Induction of bnAbs: how and when will we get there?

Cent Gardes Meeting

October 1st, 2019

NIH National Institute of Allergy and Infectious Diseases

CHAVD Duke Consortium for HIV/AIDS Vaccine Discovery

Topics for discussion

- **Biology of broadly neutralizing antibody generation**
- **Promising Duke CHAVD immunogens moving into clinical testing**
- **Need for coordination/collaboration**

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Hypothesis: Broadly neutralizing antibody development is hindered by host immune tolerance mechanisms (Science 308: 1906, 2005; PNAS 107: 181, 2010; J. Exp. Med. 210: 241, 2013)

- **Long antibody combining sites -Controlled by deletional tolerance mechanisms**
- **Extremely Somatically Mutated- either a rare event, or escape from tolerance controls**
- **Self-reactive- Controlled by tolerance mechanisms**
- **Epitopes of Env recognized as autoantigens (high mannose glycans, lipids, specific epitopes e.g. ELDKWA of gp41)**
- **BnAb knock-in mice show various mechanisms of tolerance control, i.e. deletion, receptor editing or anergy**

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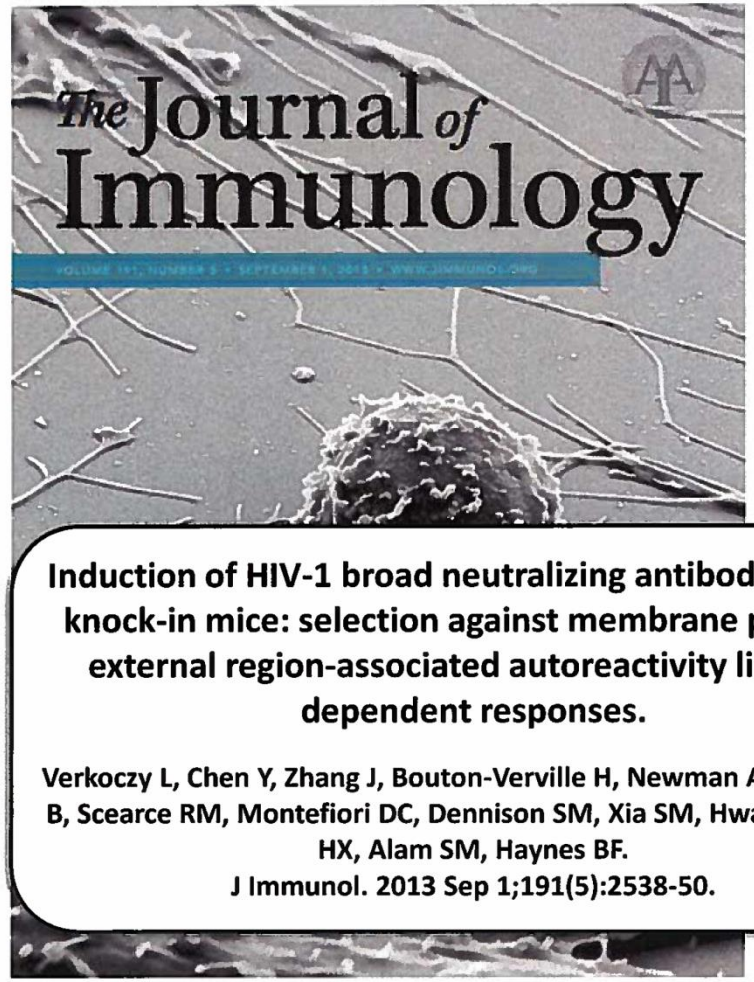
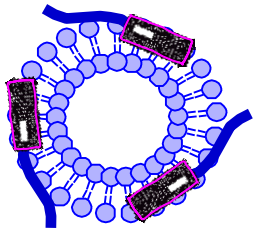
Strong adjuvants can overcome bnAb B cell anergy



Induction of HIV-1 broad neutralizing antibodies in 2F5 knock-in mice: selection against membrane proximal external region-associated autoreactivity limits T-dependent responses.

Verkoczy L, Chen Y, Zhang J, Bouton-Verville H, Newman A, Lockwood B, Scearce RM, Montefiori DC, Dennison SM, Xia SM, Hwang KK, Liao HX, Alam SM, Haynes BF.
J Immunol. 2013 Sep 1;191(5):2538-50.

- In 2F5 or 4E10 bnAb VH + VL knock-in mice, ~95% of B cells are deleted in bone marrow.
- ~5% of B cells reach the periphery but are anergic.



- Immunization with MPER peptide-liposome formulated with TLR4-agonist MPLA, reversed anergy and induced ~300 ug/ml plasma 2F5 bnAb.

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3M052—A TLR-7,8 agonist in Alum

- **Julie McElrath adjuvant trial with BG505 trimer includes 3M052-Alum**

- **3M052-Alum superior to other adjuvants CH505 TF trimer in macaques for initiating tier 2 virus neutralizing CD4 bs and V1V2 B cell lineages**

