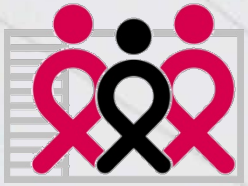


Dale and Betty Bumpers
Vaccine Research Center
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Department of Health and Human Services

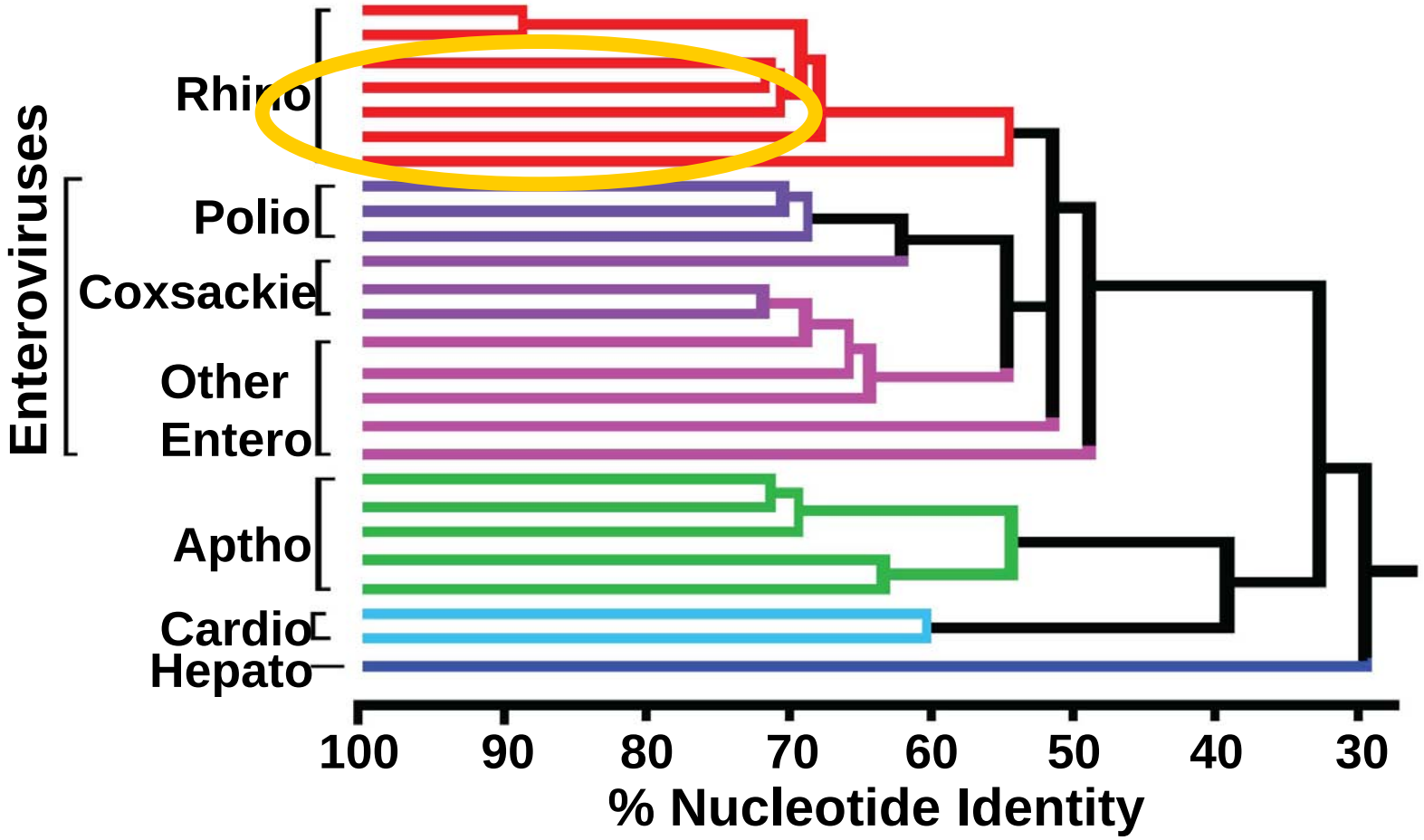
Combinatorial Vaccines for AIDS and other Infectious Diseases

IOM Cancer Policy Forum
Combination Investigational Cancer Therapies
Institute of Medicine
Washington, DC

