HIV Vaccine Development: Current State of the Science

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Scientific Challenges in Constructing an Effective HIV Vaccine

• One needs to prevent acquisition or cure early established disease; a much higher bar than traditional vaccines, such as COVID-19
• Genetic diversity of the virus is greater than any other pathogen
• Envelope is less immunogenic than any other virus envelope proteins; perhaps because of its glycan shield
• Many parts of the HIV trimer create “diversionary antibodies” and we don’t have a systematic approach to define these and “cut them out”
• There are many fewer trimers on the surface than most viruses (it’s a very “bald virus”) and neutralizing antibodies cannot cross link
• There are no human cures of HIV (0 of 74 million and counting), hence no immunological models to mimic
Large inter-spike distances between HIV trimers prevent Fab cross-linkages

Klein and Bjorkman, 2010, PLoS Pathogens

For most viruses, two identical Fabs in IgGs permit bivalent binding through inter-spike crosslinking.

For HIV, inter-spike crosslinking is rare because spikes are present at low densities.

SARS CoV-2 / CDC  Zhu et al., 2006, Nature

HIV spikes are relatively immobile in virus membrane
HIV’s low spike density plus its rapid mutation – creates the high neutralizing antibody bar for HIV.

Inter-spike crosslinking
Intra-spike crosslinking

Env mutations lower the affinity of an antibody for Env.

Neutralizing antibodies against HIV Env are susceptible to Env mutations because they can’t compensate for low affinity with avidity.

This issue is likely operant for non-neutralizing antibodies also.
The HVTN Experimental Medicine Program - current “Product Profile” is to develop a vaccine regimen that elicits high levels of broadly neutralizing antibodies; ID80 about 200 to at least two known separate bnAb regions of the HIV virion

Main platform is to develop immunogens that are expressed on nanoparticles or viral like particles
There is still a desire/need to combine these neutralizing immunogens with approaches that also elicit significant cellular/innate responses

- Picker CMV vector leading approach
Design a vaccine that can induce 2-3 epitope specific lineages/germlines with high breadth


<table>
<thead>
<tr>
<th>Antigen Site</th>
<th>Germline Priming Required</th>
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<tbody>
<tr>
<td>CD4 BS</td>
<td>Yes</td>
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<td>V2 glycan</td>
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<td>Fusion peptide</td>
<td>No</td>
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<tr>
<td>MPER region</td>
<td>No</td>
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Three major approaches to bnAb-based vaccine design

- **Lineage-based**: series of immunogens designed to mimic naturally derived bnAbs in humans. The prime is designed to bind the UCA from one lineage. Boosts induce uncommon key mutations along the development pathway.
  - **Targeted lineages**: CH103, CH235, DH270 (all Bart Haynes)

- **Germline-targeting**: priming immunogen designed to activate diverse precursors within a bnAb class (including multiple lineages), with successively more native-like boosts (shepherding → polishing steps).
  - **Targeted germlines**: 426c core (Leo Stamatatos), eOD-GT8 (Bill Schief), V3 N332-GT5 (Bill Schief)

- **Immunofocusing**: Lineage & germline agnostic, designed to focus more broadly on one or more epitope
  - **Targeted epitopes**:
    - Fusion peptide (Peter Kwong),
    - Deglycosylated CD4bs (Rich Wyatt, Peter Kwong, Rogier Sanders, Paolo Lusso)
    - Deglycosylated V3-glycan (Pamela Bjorkman)
Unmutated BCRs

- Naive B cell ‘unmutated’ BCR
- ‘germline-targeting’ immunogen
- The Abs are non-neutralizing

Partially matured BCRs

- Antigen-specific B cell expressing partially matured BCR
- Sequential Env immunogens
- Select for particular VH/VL pairs
- Abs with gradually improved neutralizing activities

Fully matured BCRs

- Gradually more mature B cells with the desired mutations in their BCRs
- Production of bNAbs

Germline Ab

```
GWYVLKSCAEVRFGASVSVSKRASGTYTTVSMTYHRQAEQGQLDWSWNPHEGTLLKIGDYAVTRSATVTSISTAYHELCLISBDEOTVYCAR
```

Mature Ab

```
GQQETSPIYVRFSASQTVSGSSQTIEHVRQAEQGQLDWSWNPHEGTLLKIGDYAVTRSATVTSISTAYHELCLISBDEOTVYCAR
```

Germline-targeting immunogen

Booster immunogen 1

Booster immunogen 2

Booster immunogen 3

Germline Ab → Ab maturation process → Mature Ab
Germline-Targeting Vaccine Design: VRC01
(Schief, et al.)