Kevin Saunders

NIH National Institute of Allergy and Infectious Diseases

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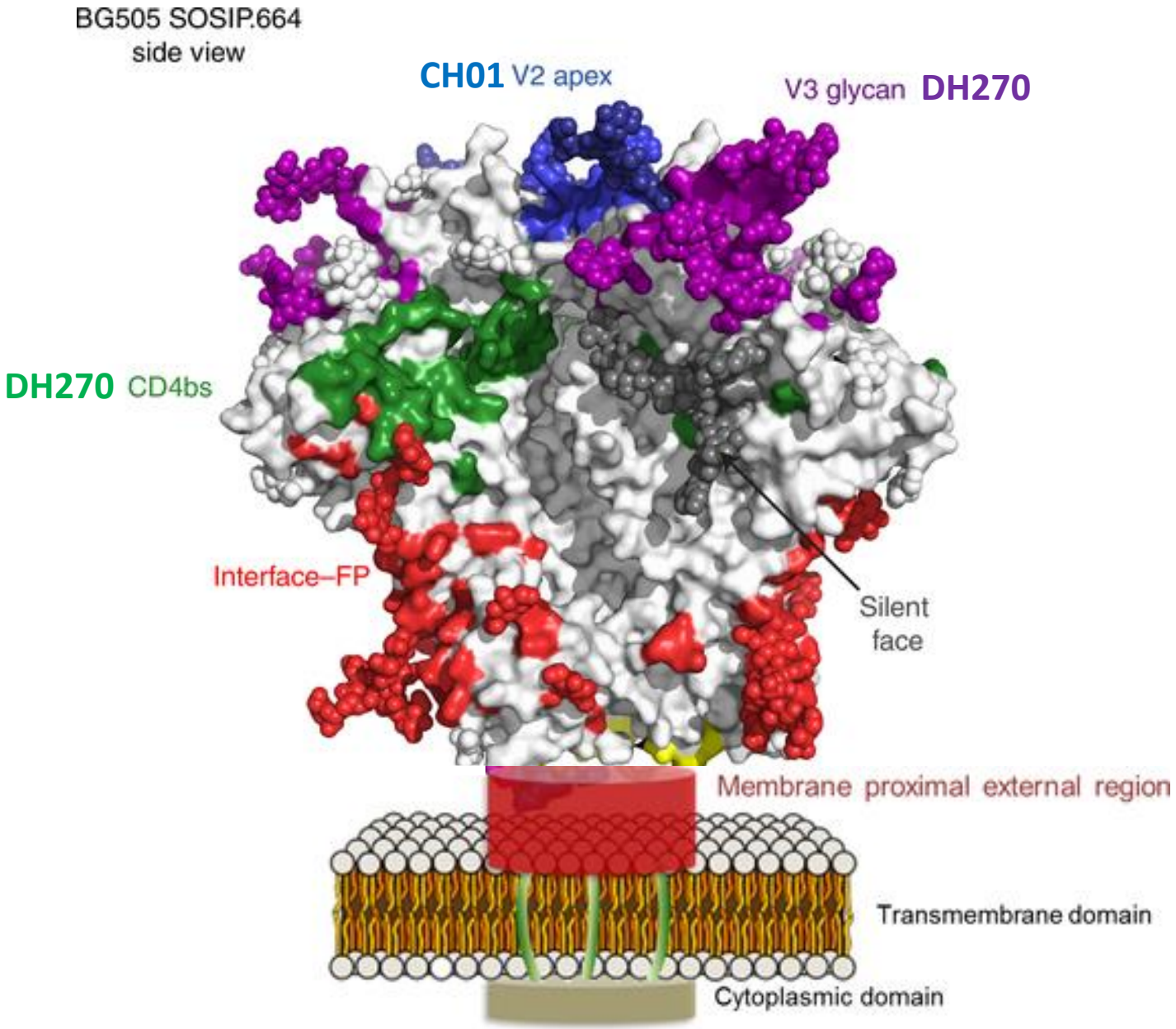

- **Structure express bnAb epitopes**
- **Not or minimize non-neutralizing epitopes**
- **Optimal configuration for localizing (and staying) in GCs.**

Sok and Burton, Nat. Immunol. 19: 1179, 2018

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Somatic Hypermutation-improbable mutations

- "Hot spot" mutations occur frequently due to AID activity and are common to many different antibody types (i.e. probable mutations).

- "Cold spot" mutations occur less frequently and are rare (i.e. improbable mutations).

- "Cold spot" mutations require the presence of an immunogen that can bind the B cell receptor of the rare B cell with an improbable mutation, to select that B cell for survival.

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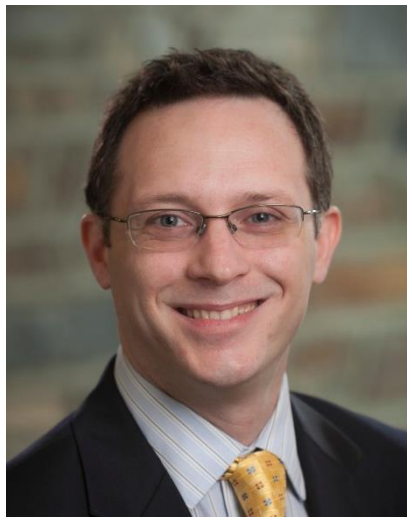
Hypothesis

Improbable mutations can act as roadblocks in bnAb development pathways.

Key Enabling Technology For Design of Sequential Envs



Mattia Bonsignori

Staged Induction of HIV-1 Glycan-dependent Broadly Neutralizing Antibodies

Bonsignori M, Kreider EF, Fera D, Meyerhoff RR, Bradley T, Wiehe K, Alam SM, Aussedat B, Walkowicz WE, Hwang KK, Saunders KO, Zhang R, Gladden MA, Monroe A, Kumar A, Xia SM, Cooper M, Louder MK, McKee K, Bailer RT, Pier BW, Jette CA, Kelsoe G, Williams WB, Morris L, Kappes J, Wagh K, Kamanga G, Cohen MS, Hraber PT, Montefiori DC, Trama A, Liao HX, Kepler TB, Moody MA, Gao F, Danishefsky SJ, Mascola JR, Shaw GM, Hahn BH, Harrison SC, Korber BT, Haynes BF

Science Translational Medicine 2017 March 15; 9, eaai7514 DOI: DOI: **10.1126**/scitranslmed.aai7514

Highlights

- Identified a single early mutation **(VH G57R)** that initiated neutralization breadth in a bnAb lineage.
- Mutations that are required to initiate neutralization **but are improbable;** pose a roadblock to lineage maturation toward breadth.
- Identified immunogens predicted to accelerate the induction of bnAbs through vaccination.

