iavi Translating **science** into **global** health impact

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Development of an HIV vaccine to elicit broadly neutralizing antibodies

Devin Sok, PhD | VP, Discovery

HIVR4P Virtual Symposia + 11 Oct 2023

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Biomedical Advanced Research and Development Authority (BARDA) | Foundation for the National Institutes of Health | National Institute of Allergy and Infectious Diseases | amfAR, The Foundation for AIDS Research | Broadway Cares/Equity Fights AIDS | Cancer Research UK | The City of New York, Economic Development Corporation | Congressionally Directed Medical Research Program (DoD) | GSK | The Hearst Foundations | Keith Haring Foundation | Merck & Co., Inc., Kenilworth, NJ, USA (known as MSD outside the USA and Canada)

And many other generous individuals and partners around the world

As of November 2022

The GT HIV vaccine program involves many key partners

moderna

Scripps Research

THE GEORGE WASHINGTON UNIVERSITY
WASHINGTON, DC

PEPFAR

USAID
FROM THE AMERICAN PEOPLE

KAVI-ICR
KAVI-Institute of Clinical Research
UNIVERSITY OF NAIROBI

CENTER FOR FAMILY HEALTH RESEARCH

EMORY UNIVERSITY

FRED HUTCH

THE AURUM INSTITUTE

KENYA MEDICAL RESEARCH INSTITUTE
KEMRI

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Vaccine Research Center
National Institutes of Allergy and Infectious Diseases

Duke Human Vaccine Institute
Duke University School of Medicine

Ragon Institute of MGH, MIT and Harvard

Institutes of Health
NIH
National Institute of Allergy and Infectious Diseases

BILL & MELINDA GATES foundation

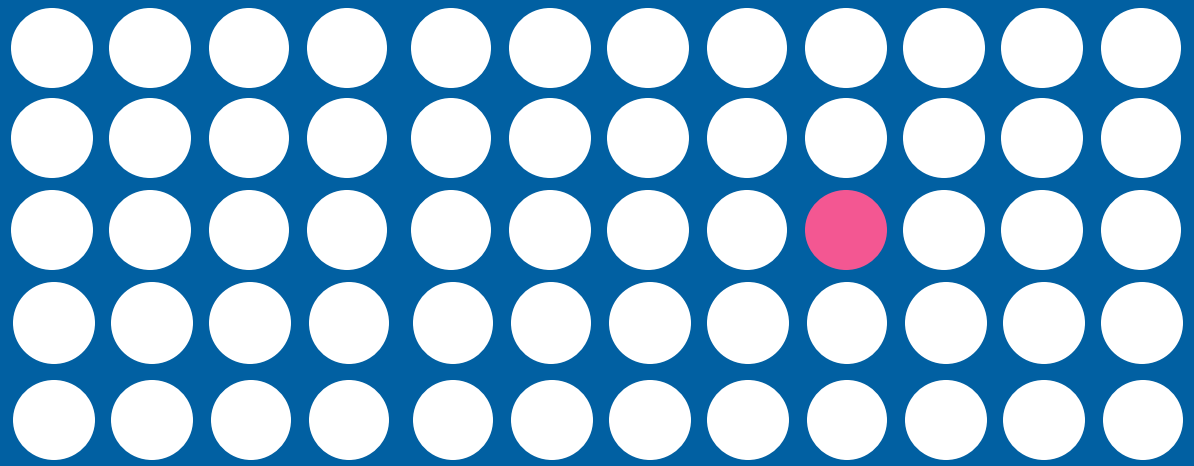
CHAVI ID

The Collaboration for AIDS Vaccine Discovery

Scripps Consortium For HIV/AIDS
CHAVD
Vaccine Development

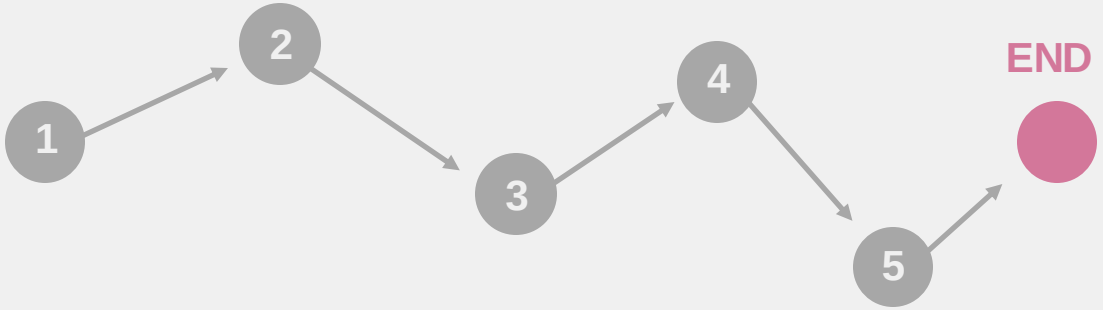
KAROLINSKA INSTITUTET ANNO 1810
Karolinska Institutet

EMPIRICAL APPROACH



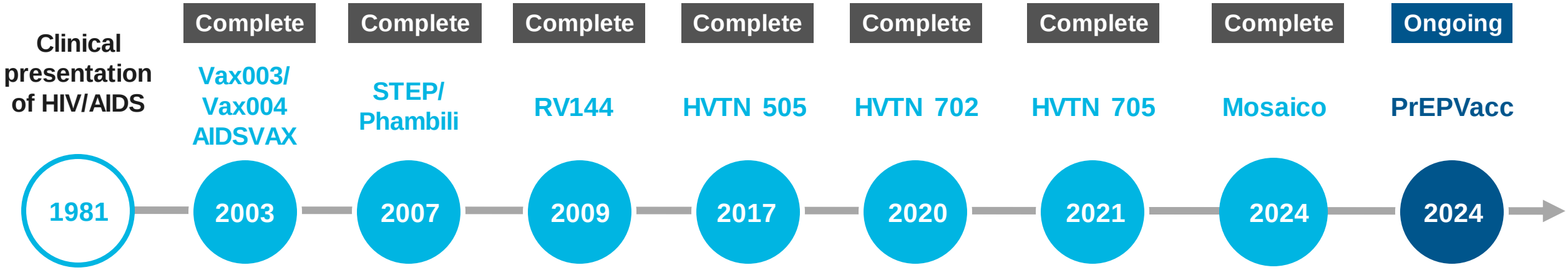
Test different vaccine candidates; if one demonstrates **protection efficacy**, then identify correlates of protection.