Gary J. Nabel M.D., Ph.D.
Vaccine Research Center
NIAID, NIH
June 14, 2011

A Biomarker for Successfully Licensed Vaccines: Serotypes

Three poliovirus strains found in Nature: three serotypes are required for a protective vaccine

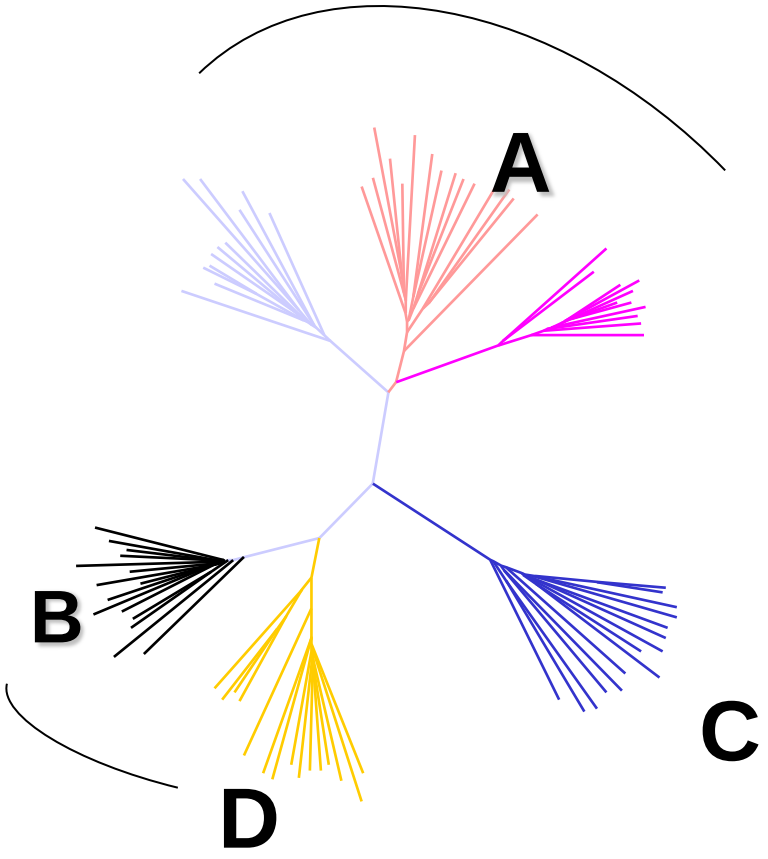


28 Licensed Vaccines to 24 Infectious Diseases

- Anthrax
- Diphtheria
- *Haemophilus influenzae* type b
- Hepatitis A
- Hepatitis B
- Herpes Zoster (shingles)
- Human papillomavirus
- Influenza A, B
- Japanese Encephalitis
- Measles
- Meningococcal disease
- Mumps
- Plague (currently not available)
- Pertussis
- Pneumococcal disease
- Polio
- Rabies
- Rotavirus
- Rubella
- Smallpox
- Tetanus
- Tuberculosis (BCG)
- Typhoid
- Varicella (chickenpox)
- Yellow Fever

Source: FDA/CBER, 10

Can HIV-1 Be Serotyped? Contrast with Polio



Infinite number of viruses

? Role of Abs in immunity

Evolving neutralization profiles

Combination Components in Vaccines

1. **Vectors/Delivery Platforms**

   --heterologous prime-boost immunization elicits qualitatively different immune responses that enhance efficacy.

2. **Inserts/Genes**

   --combinations of inserts in the same or different vector platforms increase the breadth of coverage in vaccines.

3. **Combination drug/ab treatment with immune stimulation**

   --confers protection/efficacy not otherwise seen with either agent alone.