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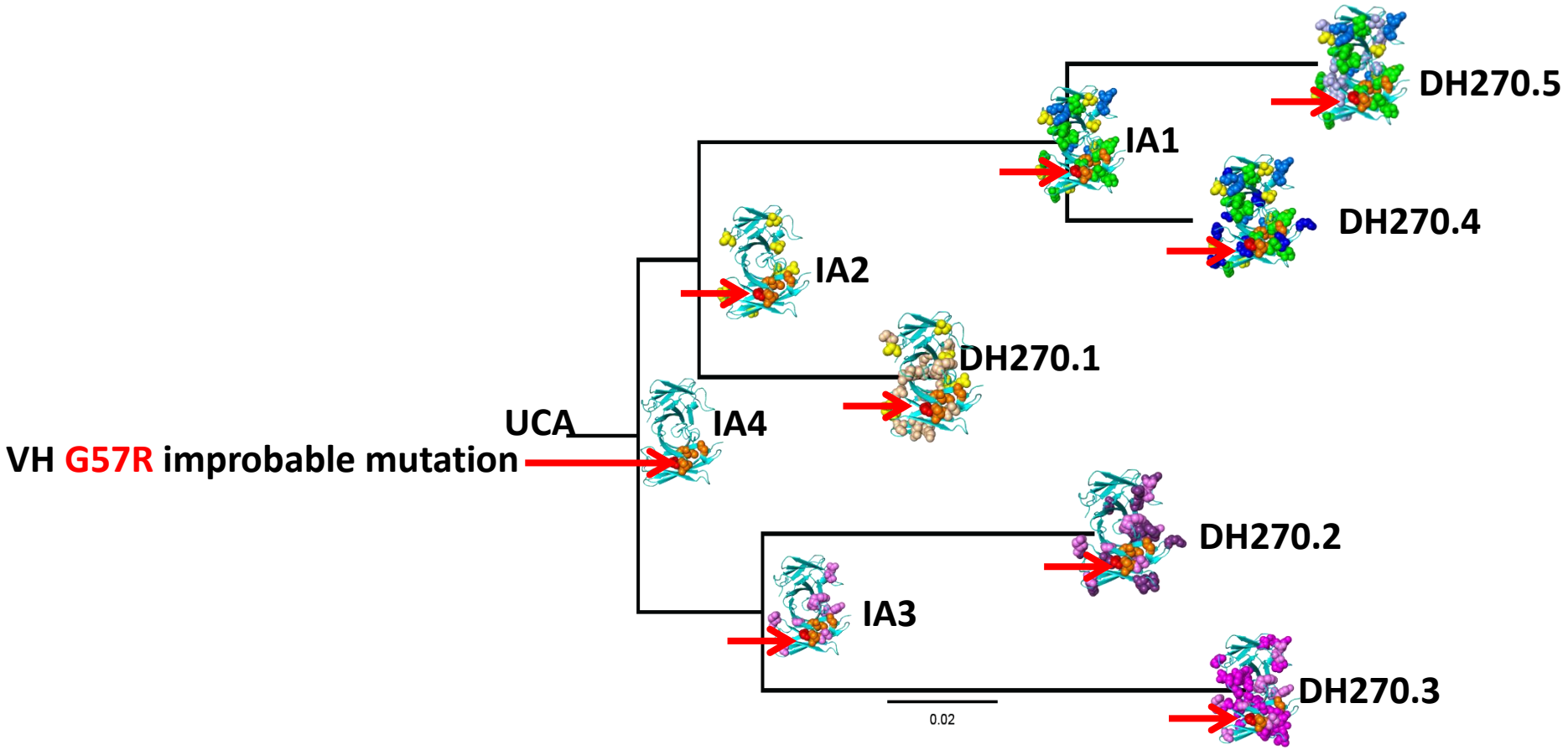
An improbable cold spot mutation, G57R, in DH270 was necessary for bnAb development



Bonsignori, M et al. Science Translational Medicine, 9: eaai7514, 2017

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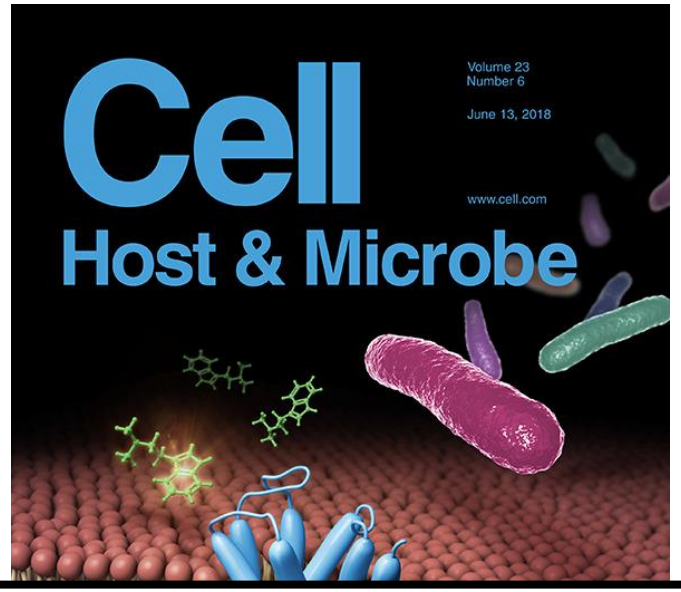
Key Enabling Technology For Design of Sequential Envs

