLKERGFFGAIAGFLE
Nucleoprotein (NP) epitope 6	FWRGENGRKTRSAYERMCNILKGK
Nucleoprotein (NP) epitope 7	SAAFEDLRVLSFIRGY
Nucleoprotein (NP) epitope 8	ELRSRYWAIRTRSG
Matrix (M) epitope 9	SLLTEVETYVP

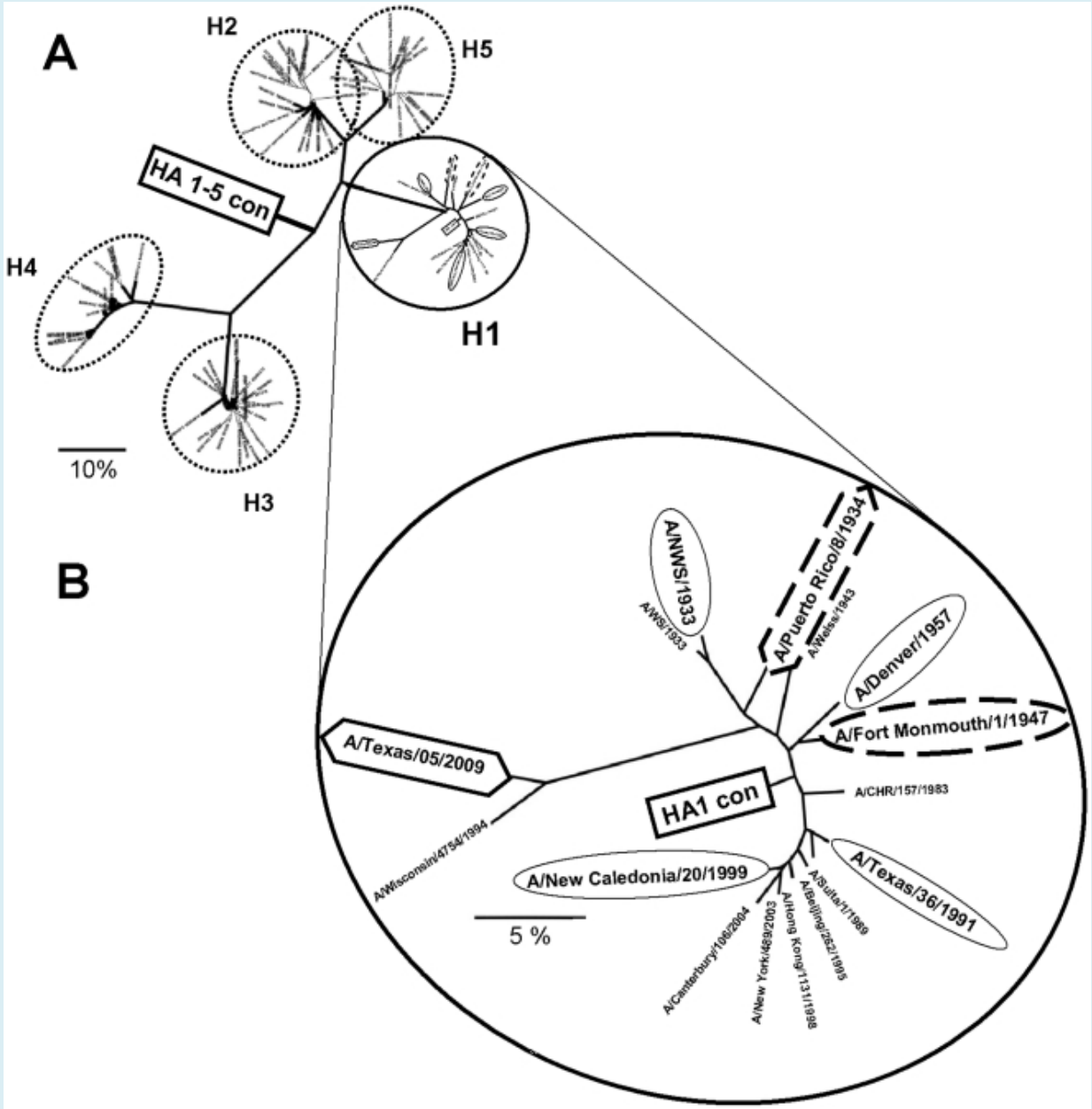


Atsmon J. Clin. Immunol 2012

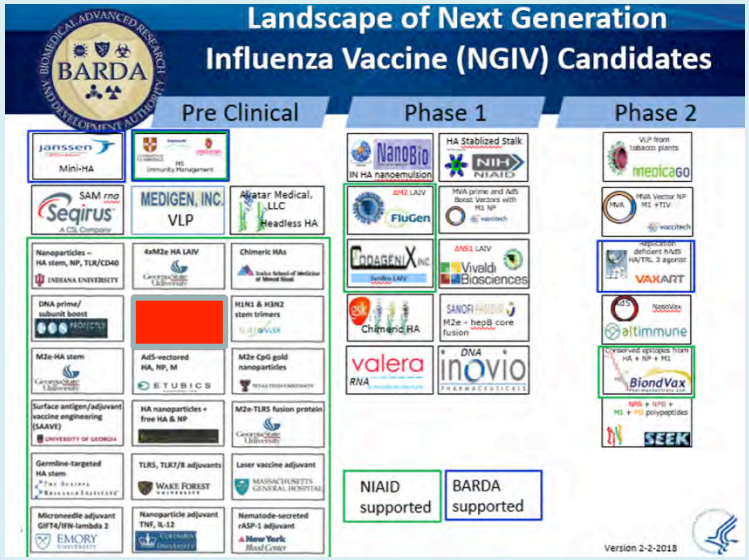
Refocused HA-based vaccines

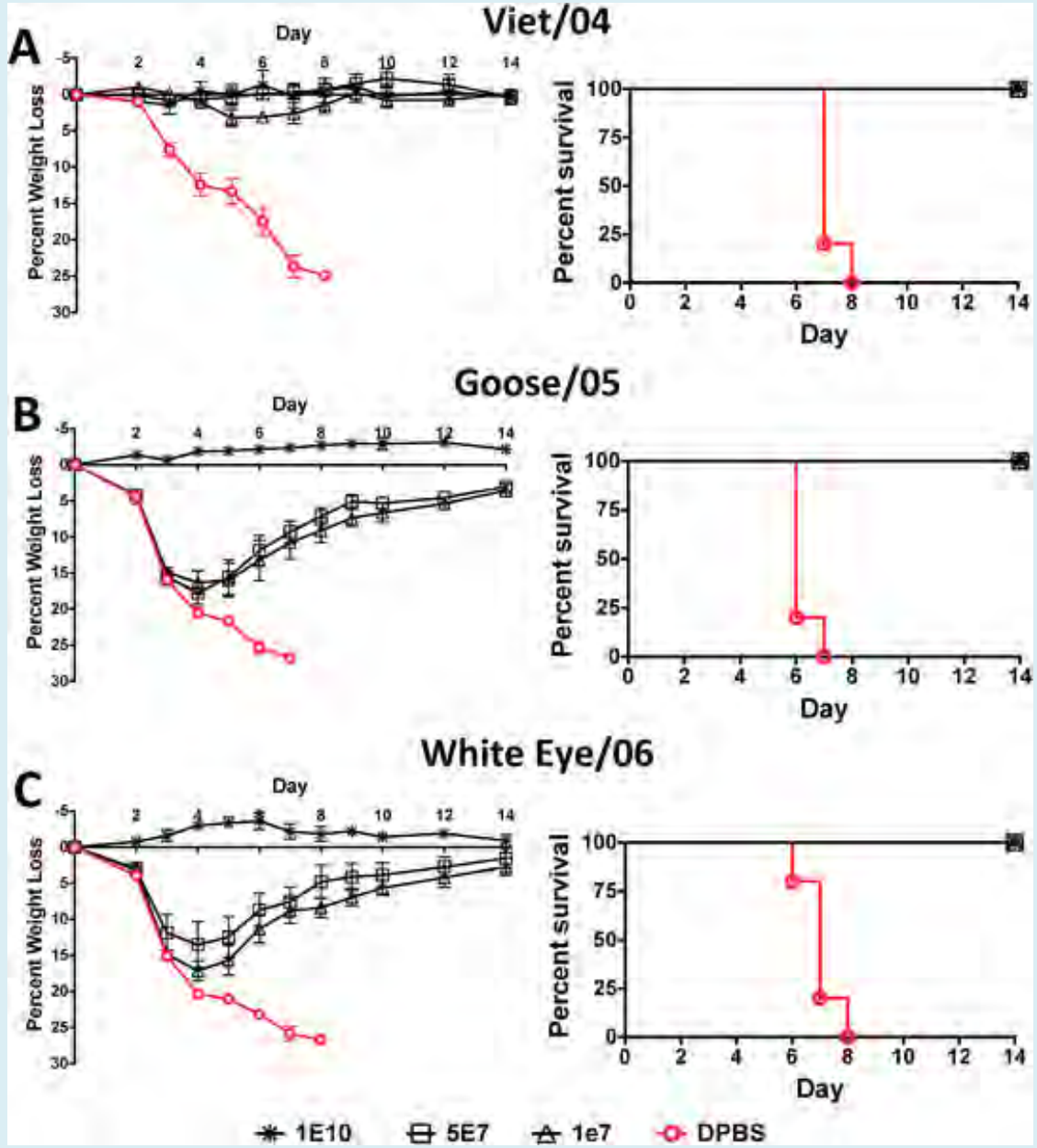
- Target more conserved regions of HA
- Some induce improved neutralising response, some function via fusion inhibition, ADCC mechanisms
- Potency in humans uncertain
- Consensus/ancestral approaches
- HA stalk

