Outline

- RV 144 Correlates Discovery
- Towards a Licensed HIV Vaccine
- Ad26/MVA Prime Boost
RV144 Correlates Discovery
RV 144 showed early but nondurable efficacy
Efficacy at 1 year appeared higher

(Kaplan-Meier-based estimates)

<table>
<thead>
<tr>
<th>month</th>
<th>mITT</th>
<th></th>
<th></th>
<th>PP</th>
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<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Efficacy</td>
<td></td>
<td>Events</td>
<td>Efficacy</td>
</tr>
<tr>
<td>6</td>
<td>16</td>
<td>54%</td>
<td>n/a</td>
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<tr>
<td>12</td>
<td>42</td>
<td>60%</td>
<td>21</td>
<td>68%</td>
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<tr>
<td>18</td>
<td>67</td>
<td>44%</td>
<td>41</td>
<td>41%</td>
<td></td>
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<tr>
<td>24</td>
<td>82</td>
<td>36%</td>
<td>53</td>
<td>27%</td>
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</tr>
<tr>
<td>30</td>
<td>95</td>
<td>36%</td>
<td>62</td>
<td>31%</td>
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Can we build on this early efficacy?
Duality of Approach

- Identification of a correlate(s) of protection could allow for rational improvements to this product and subsequent approaches.

- Improvement of efficacy of 60% at one year in terms of magnitude, durability, and generalizability could yield a public health tool.

- Pursuit of two approaches:
  - Intense search for correlates
  - Product development of ALVAC + gp120
RV 144 Correlates Discovery

**ADVISORY GROUPS**

Implications for future clinical development of this product

**Humoral & Innate Immunity**

**Cellular Immunity**

**Host Genetics**

**Animal Models**

**Scientific Advisory Groups**

**Product Development Advisory Group**

**Scientific Steering Committee**

Implications for future scientific inquiry into the result and evaluation/design of other candidates and studies

**PA H Steering Committee**

**MHRP - DAIDS Steering Committee**

**RV144 Steering Committee**
Two phase of Correlates Discovery

- **Phase I (now-Jan 2011)**
  - Broad survey of innate, humoral, systems biology, genetic, and cellular assay evaluation/comparison.
  - Multiple Nab, ADCC, ADCVI approaches
  - Statistical plan

- **Phase II (Jan 2011-April 2011)**
  - Case-control
  - Evaluation of a broad range of assays but with downselection of depth to optimize the statistical design

- We are in phase I and I will show some of these data today.
Correlates Discovery Effort is Broad

<table>
<thead>
<tr>
<th>Approved Proposals</th>
<th>Institutions*</th>
<th>Investigators</th>
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<tbody>
<tr>
<td>32</td>
<td>20</td>
<td>35</td>
</tr>
</tbody>
</table>

*Cornell, Duke, Harvard, UCSC, UCI, Rush, UMass, Northwestern, NYU, UWash, Oxford, Kings College, Mahidol, St. George’s, UMMelbourne

- Scripps
- IHV (UMD)
- VGTI (OSHU)
- MHRP
- Monogram Bio
- NIH (NIAID, NCI)

Samples distributed in early June 2010
ELISpot responses in breakthrough infections fail to overlap between vaccinees and placebo subjects

- N = 21 vaccine, 22 placebo
- Total # Gag peptides = 120
- Total # Env peptides = 165
- 15-mer/11aa
- Non-fractionated ELISpot
- Only positive epitopes shown

Dr. Mark de Souza, AFRIMS
Exploratory analysis of envelope T-cell epitopes in uninfected RV 144 vaccinees

- PBMC from 21 per protocol subjects showing ELISpot reactivity at 26 weeks post-immunization were selected for study at 2 weeks post immunization.

- Additional 46 subjects selected at random.