Kevin Wiehe



Functional Relevance of Improbable Antibody Mutations For HIV Broadly Neutralizing Antibody Development. Kevin Wiehe, Todd Bradley, R. Ryan Meyerhoff, Connor Hart, Wilton B. Williams, David Easterhoff, William J. Faison, Thomas B. Kepler, Kevin O. Saunders, S. Munir Alam, Mattia Bonsignori, Barton F. Haynes

- Described a computational program (ARMADiLLO®) that defines low-probability antibody mutations.
- HIV-1 broadly neutralizing antibodies are enriched with low-probability mutations.
- Improbable mutations can be functionally critical for bnAb neutralization breadth.
- Critical improbable mutations are high-value targets for selection with vaccines.

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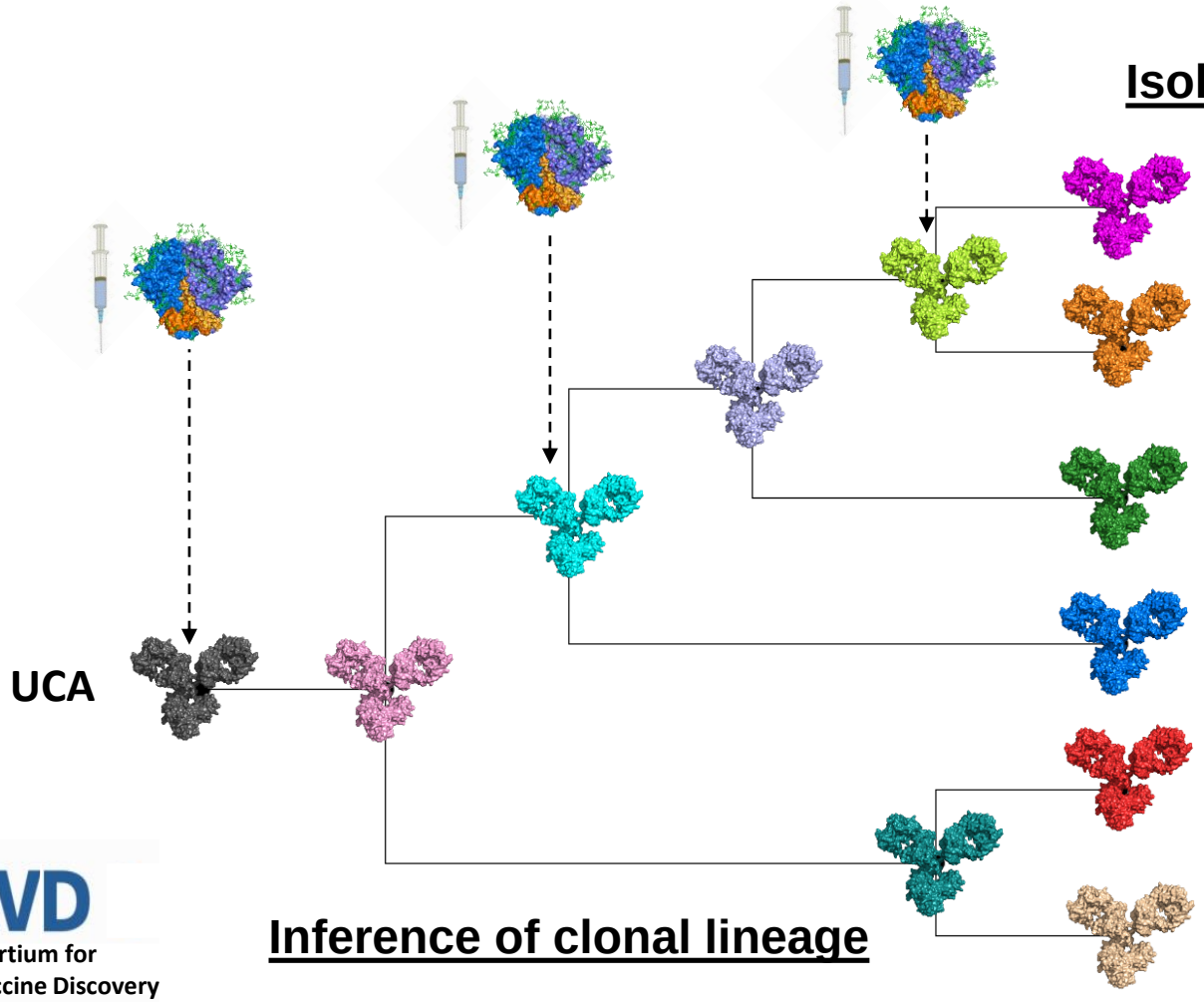
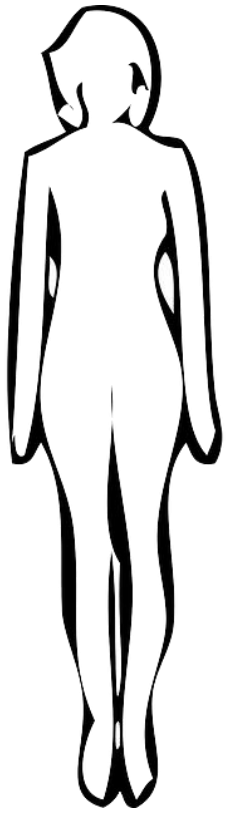
From BnAb-Virus Co-Evolution Studies, We Know For BnAb Induction, We Will Need To Use Sequential Immunizations