Consensus/ancestral HA approaches



Weaver PLoS one 2011





Webby, Weaver PLoS one 2015

HA stalk approaches

nature structural & molecular biology

ARTICLES

Structural and functional bases for broad-spectrum neutralization of avian and human influenza A viruses

Jianhua Sui[1,4], William C Hwang[2,4], Sandra Perez[3], Ge Wei[2], Daniel Aird[1], Li-mei Chen[3], Eugenio Santelli[2], Boguslaw Stec[2], Greg Cadwell[2], Maryam Ali[1], Hongquan Wan[3], Akikazu Murakami[1], Anuradha [illegible], Thomas Han[1], Nancy J Cox[3], Laurie A Bankston[2], Ruben O Donis[3], Robert C Liddington[2] & Wayne A Marasco[1]

ARTICLE

doi:10.1038/nature11414

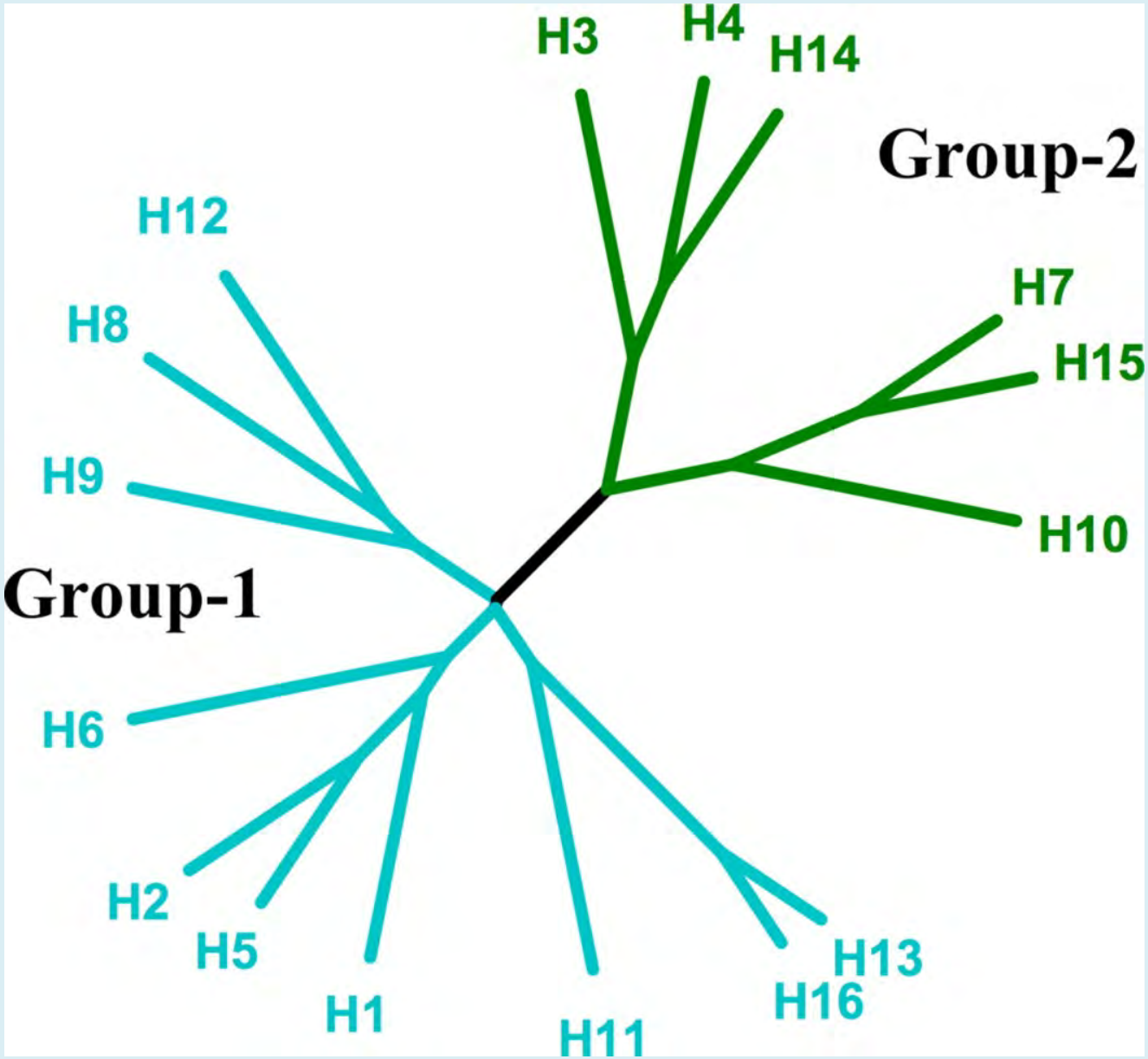
Cross-neutralization of influenza A viruses mediated by a single [illegible]

Damian C. Ekiert[1]†*, Arun K. Kashyap[2]*, John Steel[3]†, Adam [illegible], Michael A. Dillon[2]†, Ryann E. O'Neil[2]†, Aleksandr M [illegible], Peter Palese[3], Richard Webby[4], Richard A. Lerner[1] & Ian A. Wilson[1,2]