VRC01-class bnAbs
- Engage the gp120 CD4bs
- Require VH1-2 and 5AA L-CDR3 to engage CD4bs
- Have diverse H-CDR3s and light chains

➢ Need priming immunogen with appreciable affinity and avidity for diverse VRC01-class human naïve precursors

Germline-Targeting Immunogen
- eOD-GT8 60mer
- Self-assembling nanoparticle presenting 60 copies of an engineered gp120 outer domain

✓ Has appreciable affinity and avidity for diverse VRC01-class human naïve precursors
✓ Primes VRC01-class responses in stringent mouse models
✓ Induces VRC01-class memory responses that can be boosted toward bnAb development in mouse models

Huang et al. PNAS 2020; Wang et al. EMBOJ 2021
GT8 induces substantial VRC01-class frequencies among IgG B cells in PBMCs.

We factored in VRC01-class % of IgG+ B cells for the low and high dose groups:

For reference: frequency of GT8-specific VRC01-class precursors among human naive IgM B cells is 1 in 300,000 (Jardine et al. Science 2016; Havenar-Daughton et al Sci. Trans. Med 2018)

Thus, two shot vaccine gives ~100-fold expansion from IgM to IgG (averaging low + high dose)

one shot vaccine gives ~15-fold expansion
VRC01-class precursors (unmutated BCRs) 
~0.01%

Partially mutated BCRs
>>0.01% eg 1 in 3000
Shepherding the Germline Induced Cell

- The scientific process or “rules” to induce the future maturation of B cells to develop the mutations that are needed for developing a highly potent bnAb are unclear; informed empiricism, at best
- HVTN is most worried about this stage of the process regarding need for iteration and here is where mRNA emerges as a critical tool in the scientific process for developing an HIV vaccine
- Part of the informed empiricism is to conduct these post-germline induction studies in HIV negative, as well as PLWH (HIV+)
  - Use an Acute Treatment Interruption to allow the virus to “teach us how” to mature the germline induced B cells
Immunizing HIV + Persons for Shepherding VRC01 germ line B cells

- Immunization of people with HIV with 426c.Mod.Core nanoparticles or EoD GT8 will activate VRC01-class B cell precursors
- These B cells will then enter the GC reaction and will start accumulating somatic mutations
- During ATI, viral rebound will take place and virus-associated Envs with features that are necessary to activate the partially mutated class B cells will emerge
- These Envs will further activate the partially mutated VRC01-class B cells and the corresponding BCRs will evolve closer towards their broadly neutralizing forms
- These Envs can be used as ‘booster’ immunogens during the vaccination of HIV- subjects (follow ups to HVTN301)
- Many non-VRC01-class B cells will also get activated by the virus
- The emergence of VRC01-like antibody responses will affect the kinetics of viral replication
- Many activated B cells that produce non-neutralizing Abs
- No activation of germline VRC01 B cells
Where’s the HIV Vaccine Immunogen Design Field NOW?
Design a vaccine that can induce 2-3 epitope specific lineages/germlines with high breadth


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Neutralizing Vaccine Program

<table>
<thead>
<tr>
<th>CD4bs</th>
<th>Antigen</th>
<th>Formulation</th>
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<tbody>
<tr>
<td>300</td>
<td>CH505 TF 3M-052-AF/Alum</td>
<td>Protein</td>
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<tr>
<td>301</td>
<td>426c Core NP</td>
<td>Protein</td>
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<tr>
<td>302</td>
<td>BG505 trimers</td>
<td>mRNA</td>
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<tr>
<td>305</td>
<td>eOD-GT8</td>
<td>DNA</td>
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<tr>
<td>308</td>
<td>Deglycosylated NFL timer</td>
<td>Protein</td>
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<tr>
<td>309</td>
<td>CH505M5 trimer NP + CH505 TF</td>
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<tr>
<td>310</td>
<td>Deglycosylated 426 trimer</td>
<td>mRNA</td>
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Neutralizing Vaccine Program