Sequential Env immunization to guide maturation and to select for functional improbable mutations



Inference of clonal lineage

Isolation of bnAb clone



HIV infected individual with bnAb

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Haynes et al. Nature Biotech. 30: 423, 2012; Liao HX et al. Nature 496: 469, 2013; Doria-Rose, N et al. Nature 509: 55, 2014; MacLeod et al. Immunity 44: 1215, 2016; Simonich et al. Cell 166:77, 2016; Bhiman JN et al. Nat. Med. 509: 55, 2014

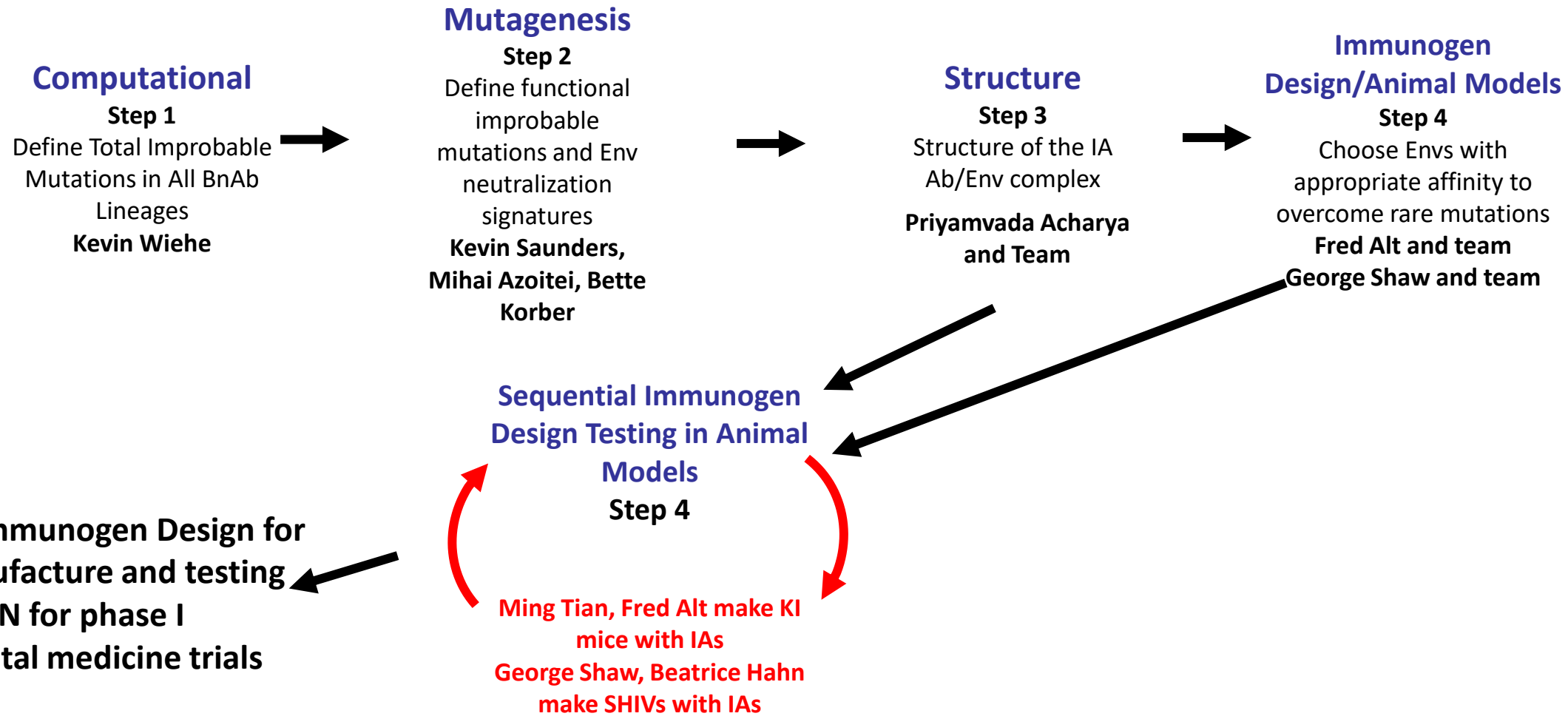
Targets for Immunogen Design

- Goal is to have immunogens that can expand bnAb B cell precursors, and select by boosting bnAb intermediates and mature bnAb B cells.
- Goal is to induce a polyclonal B cell response to at least 2 or more bnAb Env epitopes.
- Need to learn to accurately design boosting immunogens.

Immunogen Design: Time for a Manhattan Project

- **Kalma Project- Iterative immunogen design based on selecting improbable mutations, structural designs and signature analysis (mosaics) for loop and glycan accommodation.**
- **Trimers and nanoparticles; proteins and mRNAs**
- **Adjuvants to overcome anergy**

The Duke CHAVI-ID Immunogen Design *Project Kalma*



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Promising Immunogens Targeting BnAb UCAs

- **CH848 10.17 V1-deleted (DT) stabilized SOSIP trimer nanoparticle- targets V3-glycan UCA**
- **CH505 M5 G458Y GNT1- stabilized SOSIP trimer nanoparticle- targets CD4 bs ANC131/CH235-class UCAs**
- **CH505 chimeric stabilized SOSIP trimers- target CD4 bs and V1V2 UCAs**

CH848 Chimeric Stabilized SOSIP V1 glycan-deleted (DT) Trimer Nanoparticle

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CH505 M5 G458Y GNT1- Chimeric Stabilized SOSIP Trimer Nanoparticle