RATIONAL DESIGN APPROACH



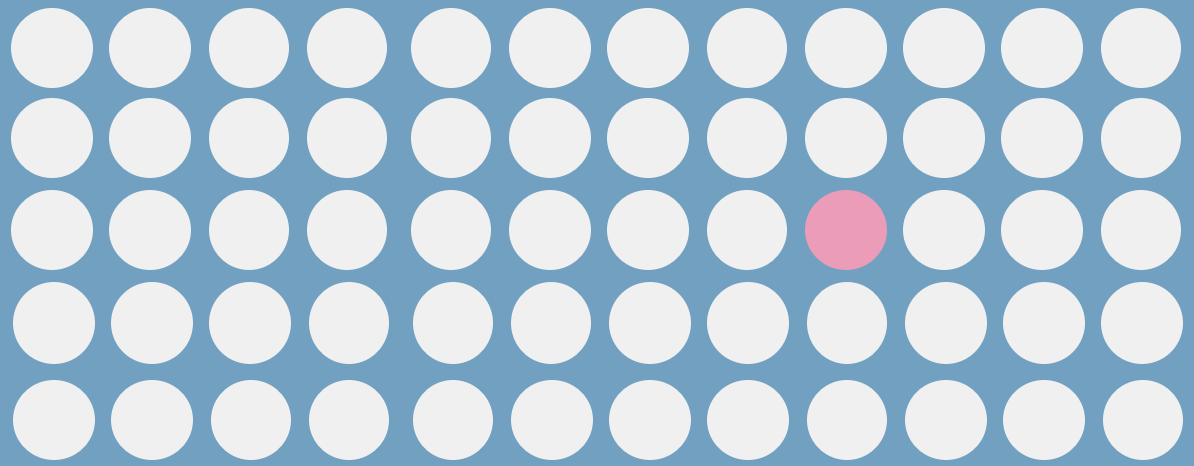
Identify a **correlate of protection**, then create a strategy to elicit that correlate of protection by rational design.

HIV vaccine efficacy trials to date have not elicited broadly neutralizing antibody responses, which is a key component of an HIV vaccine



Nine Phase II/III clinical trials have been completed since the discovery of HIV/AIDS. These vaccine candidates were designed using an **empirical approach** where different parts of the virus were formulated to stimulate either B- or T-cell response following vaccination. ***No vaccine candidates tested to date have induced broadly neutralizing antibody responses.***

EMPIRICAL APPROACH



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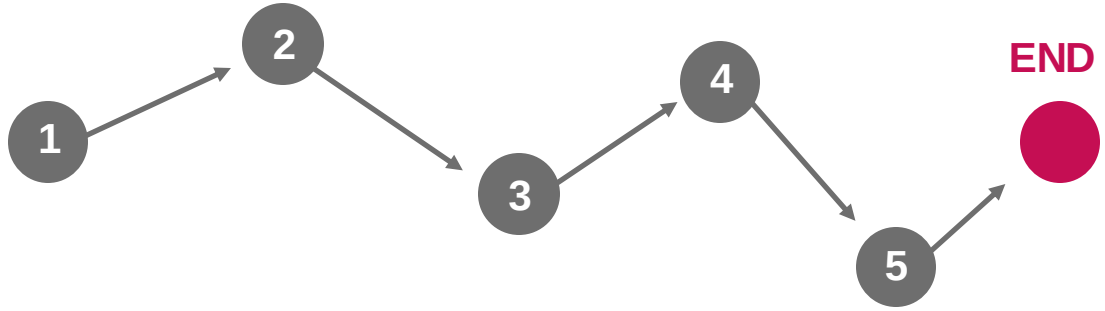
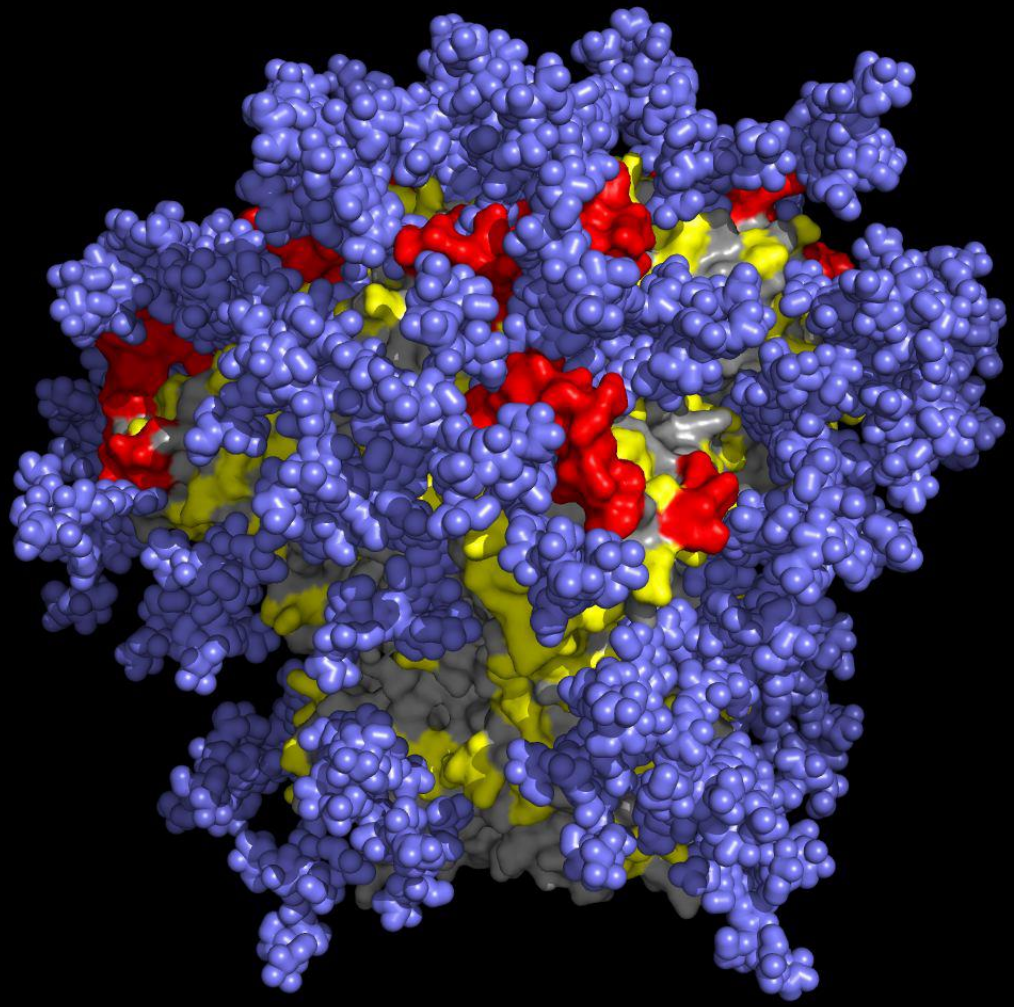
RATIONAL DESIGN APPROACH