- Matrix format ELISpot with HIV Env TH023 peptides (matched to ALVAC-HIV).
  - Peptides were 15 aa overlapping by 11aa
  - Matrix of approximately 9-13 peptides per pool for a total of 165 peptides. Each pool tested singly

- Positive response: > 20 SFC/million PBMC and > 4 X background
Frequency – all vaccinees – N=60

Dr. Mark de Souza and Dr. Alex Schuetz, AFRIMS

HLA association: DQB1*0302, 0303

Peptide 44

Median # responses = 2

Peptide 49
GSID gp120 MN

Yu, B. et al. 2010. J. Virol. 84(3):1513
Peptide 44: % similarity between subtypes B, C, E

PEPTIDE 44: 92TH023 Sequence
V2 ELISpot responses not seen in breakthrough infections nor in natural history precedents

Peptide 44 and 49 have been recognized in only 1 Thai HIV infected subject each

Dr. Mark de Souza and Dr. Alex Schuetz, AFRIMS
Sample RV144.519425: CD4 Analysis

Proliferating CD4 T cells

Interferon-γ

IL-2

CD107a

TNFα

CM240 GAG Peptide Pool

CM235 ENV Peptide Pool

ENV-32 (Pep44 Cognate)

Dr. Jeff Currier, Dr. Silvia Ratto-Kim
B-cell Linear Epitope Mapping Studies (VRC)

- **Peptides:**
  - 15mer peptides overlapping by 3 designed by LANL to cover the diversity of 7 major genomic subtypes
  - Peptides synthesized and array slides produced by JPT Peptide Technologies
    - Total of 874 peptides

- **Assay:**
  - Sera/Plasma incubated onto array slides
    - 15 HVTN204 peak sera (DNA + rAd5 phase IIA)
    - 15 RV144 peak plasma
    - 72 HIV+ sera (CHAVI and CAVD)
  - Serum/Plasma binding to each peptide determined by laser scanning after incubation with anti-IgG Cy5

- **Data Analysis:**
  - Geometric mean of signal strength across all genomic variants was plotted for each peptide by sample population (HIV+, RV144 and HVTN204)

*Dr. Bob Bailer, Dr. Rick Koup*
V2 antibody responses are notable

Peptides 54-56 = Peptide 44

RV144 > HVTN204

HVTN204 > RV144

CD4BS

V1, V2, V3, V4, V5

Dr. Bob Bailer, Dr. Rick Koup, VRC/NIAID
V2 Response to Different Genotypes (VRC)

Peptide sequence:
- CRF-1
- CRF-2
- A
- B
- C
- D
- M

HVTN204

RV144

Peptides 54-56 = Peptide 44

Dr. Bob Bailer, Dr. Rick Koup
Conclusions

- Some vaccine recipients have CD4+ peptide responses to 2 distinct epitopes in V2 that are very rare in HIV+ Thais or in the RV152 breakthrough infection cohort
  - Cells are CD4+, CD107+, polyfunctional
  - Peptide 44 includes the $\alpha_4\beta_7$ binding motif
- RV144 vaccine recipients show V2 antibody responses that are different from Ab responses induced with DNA/Ad5
Towards a Licensed HIV Vaccine
Objective

Discussion of critical issues shaping a global HIV vaccine development strategy.

Objectives:

1. To build on the promising results of the RV144 trial and test key products in relevant, at-risk populations.

2. To underscore the dual importance of product development and correlates oriented trials in building the most efficient pathway to licensure of a global HIV vaccine.

3. To define the necessary partnerships with industry and regional collaborators that have been built and will be rapidly mobilized to support the successful execution of efficacy trials.
Developing a Globally-Effective HIV Vaccine

The HIV vaccine community is driven by the goal of developing and licensing a globally-effective HIV vaccine as efficiently as possible.

- Effective in at-risk populations, including high-risk
- Multi-clade protection
- Durable, safe and effective
- Public health access enabled by key partnerships

GLOBALLY EFFECTIVE HIV VACCINE
RV144 demonstrated both safety and modest efficacy and established the necessary partnerships to answer key scientific and post-trial questions encountered in the product development pathway.
Pursue a strategy that will deliver the public health potential of this product as efficiently as possible.