<table>
<thead>
<tr>
<th>V3 glycan</th>
<th>Antigen</th>
<th>Notes</th>
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<tbody>
<tr>
<td>306</td>
<td>N332 GT5 + SMNP</td>
<td>mRNA</td>
</tr>
<tr>
<td>307</td>
<td>V3G CH848 trimer NP + M-052-AF + mRNA trimer</td>
<td>Protein + mRNA</td>
</tr>
<tr>
<td>310</td>
<td>426c + BG505</td>
<td>VLP</td>
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Neutralizing Vaccine Program

B-cell & mAb analysis

ANALYSIS WORKFLOW & OUTPUTS

Immunogen** tagged B-cell flow cytometry

- Pre-vaccination frequency
  - Immunogen** naïve B cells
- Post-vaccination frequency
  - Immunogen** B cells
  - Epitope specific B cells
  - Class specific B cells

Single cell BCR sequencing

- BCR variable region allelic phenotype
- Key VH/VL mutations
- SHM

mAb cloning

- mAb Affinity (SPR)
- 3D binding & structure (cryoEM)
HVTN 310: Dual epitope targeting chimera
Chimeric CD4bs VRC01 UCA + V2-apex CH01 UCA trimer (NIAID)

The Chimera
**HVTN 310: CD4bs & V2-apex targeting mRNA VLPs**

### Table 1-1 Schema

<table>
<thead>
<tr>
<th>Study arm</th>
<th>N</th>
<th>Total dose mRNA</th>
<th>Month 0 Week 0</th>
<th>Month 2 Week 8</th>
<th>Month 4 Week 16</th>
<th>Month 6 Week 24</th>
<th>Month 8 Week 32</th>
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<tbody>
<tr>
<td><strong>Part A</strong></td>
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<td></td>
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<tr>
<td>1</td>
<td>8</td>
<td>100 mcg</td>
<td>426c deglyco-3</td>
<td>426c deglyco-3</td>
<td>426c WT</td>
<td>BG505 + REJO</td>
<td>BG505 + REJO</td>
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<tr>
<td>2</td>
<td>8</td>
<td>100 mcg</td>
<td>426c deglyco-3</td>
<td>426c deglyco-1</td>
<td>426c WT</td>
<td>BG505 + REJO</td>
<td>BG505 + REJO</td>
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<tr>
<td>3</td>
<td>8</td>
<td>100 mcg</td>
<td>426cQ23 chimera</td>
<td>426c Q23 chimera</td>
<td>426c WT</td>
<td>BG505 + REJO</td>
<td>BG505 + REJO</td>
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<tr>
<td>4</td>
<td>5</td>
<td>Placebo</td>
<td>Saline</td>
<td>Saline</td>
<td>Saline</td>
<td>Saline</td>
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<td><strong>Total Part A: 29</strong></td>
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<tr>
<td><strong>Part B</strong></td>
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</tr>
<tr>
<td>5</td>
<td>8</td>
<td>250 mcg*</td>
<td>426c deglyco-3</td>
<td>426c deglyco-3</td>
<td>426c WT</td>
<td>BG505 + REJO</td>
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<tr>
<td><strong>Total Part B: 29</strong></td>
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<td><strong>Total Part A + Part B: 58</strong></td>
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*The dose in part B may be adjusted to 100 – 200 mcg based on safety and tolerability data from Part A. Need to spell out safety trigger in the protocol.
Making an HIV vaccine is scientifically hard; likely the hardest antibody mediated vaccine in the virological world

Making an HIV vaccine is still necessary

Making an HIV vaccine has both direct and indirect effects
  - The HIV vaccine infrastructure was the NASA of COVID-19 vaccine development

Immunogen design for an HIV vaccine is directed at making broadly neutralizing antibodies to more than one site
  - Currently, this requires different immunogens for each site; an epitope specific vaccine

Target titer is serum neutralization of >1:200 in TZMBI assay

We have a rich scientific portfolio in approaches and our scientific challenge is to put these different approaches into a coherent vaccine regimen

Addition of the mRNA platform is necessary to iterate the informed empiricism needed to develop an effective vaccine regimen

Doesn't mean it’s the only or final platform in achieving success, but it’s a necessary tool to get there
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