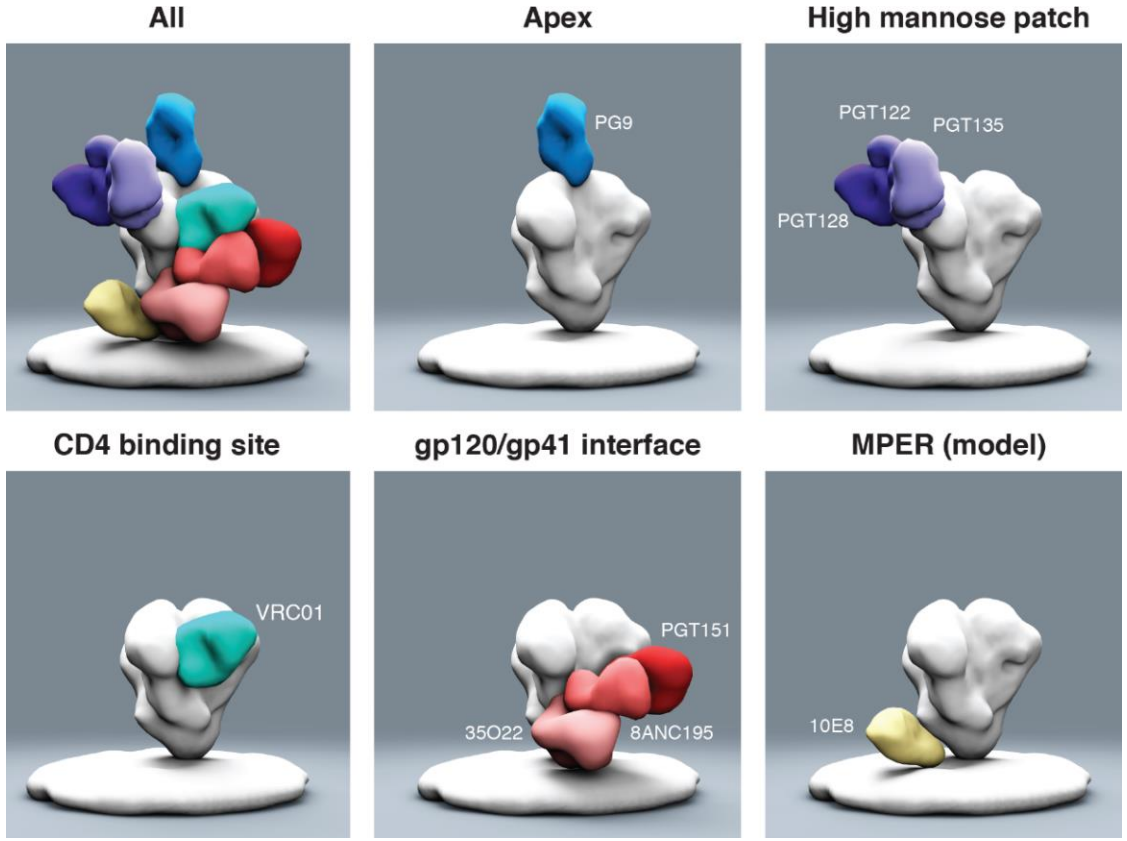
Identify a **correlate of protection**, then create a strategy to elicit that correlate of protection by rational design.

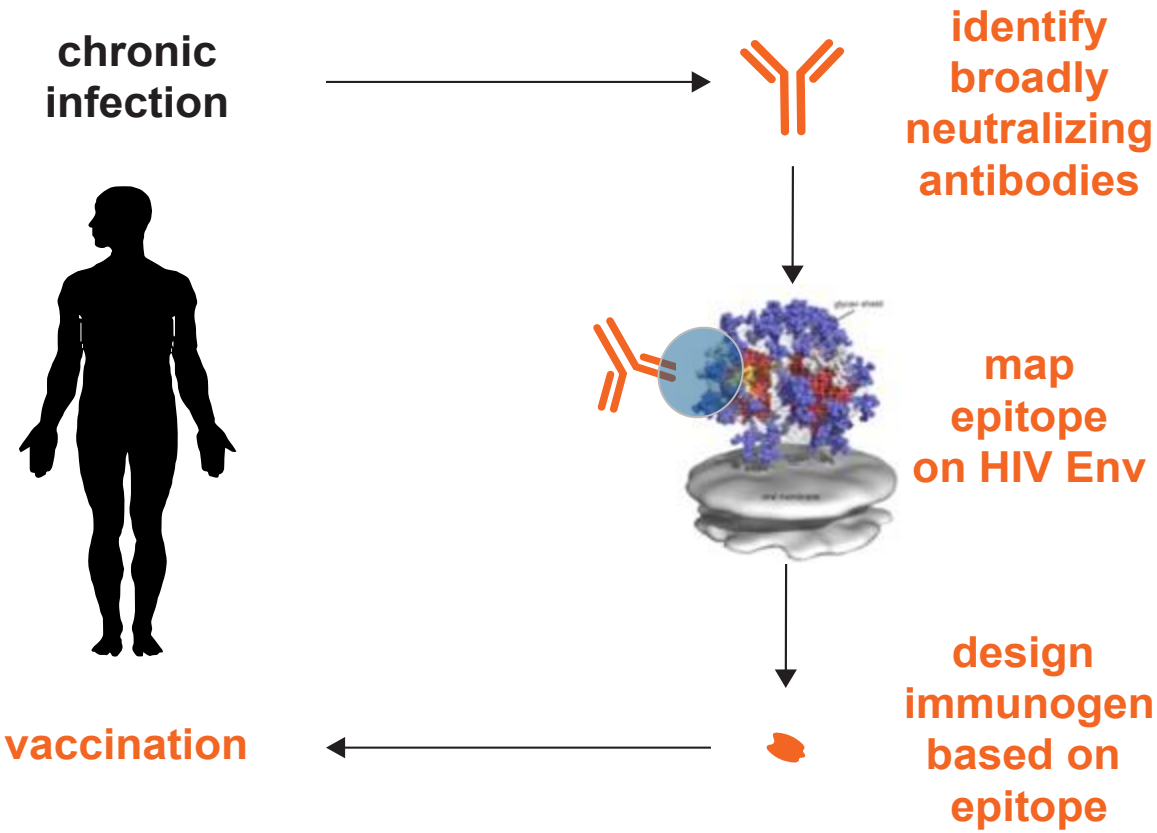
HIV Envelope Trimer: the target of neutralizing antibodies



Structure, Glycosylation, and Sequence Variation Pose Major Challenges to the Development of Broadly Neutralizing Antibodies

