HIV Vaccine Enterprise – Product Development Boot Camp

Principles of Portfolio Management: a VRP Perspective

November 5, 2015

Mary Marovich, M.D.

Director, Vaccine Research Program

Presentation Outline

- VRP Mission
- NIAID/DAIDS Vaccine Research Programs
- VRP Programmatic Focus
- VRP Portfolio Management
- Landscape
- Acknowledgements

National Institute of Allergy and Infectious Diseases

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 (bNAbs)
  - Promote discovery of novel vaccine candidates and strategies
  - Establish/support GMP production infrastructure and testing of novel immunogens and bNAbs
  - Develop strategies to optimize protective B-cell responses
  - Assess correlates of immunity/protection elicited by experimental vaccines

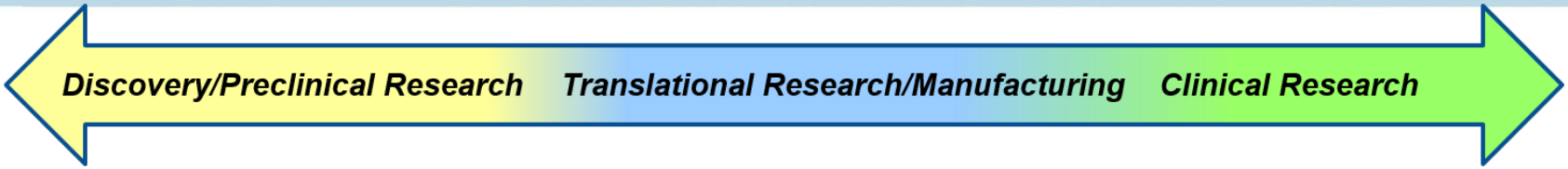
NIH/VRP Priorities

- 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)



- 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

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

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 bNAbs?
  - 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

NIH National Institute of Allergy and Infectious Diseases

NIAID

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

National Institute of Allergy and Infectious Diseases

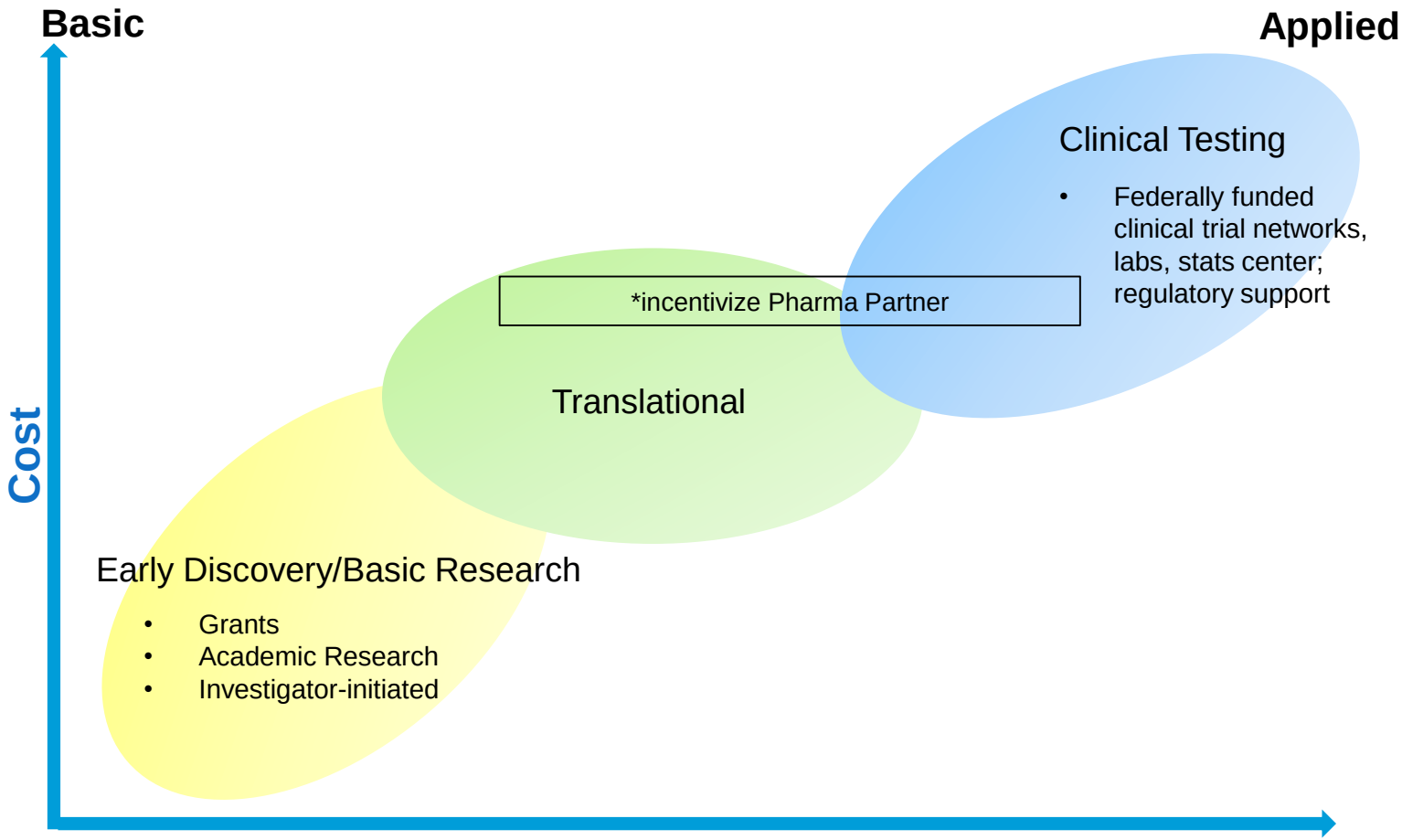
Vaccine Translational Research Branch Portfolio – 100% product related