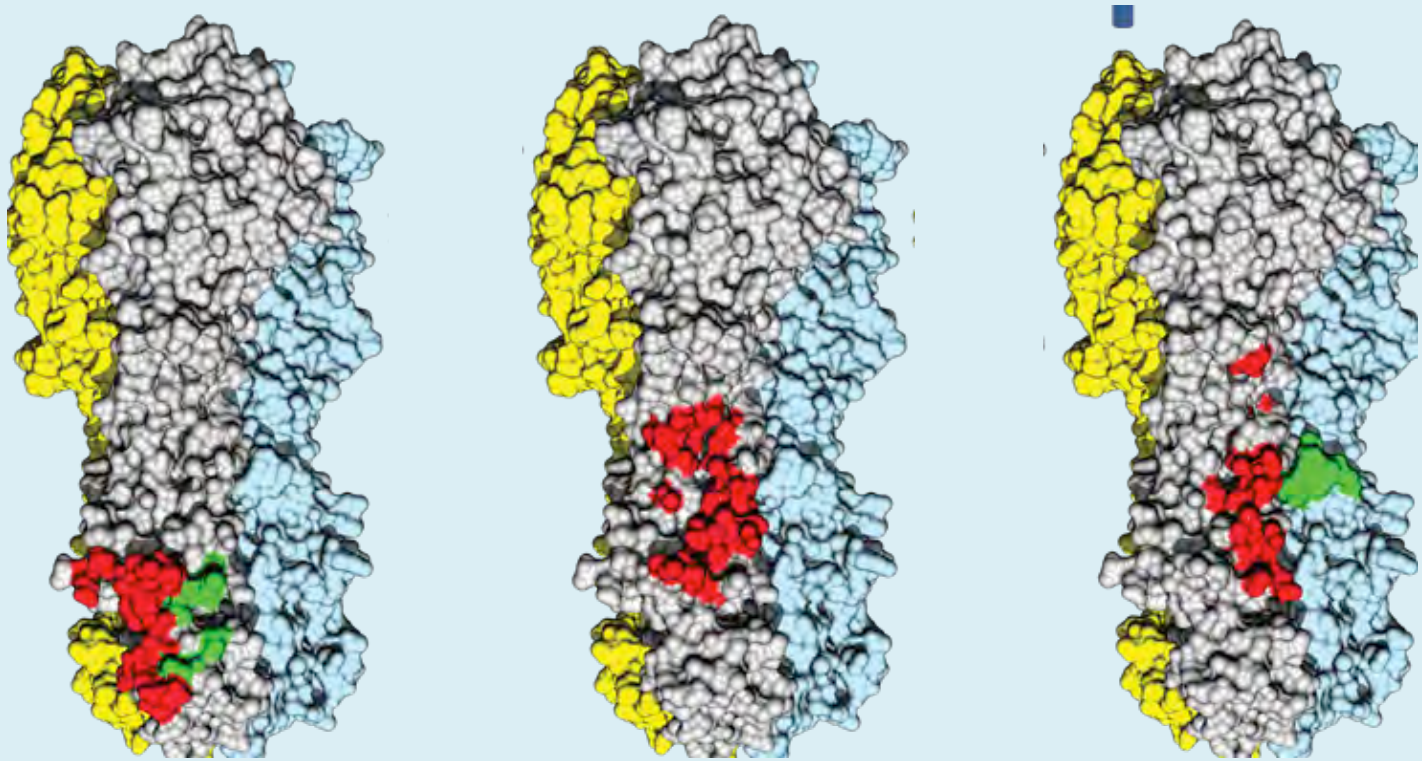
A Neutralizing Antibody Selected from Plasma Cells That Binds to Group 1 and Group 2 Influenza A Hemagglutinins

Davide Corti,[1,2*] Jarrod Voss,[3*] Steven J. Gamblin,[3*] Giosiana Codoni,[1*] Annalisa Macagno,[1] David Jarrossay,[1] Sebastien G. Vachieri,[3] Debora Pinna,[1] Andrea Minola,[1] Fabrizia Vanzetta,[2] Chiara Silacci,[1] Blanca M. Fernandez-Rodriguez,[1] Gloria Agatic,[2] Siro Bianchi,[2] Isabella Giacchetto-Sasselli,[1] Lesley Calder,[3] Federica Sallusto,[1] Patrick Collins,[3] Lesley F. Haire,[3] Nigel Temperton,[4] Johannes P. M. Langedijk,[5]† John J. Skehel,[3]‡ Antonio Lanzavecchia[1,6]‡