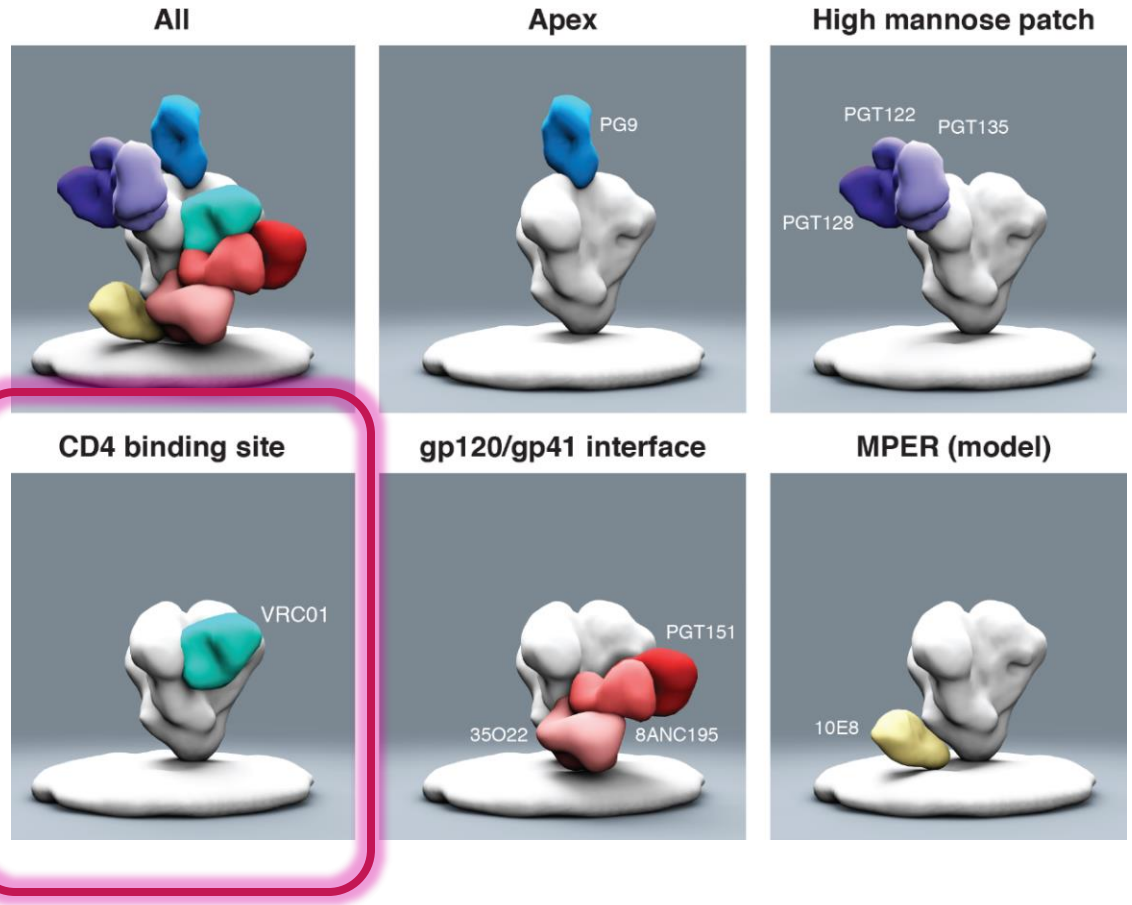
HIV broadly neutralizing antibodies reveal conserved epitopes on the HIV envelope, which serve as targets for vaccine design





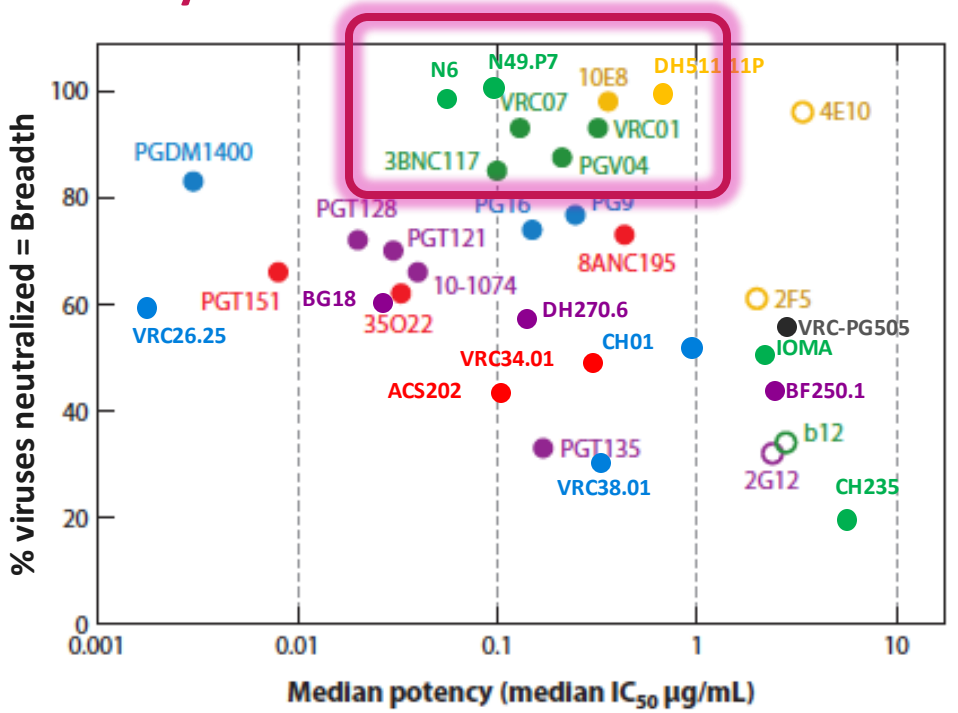
Burton & Hangartner, Ann. Rev. Immunol., 2016

A key target for HIV vaccine design: VRC01-class bnAbs target the CD4 receptor binding site on HIV Env and are highly broad



→ HIV infects T cells via the CD4 receptor

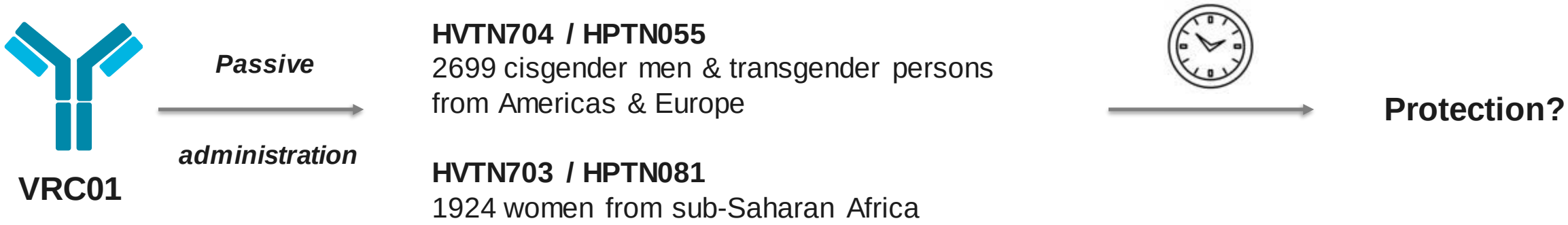
→ HIV bnAbs to the CD4 binding site on HIV Env are **very broad**