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
- Wil non-human Ad serotypes be needed? e.g. ChimpAd
- Transient expression of proteins:
  - accelerated production, lower cost, earlier clinical testing

National Institute of Allergy and Infectious Diseases

VRP Portfolio Management



NIH National Institute of Allergy and Infectious Diseases

NIAID

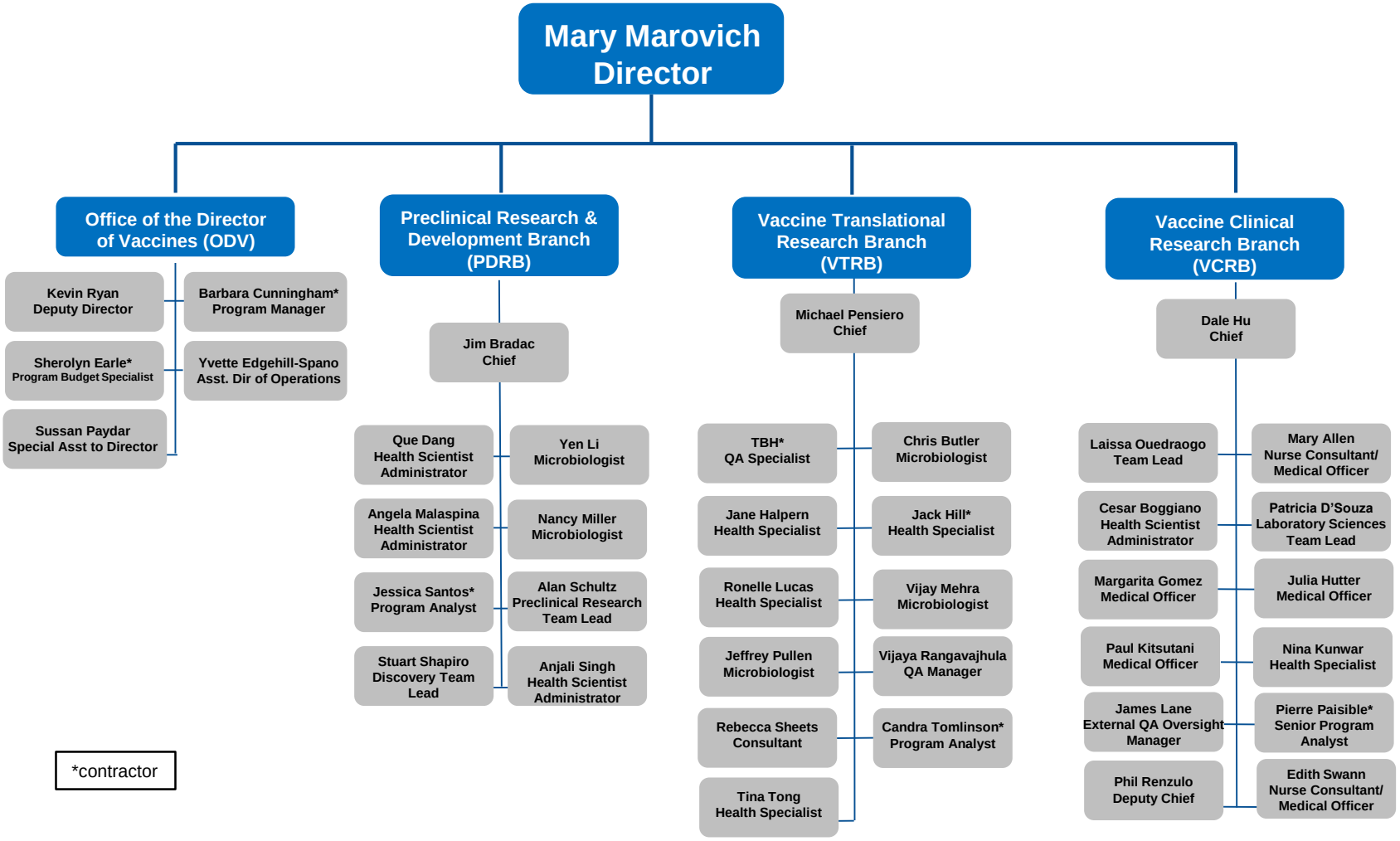
How does NIAID/VRP manage vaccine portfolio?

- 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

Concept	Activities	Candidate
P5 Pox Protein	Confirm RV144 in South Africa and Thailand	• ALVAC/ALVAC + env
	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 Assess anti-vector immunity attenuation of HIV-specific immunity	• 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

Acknowledgements



*contractor

National Institute of Allergy and Infectious Diseases

NIAID