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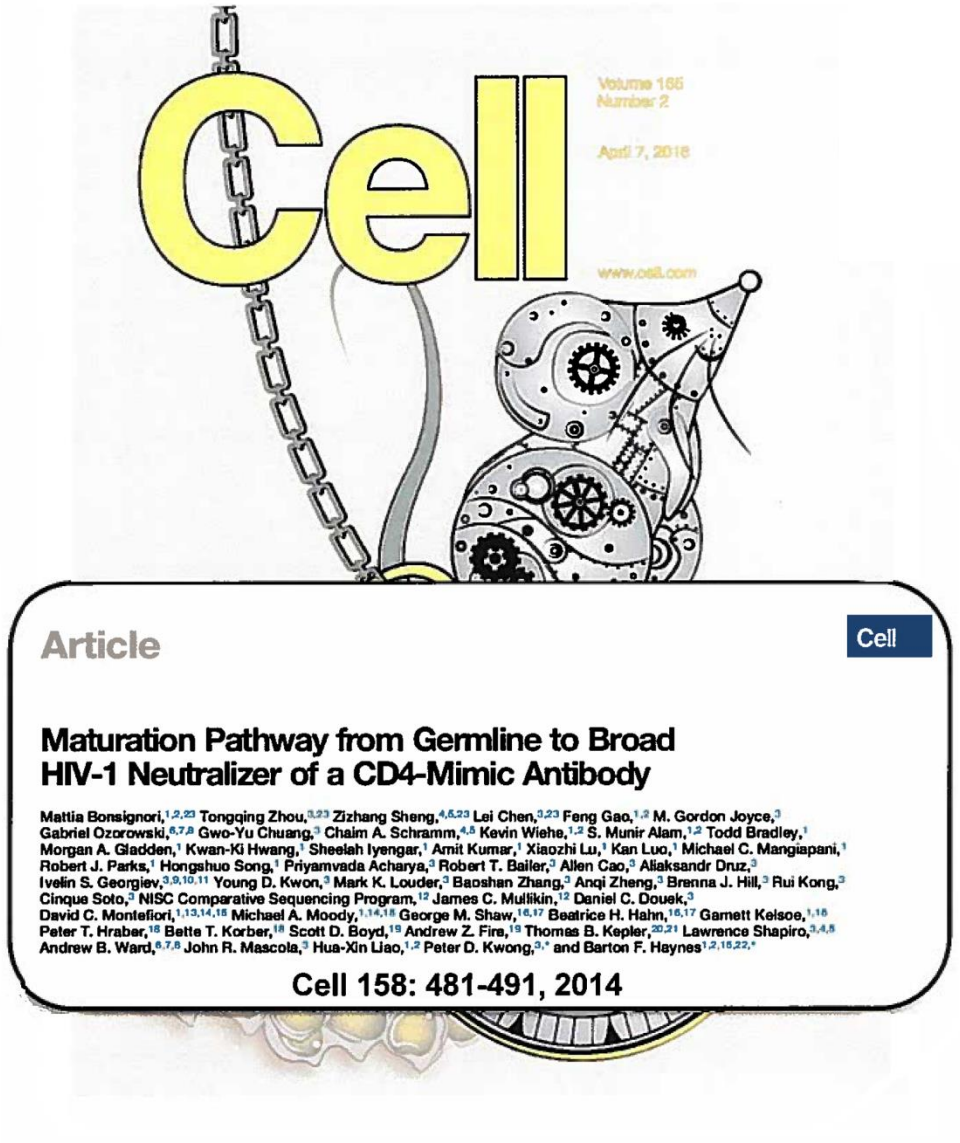
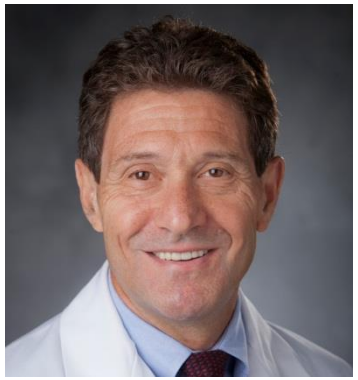
Ontogeny of the VH1-46 CH235/ANC131-class CD4-mimic CD4bs bnAb B cell lineage

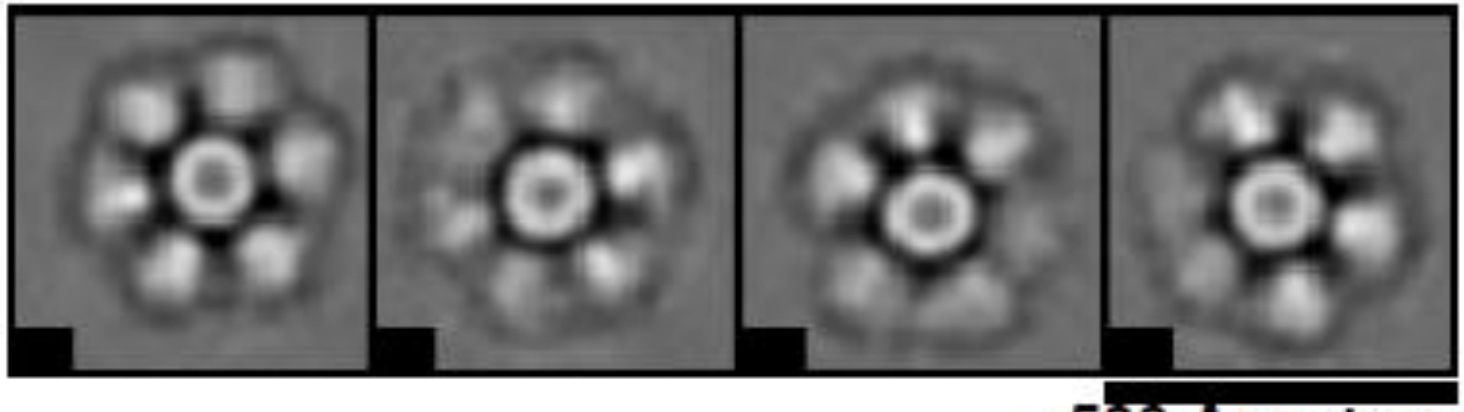


- **Stereotyped CD4 mimic-class of CD4 binding site antibodies (ANC131/CH235-class)**
- **Uses only VH1-46**
- **Normal light chain CDR3**
- **No indels**
- **Breadth and potency similar to VRC01**