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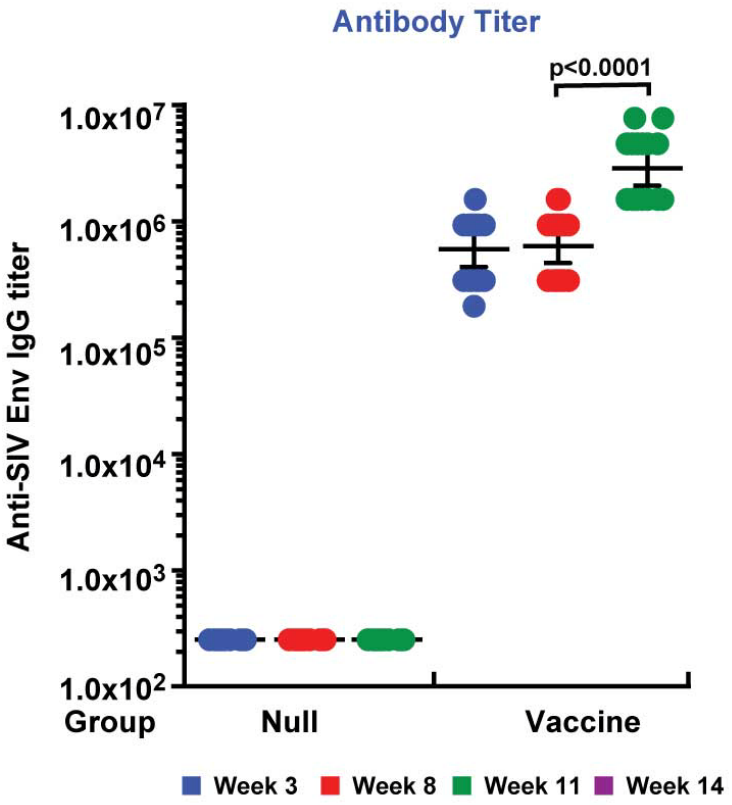
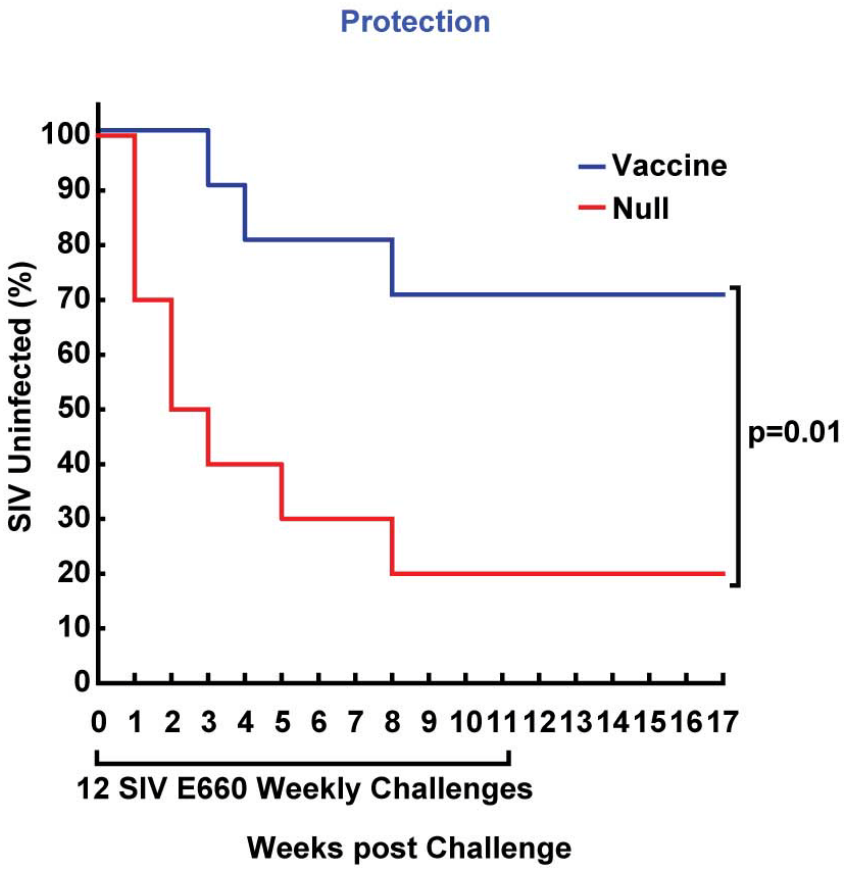
rAd5/rLCMV Env Vaccine Protects NHP from Mucosal SIVsmE660 Challenge