Broadly reactive

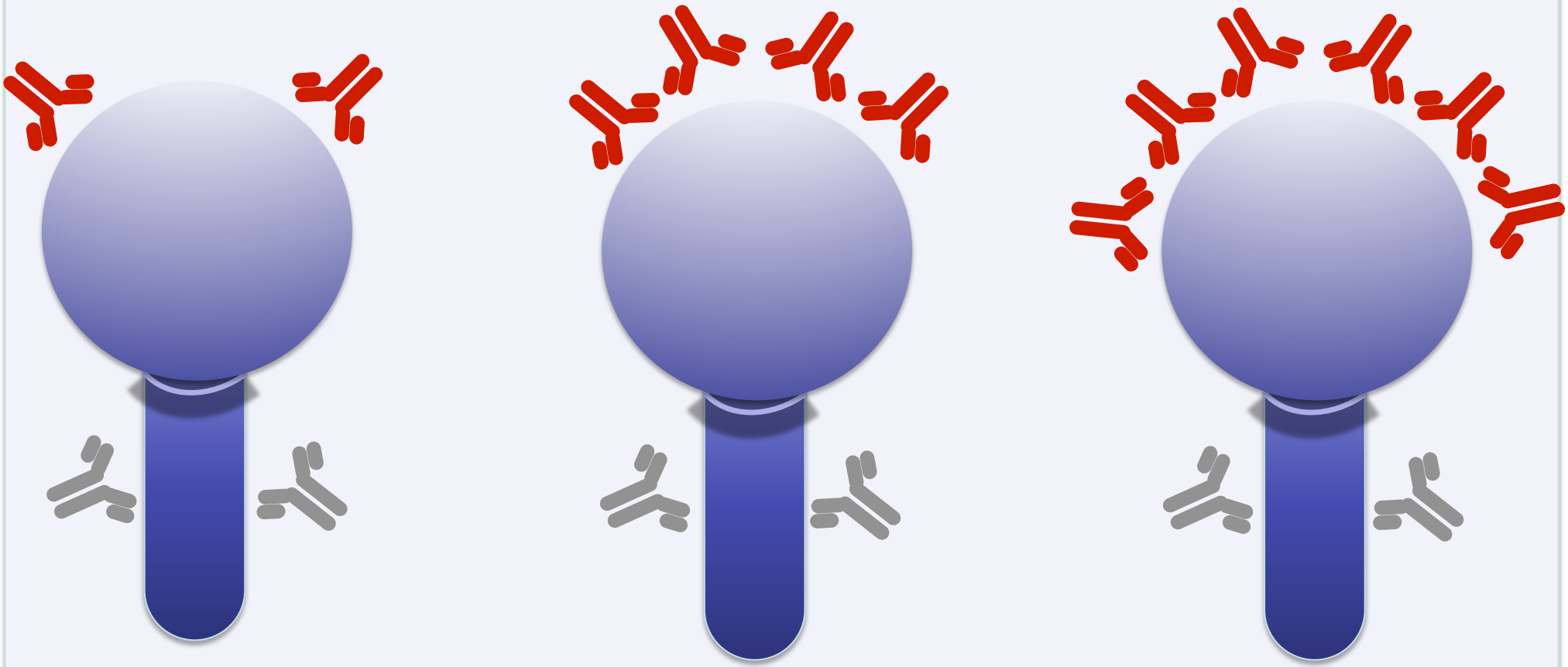


Monoclonals in clinical development



HA head is immunodominant

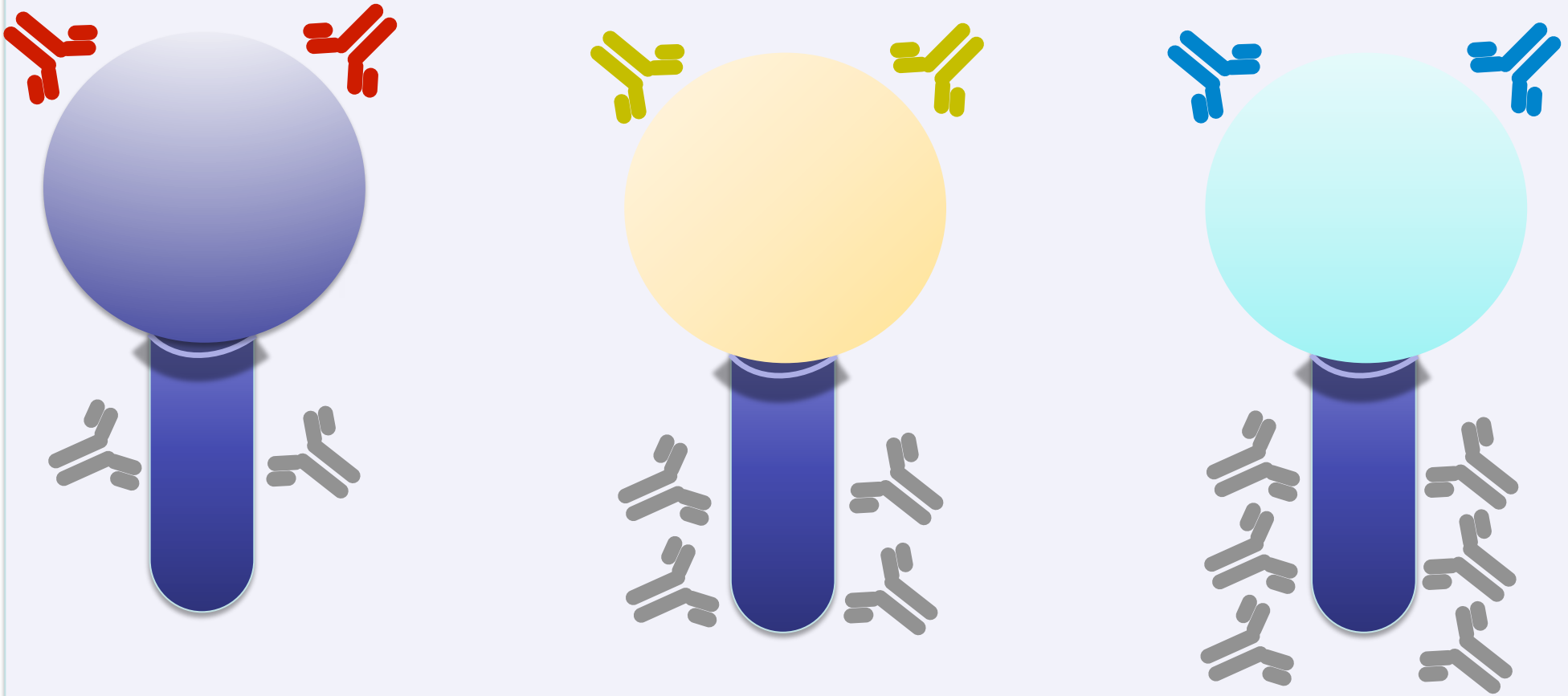
- These antibodies produced during natural infection, but not to protective levels
- Challenge is to devise immunization strategy