* Target product profile—target population, efficacy standard, dose, regimen, formulation.
MHRP’s vaccine development strategy emphasizes regional and global approaches.

1. **BUILDING ON RV144**

   **REGIONAL VACCINE STRATEGY**

   Building on the RV144 outcome and lessons learned, conduct efficacy trials of the prime-boost concept in:
   
   a) Thai MSM populations
   
   b) High-risk populations in Southern Africa

2. **DIVERSIFYING AND REFINING THE PORTFOLIO**

   **GLOBAL VACCINE STRATEGY**

   Pursuing diverse platforms (e.g. vectors, multi-valent constructs or mosaic inserts) that build on the prime-boost concept and readily translate to multi-clade testing and a globally effective vaccine.
Building on RV 144 in next efficacy studies

- **Boost again**: Incorporate additional boost 6 months after fourth vaccination visit (12 months)
- **Optimize boost**: More immunogenic gp120/MF59 adjuvant
- **Look earlier**: Power the study to assess efficacy at 18 and not 42 months.
- **Better samples**: Right specimens in right amounts from the right time points
- **Diversify risk groups**: MSM, high incidence heterosexual populations
Regional Pox-Protein Product Development Plan

**Phase IIb Licensure in Thailand**
- **Thailand**
  - RV152, RV305, RV306
  - RV144i laboratory studies
  - **Objective:** Determine a correlate of protection for use in future trials; optimize the regimen
  - **Partners/Funders:** US Army, Thai Gov’t, Gates, NIH, sanofi pasteur

**Phase IIb Efficacy**
- **RSA and Southern Africa**
  - Heterosexual, high-risk
  - **Objective:** Translate vaccine to high-risk groups with greater viral diversity
  - **Partners/Funders:** Gates, NIH, HVTN, sanofi pasteur, Novartis RSA, etc.

**Trials are prime-boost regimens with secondary boost**

- **SE Asia**
  - MSM, high-risk
  - **Objective:** Demonstrate efficacy in target population to achieve public health impact
  - **Partners/Funders:** US Army, Thai Gov’t, NIH, sanofi pasteur, Gates (?)

**RV144 Follow-on Studies**
- **Thailand**
  - RV152, RV305, RV306
  - RV144i laboratory studies
  - **Objective:** Determine a correlate of protection for use in future trials; optimize the regimen
  - **Partners/Funders:** US Army, Thai Gov’t, Gates, NIH, sanofi pasteur

**Phase IIb Licensure in Thailand**
- **Thailand**
  - RV152, RV305, RV306
  - RV144i laboratory studies
  - **Objective:** Determine a correlate of protection for use in future trials; optimize the regimen
  - **Partners/Funders:** US Army, Thai Gov’t, Gates, NIH, sanofi pasteur
In order to expedite the pathway to licensure, we are committed to conducting trials in Thailand, while advancing multiple vaccine concepts in priority regions.

i. **An MSM trial in SE Asia** is a top priority because it has the potential to lead to licensure in this region.

ii. **Focusing on the pox + protein prime-boost concept in Southern African nations** will advance a vaccine with broad public health relevance and leverage broad capacity and networks in the execution of trials.
Product Selection

Due to the availability of multiple competing products, a rational selection strategy will be required to prioritize products tested in Phase IIb efficacy trials.

Where possible, product decisions will be based on a downselection strategy that uses a constellation of inputs:

- **Scientific:** Correlates, immunological grids
- **Practical/Qualitative:** Industrial, cost, timing, regulatory
# Comparison of Vector Platforms