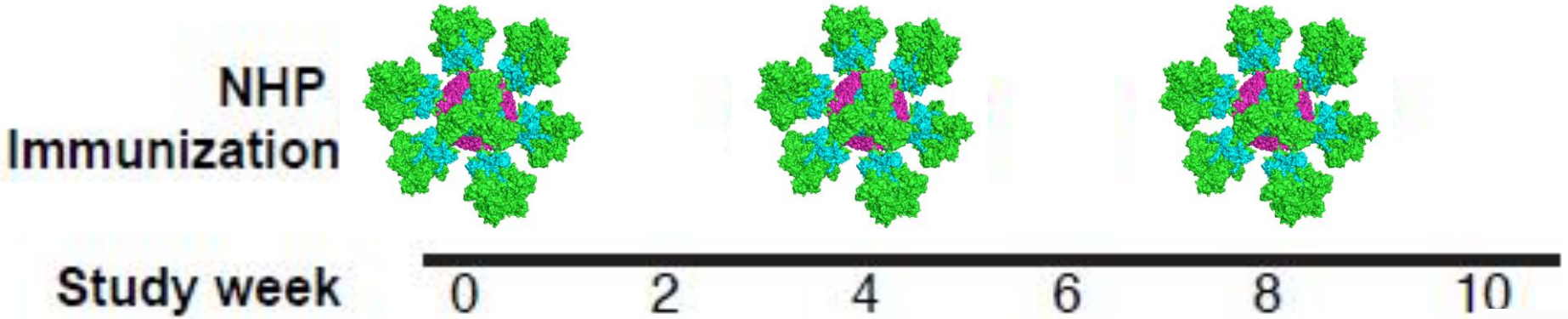
Electron microscopy of M5.G458Y SOSIP ferritin nanoparticle



David Montefiori



Sortase A conjugated M5.G458Y SOSIP ferritin nanoparticle



PLoS Pathogens Sept 17, 2019, 15:e1008026, 2019; Kevin Saunders

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CH505 transmitted/founder (TF) chimeric stabilized SOSIP Trimer

Where is the Duke CHAVD With Immunogen Design? Germline Targeting Envs

CD4 binding site:

- **CH103-CH505 TF SOSIP trimer- Q1-2020**
- **CH235/ANC131 class-CH505 M5 G458Y trimer- Q2-2021**

V3-glycan:

- **DH270 (VH1-2*02, most common VH)- CH848 10.17 DT trimer- Q4-2020**

V1V2-glycan:

- **CH01 (VH3-20) -CH505 TF SOSIP trimer—induced V2-glycan bnAbs in macaques- Q1-2020**

MPER:

- **proximal MPER peptide liposome- Q3-2019**
- **distal MPER = GT5.1 Schief/Alam- Pre-production**

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Use of combined resources to improve the throughput and coordinate immunogen development

- **Goal is to end up after 5-7 years with a rationally designed set of sequential immunogens, rather than a hodgepodge of unrelated Envs.**

- **To do this we need to look ahead now and plan for sequential immunogen regimens for specific “sterotyped” bnAb lineages.**

- **If Duke, TSRI and the VRC coordinate, we could produce GMP ~30 clinical trials materials over 7 years.**

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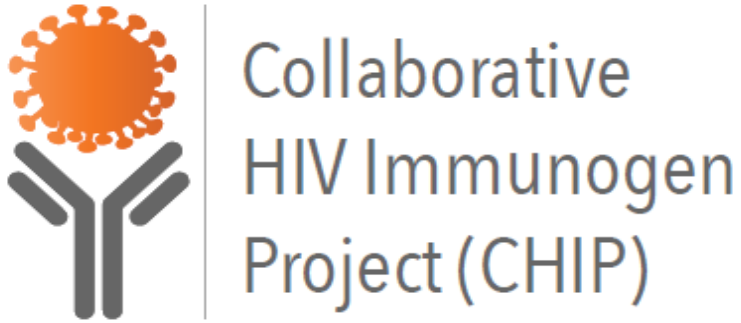
Collaborative HIV Immunogen Project (CHIP)

- **Duke CHAVD**
- **Scripps CHAVD**
- **NIAID Vaccine Research Center**
- **HVTN**