Burton & Hangartner, Ann. Rev. Immunol., 2016

Completed Phase IIb trial

The antibody mediated protection (AMP) trial demonstrated proof-of-concept that bnAbs can protect against HIV infection



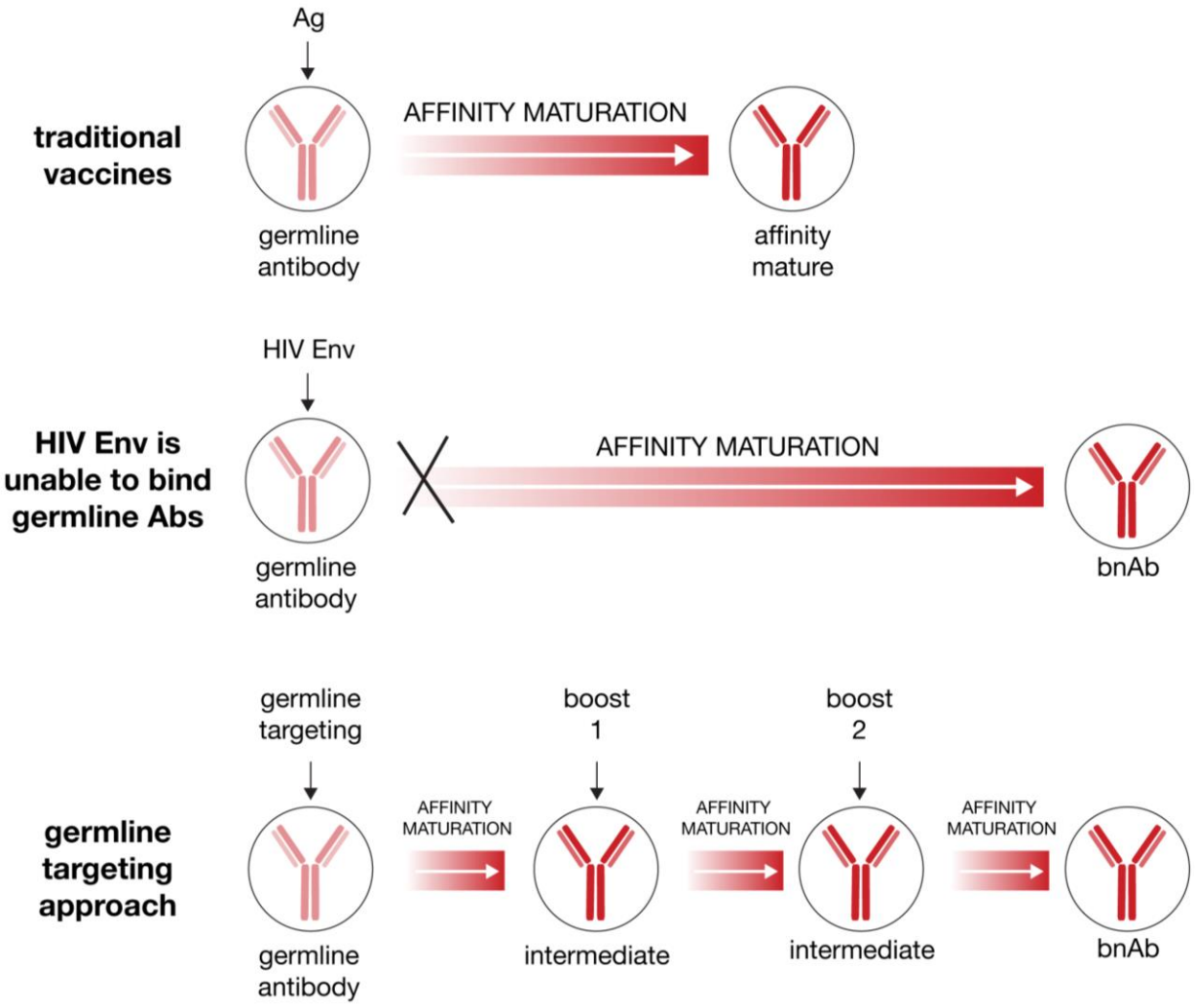
- VRC01 did not prevent overall HIV-1 acquisition in either of the trials
- VRC01 did demonstrate protective efficacy against HIV isolates that are neutralization sensitive to VRC01 (IC80 < 1 ug/ml)

Corey et al, NEJM, 2021

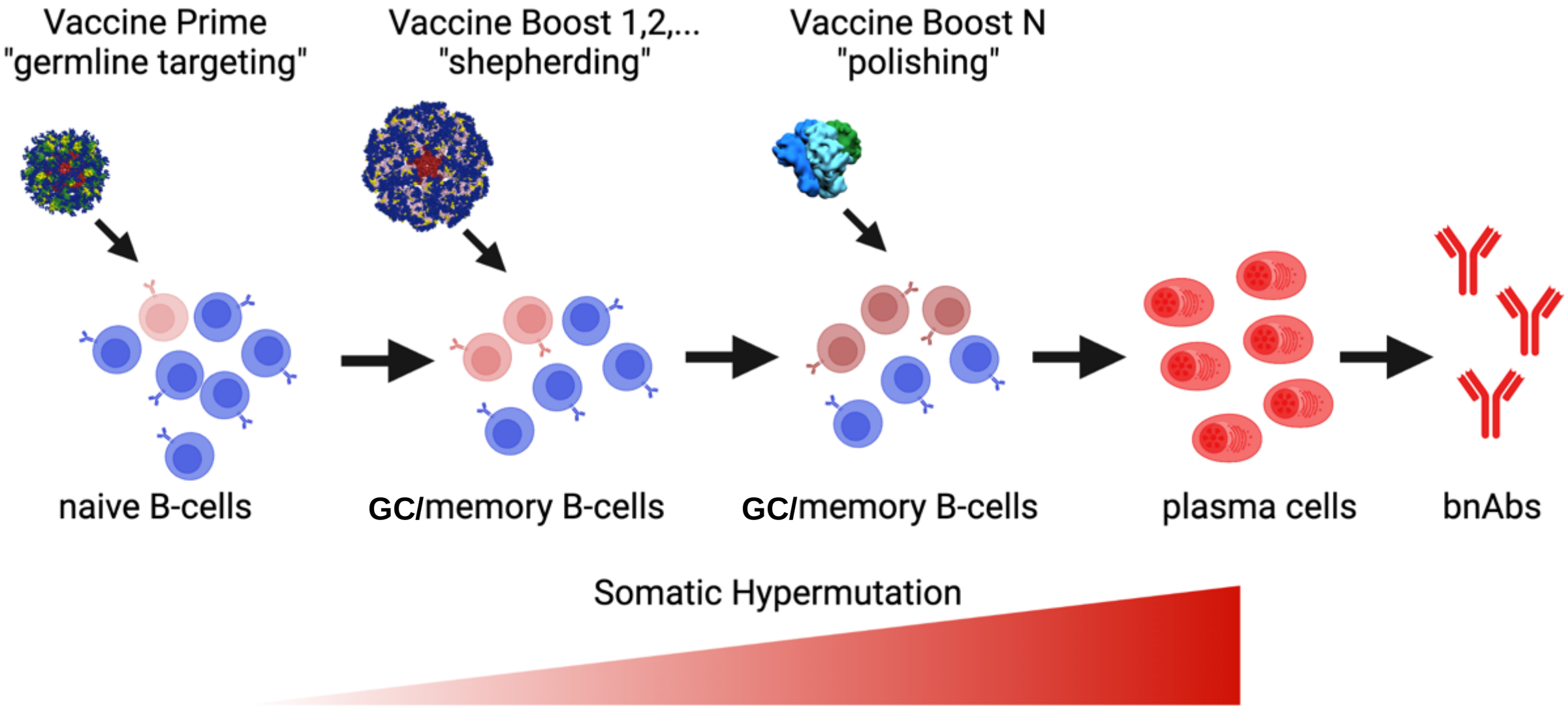
“Germline Targeting” immunogens are needed because native HIV Env does not bind to naïve bnAb precursors