<table>
<thead>
<tr>
<th></th>
<th>ALVAC</th>
<th>NYVAC</th>
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</thead>
<tbody>
<tr>
<td><strong>LICENSED PRODUCTS</strong></td>
<td>5 {RCOMBITEK, PUREVAX, Eurifel FeLV, PROTEQFLU, RECOMBITEK-WN}</td>
<td>none</td>
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<tr>
<td><strong>SAFETY</strong></td>
<td>+++</td>
<td>+*</td>
</tr>
<tr>
<td><strong>MANUFACTURING</strong></td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td><strong>RESISTANCE TO VECTOR-SPECIFIC IMMUNITY</strong></td>
<td>+++</td>
<td>+?</td>
</tr>
<tr>
<td><strong>UNDERSTANDING OF VECTOR BIOLOGY</strong></td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td><strong>JEV-SPECIFIC</strong></td>
<td></td>
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<tr>
<td><strong>SAFETY</strong></td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td><strong>INSERT-SPECIFIC NEUTRALIZING ANTIBODY RESPONSE</strong></td>
<td>- (low)</td>
<td>+++ (only in vaccinia non-immune)</td>
</tr>
<tr>
<td><strong>HIV-SPECIFIC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CD8 INDUCTION</strong></td>
<td>- (low)</td>
<td>+</td>
</tr>
<tr>
<td><strong>CD4 INDUCTION</strong></td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td><strong>PRIMING FOR SUBUNIT</strong></td>
<td>++</td>
<td>?</td>
</tr>
</tbody>
</table>

* Superior
* Equivalent
* Inferior or Unknown

* Limited human experience to date;  # Niranjan et al., Vaccine (2001):483-491

RCOMBITEK, PUREVAX, Eurifel FeLV, PROTEQFLU, RECOMBITEK-WN
Efficacy is a commanding position
Critical Issues: Recommendations I

We have a public health obligation to make product development decisions that will advance the best products to licensure as quickly and efficiently as possible.

- *Use conventional trial design for product development.*
- *Test products in key populations and locations to ensure a rapid pathway to licensure.*
- *Product decisions will be based on scientific, performance (efficacy, safety) and operational inputs.*
Product development and correlates discovery are not mutually exclusive activities.

- *Product development is the shortest pathway to a licensed HIV vaccine with ALVAC-HIV + gp120 but there is upfront risk to committing to optimizing the regimen.*

- *Other candidates need to be advanced to efficacy testing based on an understanding of immune responses derived from correlates-based clinical trials perhaps with novel designs.*

- *A balance between these two approaches should be pursued in clinical HIV vaccine research.*
Ad26/MVA Prime Boost:

An approach to a Global Vaccine Strategy
Collaboration to develop adenovirus prime, poxvirus boost HIV-1 vaccine regimens

- Immunogenicity and protective efficacy of Ad26/MVA regimens against heterologous SIV challenges in NHPs
- Immunogenicity of Ad26/MVA regimens expressing mosaic HIV-1 Gag/Pol/Env antigens in NHPs and humans
Immunogenicity and Protective Efficacy of Heterologous Ad26/MVA Regimens in Rhesus Monkeys

- 40 rhesus monkeys immunized with the following vectors expressing SIVsmE543 (E660) Gag, Pol, Env
  - DNA/MVA (N=8)
  - MVA/MVA (N=8)
  - Ad26/MVA (N=8)
  - MVA/Ad26 (N=8)
  - Sham (N=8)

- Monkeys: Mamu-A*01/B*17/B*08 negative, TRIM alleles balanced
- Prime at week 0 (or week 0, 4, 8 for DNA)
- Boost at week 24
- Low-dose, heterologous IR SIVmac251 challenges at week 52 (DB stock)
- Immunogenicity assays prior to challenge
  - ELISA
  - IFN-g ELISPOT
  - Multiparameter ICS
Ad26/MVA Regimen Optimal for Induction of Gag/Env-Specific Antibody Responses by ELISA
Ad26/MVA Regimen Optimal for Induction of Week 26 Gag/Pol/Env-Specific IFN-γ ICS Responses

Balanced CD8/CD4 and CM/EM Responses

- DNA/MVA
- MVA/MVA
- Ad26/MVA
- MVA/Ad26
- Sham
Immunogenicity Data: Conclusions