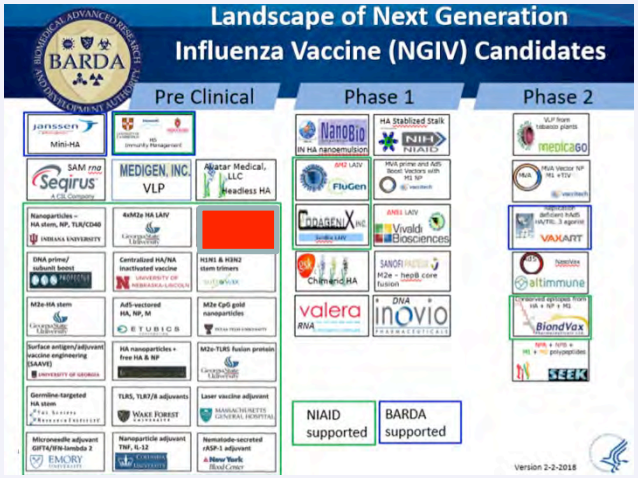


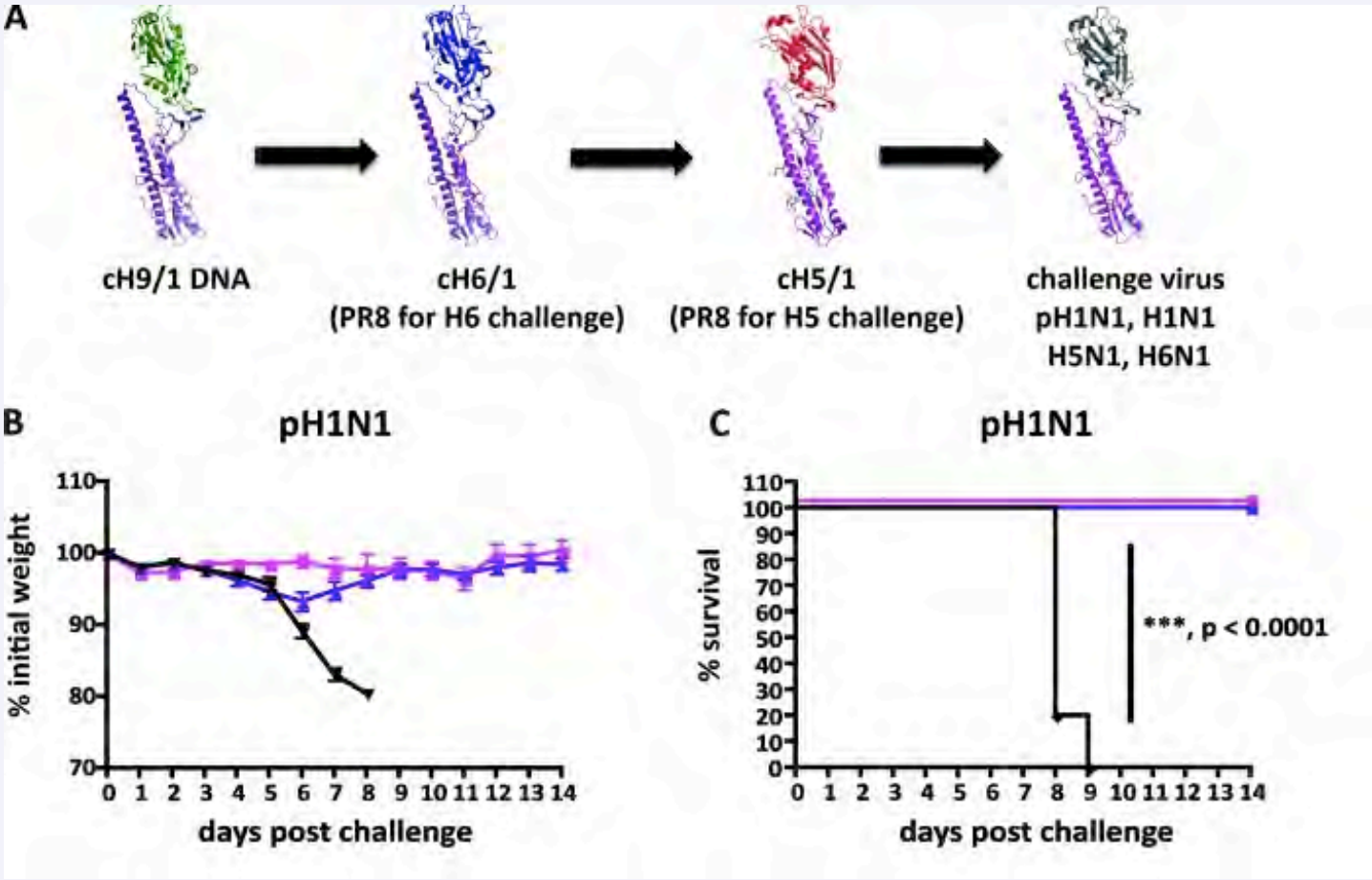
Stalk only approach

Shielding approach

Chimeric head approach







Krammer at al J. Virol 2013

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Summary

- Renewed interest in overhauling current influenza vaccine

- A number of approaches being trialed.

- Potency in humans remains a big question mark, esp for seasonal purposes- animal models are primarily powered for severe disease.

- We need to be realistic!