Need for a germline-targeting immunogen

Germline-targeting is an approach where the immune system is manipulated to elicit a very specific antibody response. This approach is needed for HIV because HIV Env binds poorly to germline HIV bNAbs



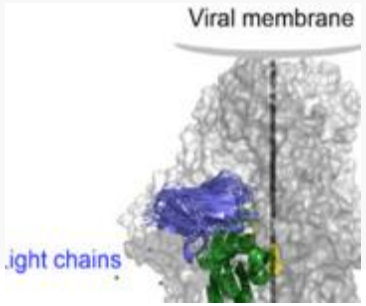
Strategy to induce broadly neutralizing antibodies: germline-targeting vaccine design



From discovery to translation: a summary of seminal work

1

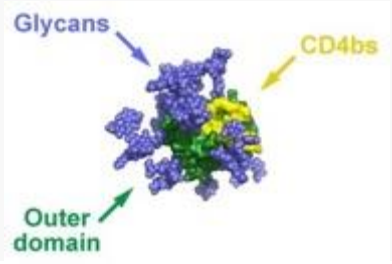
Structural and genetic homogeneity define VRC01-class of CD4bs bnAbs



Wu et al, Science 2010
Scheid et al., Science 2011
Zhou et al., Immunity 2013
Zhou et al., Cell 2015
Wu et al., Cell 2015

2

Design of eOD-GT8 60mer to prime VRC01-class precursor B-cells



Jardine et al., Science 2013
Kong et al., Immunity 2016
Jardine et al., Plos Pathog 2016
Umotoy et al., Immunity 2019

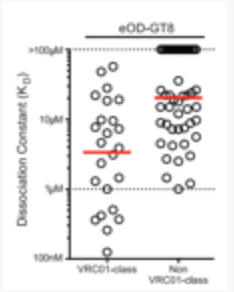
3

eOD-GT8 60mer elicit VRC01-like Ab responses in Hu/KI mice models

Jardine et al., Science 2015
Dosenovic et al., Cell 2015
Sok et al., Science 2016
Briney et al., Cell 2016
Tian et al., Cell 2016
Abbot et al., Immunity 2018

4

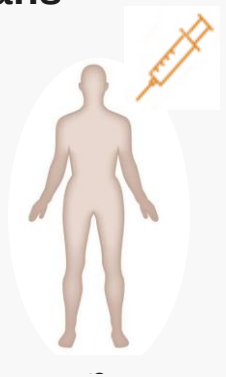
CD4bs-specific eOD-GT8+ VH1-2+ cells detected in the human naïve B-cell repertoire



Jardine et al., Science 2016
Havenar-Daughton et al. Sci.Transl.Med. 2018
Huang et al., PNAS 2020
Wang et al., EMBOJ 2020

5

eOD-GT8 60mer elicit VRC01-like Ab response in humans



IAVI G001
Leggat et al, Science 2022

IAVI G002 (ongoing)
IAVI G003 (ongoing)

2007-2011: eOD + germline targeting (GT) + particle development
2012-2013: GT + particle + mouse development and crystallography
2014-2015: GT + Kymab mouse and NHP studies

2014-2016: eOD GT8 GMP manufacturing
2016-2021: VRC01-class boost + transgenic mouse model development
2017-2021: IAVI G001 (eOD-GT8 60mer + AS01b) clinical trial

Three new Phase I trials testing mRNA-mediated delivery for HIV vaccine development

1. **IAVI G002** (**launched** November 2021 in US)

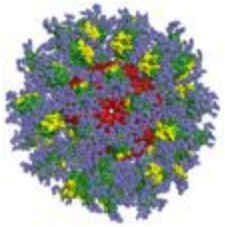
   IAVI/Moderna/BMGF partnership to test mRNA-delivered GT8 prime/core boost

2. **IAVI G003** (**launched** Q2 2022 in Rwanda and South Africa)

   IAVI/Moderna/BMGF/USAID/PEPFAR/ADVANCE partnership to test mRNA-delivered GT8 in Africa

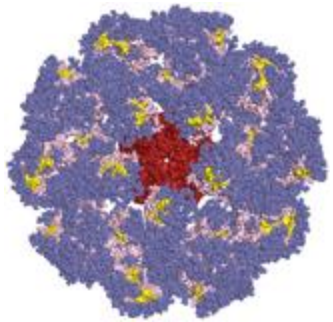
3. **HVTN 302 (launched** December 2021 in US)

   HVTN/Scripps CHAVD/NIAID/IAVI/BMGF/Moderna partnering to test mRNA delivery of native trimers



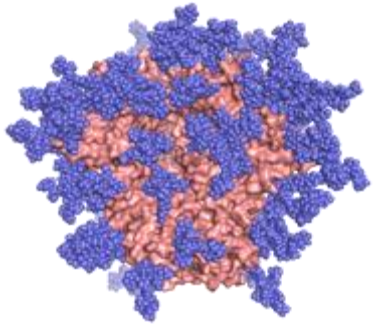
GT8 60mer

IAVI G001
IAVI G002
IAVI G003



core 60mer

IAVI G002



native-like trimer

HIV VACCINE TRIALS NETWORK

IAVI G003 Phase I Trial in Africa

A Phase 1, Randomized, Open-label Study of eOD-GT8 60mer mRNA in HIV-1 Uninfected Adults in Good General Health (Rwanda and South Africa)