- Ad26/MVA regimen more potent than MVA/Ad26, DNA/MVA, and MVA alone regimens utilizing these assays
- MVA boosted well but primed poorly in this system
- Ad26/MVA regimen elicited balanced CM/EM responses and balanced CD8/CD4 responses that are phenotypically different than Ad alone and Pox alone regimens
- 75% of cellular immune responses elicited by SIVsmE543 antigens cross-reacted with SIVmac239 peptides
Assessment for Protective Efficacy

- 6 heterologous, repetitive, low-dose, IR SIVmac251 challenges performed weekly starting at week 52
- 1:1000 dilution of SIVmac251 challenge stock (930 TCID50)
- Assessment for protective efficacy
  - Protection against infection – resistance to challenges?
  - Control of viremia – reduced peak and setpoint viral loads?

- Highly stringent challenge model
  - DNA/Ad5 affords partial protection against acquisition of IR SIVsmE660 challenge but fails against IR SIVmac251 challenge
  - SIVmac251 more neutralization resistant than SIVsmE660
  - Protection against heterologous IR SIVmac251 challenge not previously reported (except for live attenuated vaccines)
Heterologous Vector Regimens Partially Resist Heterologous, Repetitive, IR SIVmac251 Challenges
**Heterologous Vector Regimens Partially Resist Heterologous, Repetitive, IR SIVmac251 Challenges**

<table>
<thead>
<tr>
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<th># Challenges for 50% Infection</th>
<th>P-Value vs Sham*</th>
<th>Hazard Ratio (95% Confidence Limits)</th>
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<tbody>
<tr>
<td>Sham</td>
<td>1</td>
<td>N/A</td>
<td>1</td>
</tr>
<tr>
<td>MVA/MVA</td>
<td>1</td>
<td>0.5587</td>
<td>0.725 (0.247-2.129)</td>
</tr>
<tr>
<td>DNA/MVA</td>
<td>2</td>
<td>0.0055</td>
<td>0.186 (0.057-0.611)</td>
</tr>
<tr>
<td>MVA/Ad26</td>
<td>3</td>
<td>0.0062</td>
<td>0.198 (0.062-0.632)</td>
</tr>
<tr>
<td>Ad26/MVA</td>
<td>3</td>
<td>0.0037</td>
<td>0.174 (0.053-0.567)</td>
</tr>
</tbody>
</table>

* Chi-square test, proportional hazard model
MVA/Ad26 and Ad26/MVA Regimens Lower Early Setpoint Viral Loads Following SIVmac251 Infection

Sham

MVA/MVA

DNA/MVA

MVA/Ad26

Ad26/MVA

3x resistance to infection
4/8: viremia blunted 1 log
3/8: rapid virologic control
1/8: persistently uninfected
Challenge Data: Conclusions

- Ad26/MVA afforded 3-fold resistance to acquisition of infection; 50% showed reduced but sustained viremia, whereas 50% exhibited rapid virologic control or remained uninfected.

- MVA/Ad26 and DNA/MVA also exhibited partial resistance to acquisition of infection and reduced viremia.

- These data demonstrate that partial protection against both acquisition and virologic control of fully heterologous, neutralization-resistant IR SIVmac251 challenges is possible.

- Immune correlates analyses are currently in progress.

- Future studies will determine whether this degree of protection can be further augmented utilizing a purified Env protein boost.

- Ad26 and MVA with mosaics inserts will advance to phase I studies in late 2011 (MHRP-BIDMC-NIAID-Crucell).
Acknowledgements

- RV144 volunteers and community members
- AFRIMS – US and Thai Component
- National Institute of Allergy and Infectious Diseases, NIH (intra and extramural)
- Faculty of Tropical Medicine, Mahidol University
- Global Solutions for Infectious Diseases
- Ministry of Public Health, Thailand
- sanofi pasteur
- Bill and Melinda Gates Foundation
- Beth Israel Deaconess Medical Center, Harvard Medical School
- Crucell
- All RV 144 Secondary Study investigators