HIV Vaccine Enterprise – Product Development Boot Camp

Principles of Portfolio Management: a VRP Perspective

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Presentation Outline

- VRP Mission
- NIAID/DAIDS Vaccine Research Programs
- VRP Programmatic Focus
- VRP Portfolio Management
- Landscape
- Acknowledgements
VRP Mission: safe and effective HIV vaccine

- Portfolio of preclinical, translational, and clinical research:
  - Identify and characterize selected viral envelopes that stimulate broadly neutralizing antibodies (bNAb)
  - Promote discovery of novel vaccine candidates and strategies
  - Establish/support GMP production infrastructure and testing of novel immunogens and bNAb
  - Develop strategies to optimize protective B-cell responses
  - Assess correlates of immunity/protection elicited by experimental vaccines
NIH/VRP Priorities

- Focus: important public health issues
  - AIDS vaccine

- Fund and enable high quality scientific research
  - Foundational R&D for vaccines
  - Spectrum from basic/discovery to translational/applied
  - Enable and support clinical efficacy testing

- Generalizable scientific knowledge
NIAID/DAIDS Vaccine Research Programs (2016-2017)

**Discovery/Preclinical Research**
- Research Project Grants
- Solicited Grant Programs
  - Innovation in HIV Vaccine Discovery
  - FcR and Antibody Effector Functions
  - NK Cells to induce Immunological Memory
  - Role of Microbiome in Vaccine Responses
  - Vaccine Vector-Host Interactions

**Translational Research/Manufacturing**
- Preclinical Development Master Contract Support
- Staged Vaccine Development (SVD) - BAA
- Integrated Preclinical-Clinical AIDS Vaccine Development (IPCAVD) U19 Grant
- Process Development and Analytic Support (PAS) FY16 - BAA

**Clinical Research**
- HIV Vaccine Trials Network (HVTN)

**Consortia for AIDS Vaccine Research in NHPs, Simian Vaccine Evaluation Units**
- HIV Vaccine Research and Design (HIVRAD)

**Centers for HIV/AIDS Vaccine Immunology and Immunogen Discovery (CHAVI-ID)**

**Military HIV Research Program (MHRP)**
DAIDS VRP Programmatic Focus by Area

- **Pre-clinical/Discovery Research**
  - Long-range goal is a predictive model of immune response
  - How can we induce bNAb?
  - Can non-neutralizing antibodies protect?
  - How do we increase durability of protective responses? – Optimizing immune design
  - What lab correlates predict vaccine efficacy?

- **Translational Research**
  - What analytics are most important for protein immunogen effectiveness?
  - Can protein immunogens be manufactured: cost-effectively, efficiently, of high quality?
  - How can product yields be increased (e.g. higher expression or reduced losses)?
  - How can lessons-learned about PD, GMP scale-up be shared most effectively?

- **Clinical Research**
  - Design and conduct phase 1, 2 & 3 trials; study correlates
  - Advance concepts to elicit, technology to assess, adaptive cellular, humoral, mucosal, and innate responses
  - Incorporate research on behavioral & social factors in prevention and transmission of HIV
  - Actively integrate clinical research with basic/preclinical/NHP investigators
Pre-Clinical Development and Research Portfolio – 50% product oriented

- **Env-containing product focus for humoral immunity:**
  - Induction of bnAbs by targeting germline genes
  - Lineage driving immunogens, germline targeting
  - Stabilized trimer proteins
  - MPER scaffolds
  - Glycan epitopes
  - V1V2 targeted vaccines

- **Vector and Insert-focused**

- **Adjuvant/Immune Modulator**
Foundational, front-end science feeding the pipeline

• Will rhCMV will translate to the human immune system?

• AAV immunoprophylaxis – Good vector? Good strategy?

• Vaccine Delivery – DNA via needle & syringe (IM) vs. new devices designed to optimize delivery

• Will alternative Adenovirus vectors work?
  • Ad26/MVA/protein slated for efficacy testing
  • Funding of alternative Ads in light of STEP results

• Will non-human Ad serotypes be needed? e.g. ChimpAd

• Transient expression of proteins:
  • accelerated production, lower cost, earlier clinical testing
VRP Portfolio Management

Early Discovery/Basic Research
- Grants
- Academic Research
- Investigator-initiated

Translational

Clinical Testing
- Federally funded clinical trial networks, labs, stats center; regulatory support

*incentivize Pharma Partner

Basic

Applied

Time
Programmatic participation

High Risk, lower expectations
Relatively low investment

High Risk, high expectations
Major investment
How does NIAID/VRP manage vaccine portfolio?

- Science and data-based decision-making
- Rely on Peer-review system
- Often basic-innovative concepts
- Concepts grow into platforms and candidates
- Staged and milestone driven processes
- Darwinian forces come into play
- Stronger candidates emerge with compelling data (tested in small animals, primates)
- Manufacturability, feasibility and analytics considered
- Defensible rationale to test in humans
## Concepts in Near-Term/Ongoing Trials

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<thead>
<tr>
<th>Concept</th>
<th>Activities</th>
<th>Candidate</th>
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<tbody>
<tr>
<td>P5 Pox Protein</td>
<td><strong>Confirm RV144 in South Africa and Thailand</strong></td>
<td>• ALVAC/ALVAC + env</td>
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</table>
|                              | Improve on RV144, define correlates, evaluate potency, durability, and mucosal targeting of immune responses to DNA/pox/protein with different adjuvants | • ALVAC/ALVAC + env  
• DNA/DNA + env  
• DNA/Pox or Pox/Pox + env Adjuvants: MF59, AS01B, Alum |
| bNAbs                        | Evaluate protective Ab titers/function in blood and mucosa, using passive and vectored Ab-immunoprophylaxis | • VRC-01, VRC01-LS, VRC-07  
• AAV PG-9  
• AAV8 VRC-07 |
| Alternative Prime-Boost Regimens | Evaluate priming capacity of various vectors, DNA and/or protein prime/boost combinations; extend Ab durability and overcome vector immunity | • rAd26 combinations  
• DNA/MVA or MVA/MVA  
• DNA/VSV  
• Multi-clade/Mosaic DNA/env + Adjuvant  
• DNA/rTT-Vaccinia/ env |
| Viral Vectors                | Evaluate specific vectors, alone or in combination with other vaccines to preferentially drive CD4⁺, CD8⁺ T cells, Ab responses | • ALVAC, MVA, NYVAC (replication incompetent)  
• rAd26 (alternate Ad)  
• rAd4, VSV (replication competent)  
• CMV (persistent) |
| Antigen Delivery and Priming | Evaluate impact of env antigen design and delivery on the potency and breadth of immune responses | • T/F proteins/ SOSIPs/ Outer Domain – scaffolds, nanoparticles, arrays  
• Trimeric gp145, gp140 (Clade C)  
• Electroporation/ Biojector  
• Heterologous priming, polytopic delivery, antigenic competition, co-administration  
• Immunization schedule, intervals |