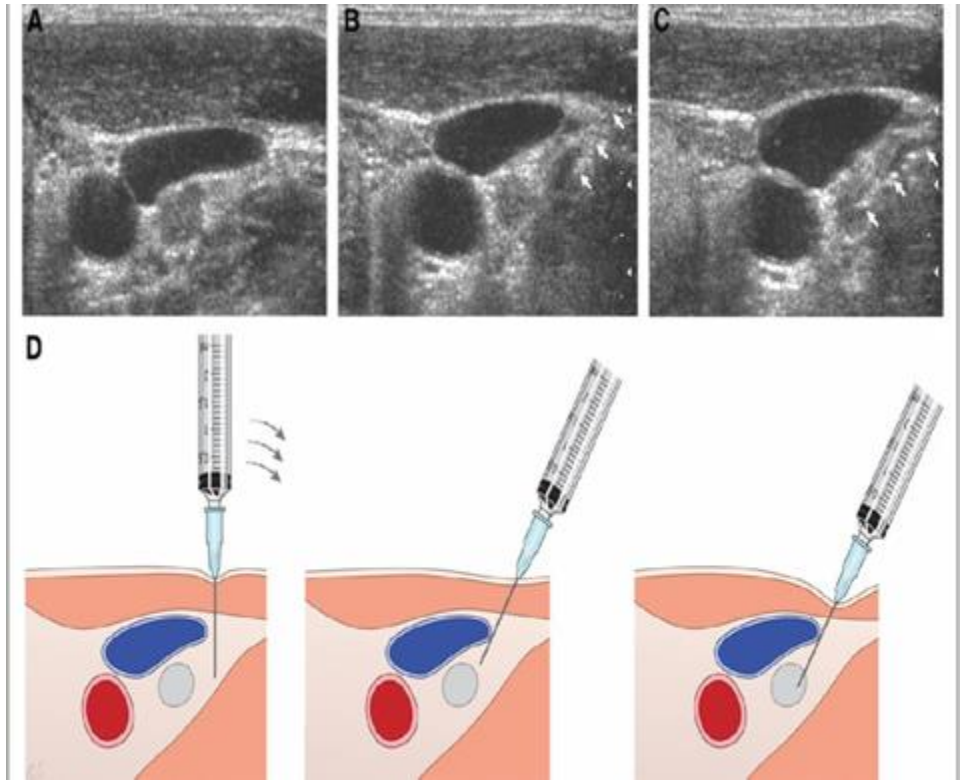
Key Aims of the trial:

1. **Evaluate safety and immunogenicity** of the **eOG-GT8 60mer mRNA** (**100ug** at **Wk0** & **Wk8,** N=**18**)
2. **Test eOD-GT8 60mer mRNA priming** — will mRNA generate similar VRC01-class responses as in G001, and G002 in an African population where HIV vaccine is most needed
3. **Increase capacity for novel sampling methods and cutting-edge immunological analyses in Africa** - Immunological analyses to be conducted by African scientists in country (BAMA, 10X Genomics)
4. **Introduce discovery medicine trial and new vaccine concepts to communities and regulatory bodies -** feasibility (Regulatory, Technical expertise) and acceptability (Social Behavioral Research) of new sampling techniques (FNA, Leukapheresis)

Through G003 we aim to demonstrate next generation vaccine trial implementation and analysis in Africa, led by African scientists

Establishment of New Clinical Capacity

Fine Needle Aspiration (Aurum and CFHR)



Allows “real-time” monitoring of B-cells responses in germinal centers

2 weeks post immunization

Leukapheresis (Aurum only)

Allows in depth characterization of B-cell responses with lower overall blood volume

Week 16 (8 weeks post 2nd dose)

The G003 trial was successfully completed in Rwanda and South Africa

Main takeaways

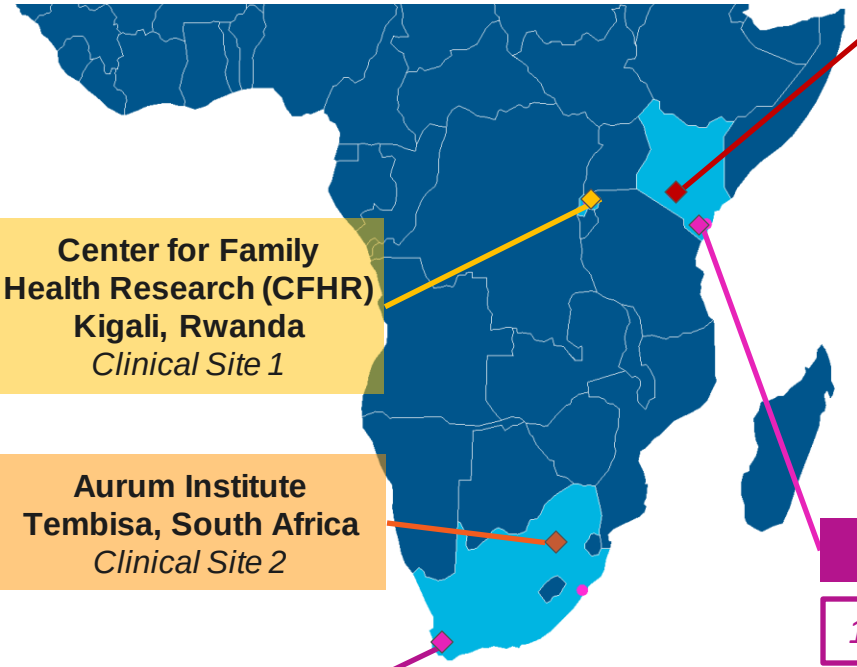
Successful completion of the Ph I trial

- No SAEs observed; 2/18 (11.1%) have reported pruritis of short duration (<8 days)
- Successful leukapheresis in 7/8 participants. (Failure – blood clots in tubing)
- FNA – 17/18 successfully achieved at both time points (~3.6 million on average per LN; Failure – undetectable LN).

Rapid enrollment at African trial sites

- Rwanda trial site (CFHR): 70 days from 1st screen to completion of enrolment
- RSA trial site (Aurum): 106 days from 1st screen to completion of enrolment

G003 Immunology and Analysis Teams



Center for Family Health Research (CFHR) Kigali, Rwanda
Clinical Site 1

Aurum Institute Tembisa, South Africa
Clinical Site 2

KAVI-ICR, Nairobi, Kenya

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Michelle Muthui
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Sharon Owuor

James Chemweno

D. Collins Owuor

CAPE TOWN HVTN
IMMUNOLOGY LABORATORY

10X library sequencing

Statistical Center for HIV/AIDS Research and Prevention
SCHARP at FRED HUTCH

Statistical Analysis

BioInformatics

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La Jolla, CA, USA

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Troy Sincomb

Chris Cottrell

Bill Schief

Clinical Immunology Capacity Transfer Timeline

Linda Murungi

Elise Landais

COVID19 disruptions

2018	2019	2020	2021	2022	2023

Single B-cell sorting and Sanger sequencing KAVI & KEMRI for W001 Trial Analysis

10X Optimization NAC

10X Sequencing Transfer to KEMRI

Assay Qualification & Validation (G001)