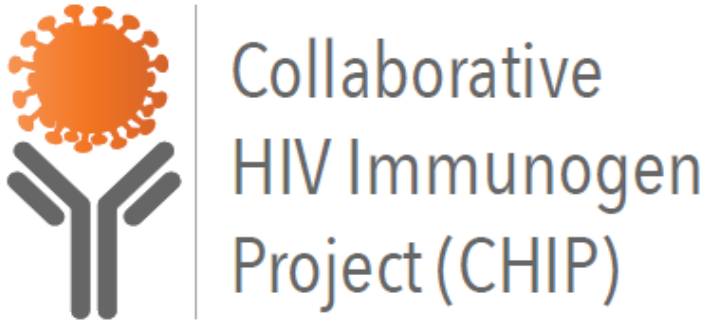


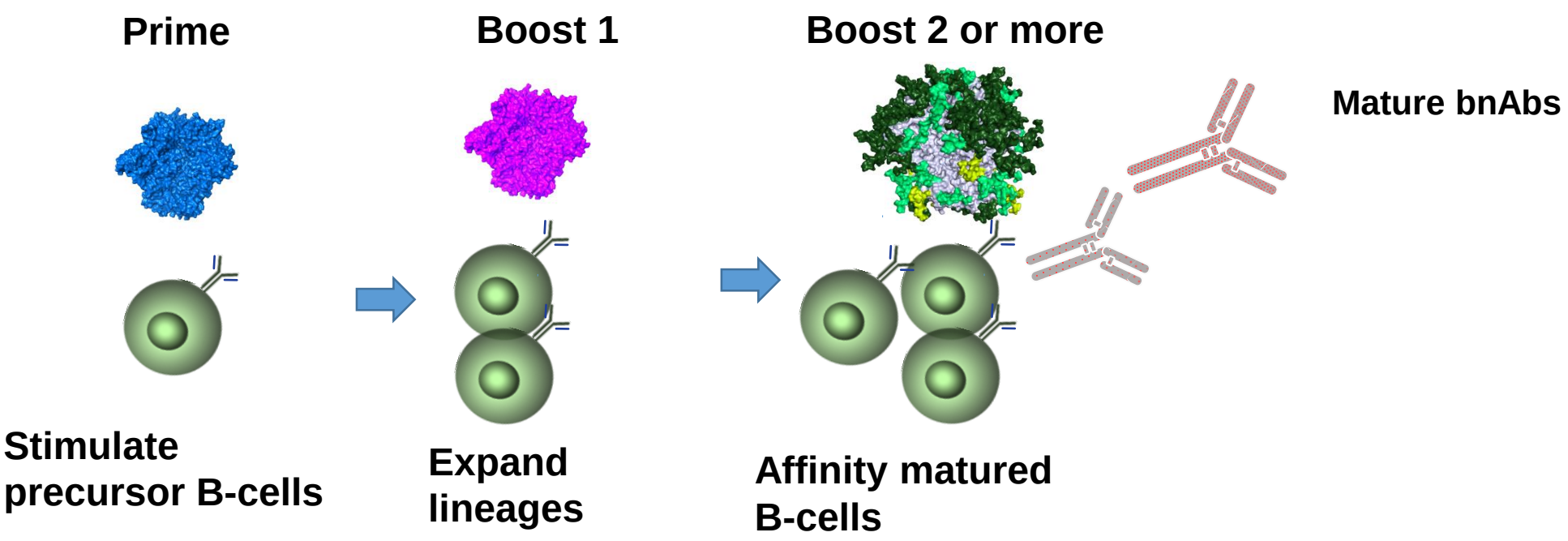
Goal is to coordinate the development of NIAID-funded germline targeting and sequential Envs for GMP manufacture and clinical testing.

Speed HIV vaccine development!

Collaborative HIV Immunogen Project (CHIP)

- **Inclusive**
- **Collaborate when needed, productive**
- **Work out how to communicate, meet**
- **First meeting Duke CHAVD meeting in October to figure out how two CHAVDs, VRC, HVTN can work together and then next, work with others in the field.**





CD4 binding site (VRC01-class)

CD4 binding site (ANC131/ CH235 class)

V3-glycan (PGT121, DH270 types)

V1V2-glycan (PG9, CH01, BG18 types)

Gp41 MPER

Fusion domain (VRC34-type)

Haynes ,Burton, Mascola, submitted, 2019

Route to a practical vaccine

- Identify improbable mutations for all known bnAb B cell lineages (order of magnitude 100s).
- Of those define functional improbable mutations and initially target those (order of magnitude 10s to 100s).
- Design immunogens to overcome improbable mutations.
- Goal: induce a polyclonal bnAb response to multiple bnAb epitopes. The only way to do this is rapid iterative Phase I clinical trials and coordination/collaboration.

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Summary

- Due to non-uniform AID targeting, antibody mutations have varying probabilities prior to antigenic selection.
- Improbable mutations that are critical for neutralization can act as bottlenecks in bnAb development.
- By targeting improbable mutations for selection with a specific immunogen, these developmental bottlenecks can be overcome.
- We have proof-of-concept that this strategy can result in immunogens that select for improbable bnAb mutations, and overcome roadblocks in bnAb development.

Summary

- **Optimal success in iteration of Phase 1 clinical trials will come from coordination of efforts of the field.**

- **If we coordinate our work and each team works to make one or more complete and successful set of sequential immunogens that can be combined at the end of the 5-7 years, then the chances for success will be enhanced.**

- **It is time to get the job done!**

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Collaborators

Duke
Kevin Saunders
Kevin Wiehe
Mattia Bonsignori
Priyamvada Acharya
Rory Henderson
Munir Alam
Mihai Azoitei
Wilton Williams
Garnett Kelsoe

Bioqual
Mark Lewis

HVTN
Larry Corey
Julie McElrath
Georgia Tomaras
Jim Kublin and Teams

Boston Childrens's
Fred Alt
Ming Tian

Penn
Beatrice Hahn
George Shaw
Drew Weissman

BIDMC
Sampa Santra

Oxford
Andrew McMichael
Persephone Borrow
Simon Brackenridge
Gerry Gillespie

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Bill Schief
Dennis Burton

VRC
John Mascola
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Duke Consortium for HIV/AIDS Vaccine Discovery

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Silvija Staprans **Susan Barnett**
Pervin Ankalasaria **Nina Russell**