G003 Trial

10X Sequencing KAVI

Leukapharesis & FNAs Aurum Institute & CFHR

Joined Meetings with G002 Immunology Teams (VRC & Duke)

JUNE 2021	JULY 2021	AUG 2021	SEPT 2021	OCT 2021	NOV 2021	DEC 2021	JAN 2022	FEB 2022	MAR 2022	APR 2022	MAY 2022	JUNE 2022	JUL 2022	AUG 2022	SEPT 2022	OCT 2022	NOV 2022	DEC 2022	JAN 2023

Conceptualization & Assay Design Qualification Plan

Assays Set-up & Optimization (Reagents Titrations, SOPs)

Assay & Instruments Qualification

Assay Validation Using G001 Samples

ADVANCE 10X Activities

Creation of Clinical Immunology Manual, Risk Assessment Contingency Planning

Process for establishing 10xG analysis capacity at KEMRI Kilifi, Kenya

Pre-qualification

Single Cell Sorting
- **Reagents Titration and Stability**
- **Staining Panel Optimization**
- **Flow Rate Optimization**
- **Application Settings Optimization** (Voltages, Compensations)

10X Sequencing
- **Establishing Platform**
- **Optimizing Recovery** (Collection buffers, volumes & formats, cell number etc…)
- **Sample Multiplexing**
- **Impact of Sort length**

Qualification

Instrument Standardization
Experimental Templates
Analysis Templates
MARIO Gating

Qualification Experiments
- **Sorting:** Dummy samples with PBMCs spiked with titrated amount of control cell line VRC01-GL
- **10X Sequencing:** Titrated number of Random IgD- B-cells using at least 4 different Hashtag

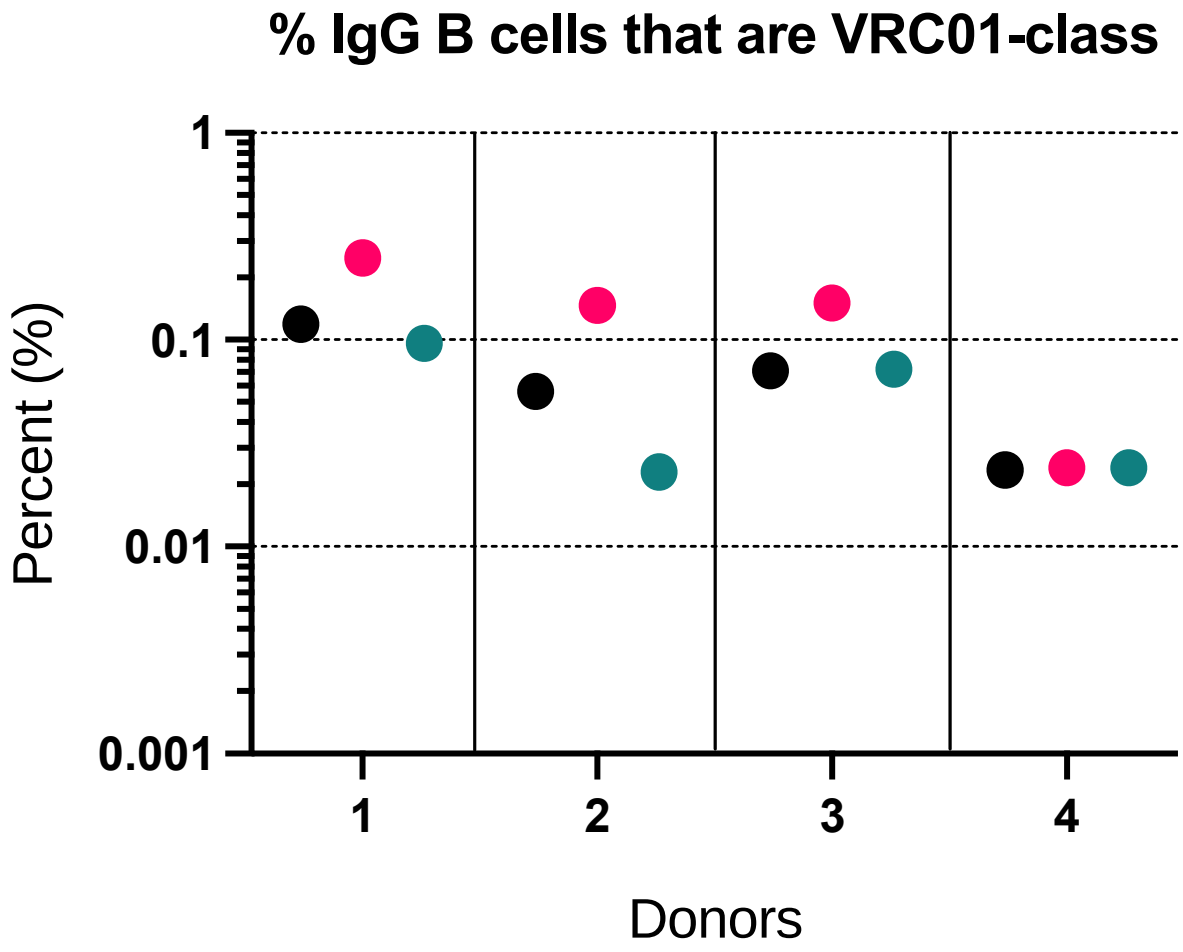
Determine Qualification parameters
1. Sensitivity
2. Specificity
3. Accuracy
4. Precision
5. Robustness: Operator, Reagents batch bridging

Validation

G001 (n=4)	G003 Week 16 (n=8) NAC & KEMRI 3Q23	G003 Weeks -5, 8, 10, 16, and 21 4Q23	G002 samples (n=?)
Can the KWTRP & NAC teams recapitulate the results of G001 using the 10xG platform	*Analyze leukapheresis timepoint post second prime at both sites*	*Analyze remaining timepoints at KWTRP*	*Data concordance between trials and analysis sites*

Epitope-Specific IgG+ B-cell Sorting and 10X Sequencing at KEMRI (frequency of VRC01-class B cells)

Data concordance between KEMRI and NAC VRC01-Class responses with original G001 trial data



BLACK = NAC
RED = KWTRP
GREEN = G001

Acknowledgements

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Rosine Ingabire
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Sharon Owuor
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Patrick Mwaura
Ruth Chirchir
Naomi Mwakisha
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Afrah Khairallah

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Susan Barnett
Nina Russell

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Madhu Prabhakaran
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Jennifer Bohl
Adrian McDermott

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Georgia Tomaras and team

HVTN
Julie McElrath and Team

Karolinska
Gunilla Karlsson Hedestam

Moderna
Andrea Carfi
Sunny Himansu
Brett Leav
Caroline Reuter

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And many other generous individuals and partners around the world

As of November 2022