Influenza Vaccines-The Yearly Cost

New vaccine every year

120-150 million doses per year

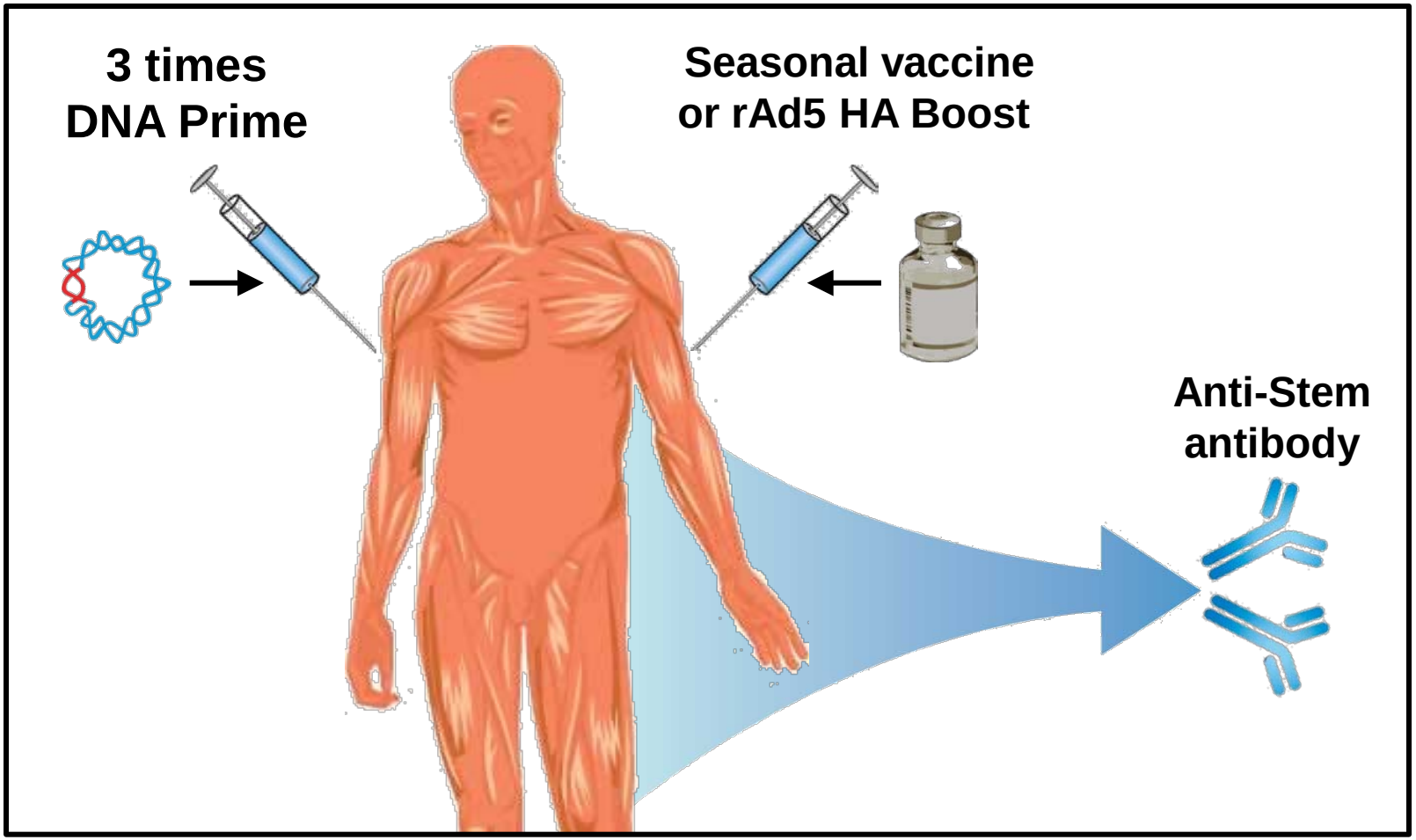
2.8-4.0 billion dollars total expenditure

Can We Make a Better Vaccine?

Improve potency

Increase breadth

Can we make a universal influenza vaccine that is administered during childhood and lasts a lifetime?



Humans could potentially be protected from a broad range of influenza strains by priming with a DNA vaccine encoding influenza hemagglutinin (HA) followed by boosting with either traditional seasonal influenza vaccine or replication-defective adenovirus 5 (rAd5) expressing HA.

Increased Breadth of Neutralization by Prime-Boost Immunization in Mice

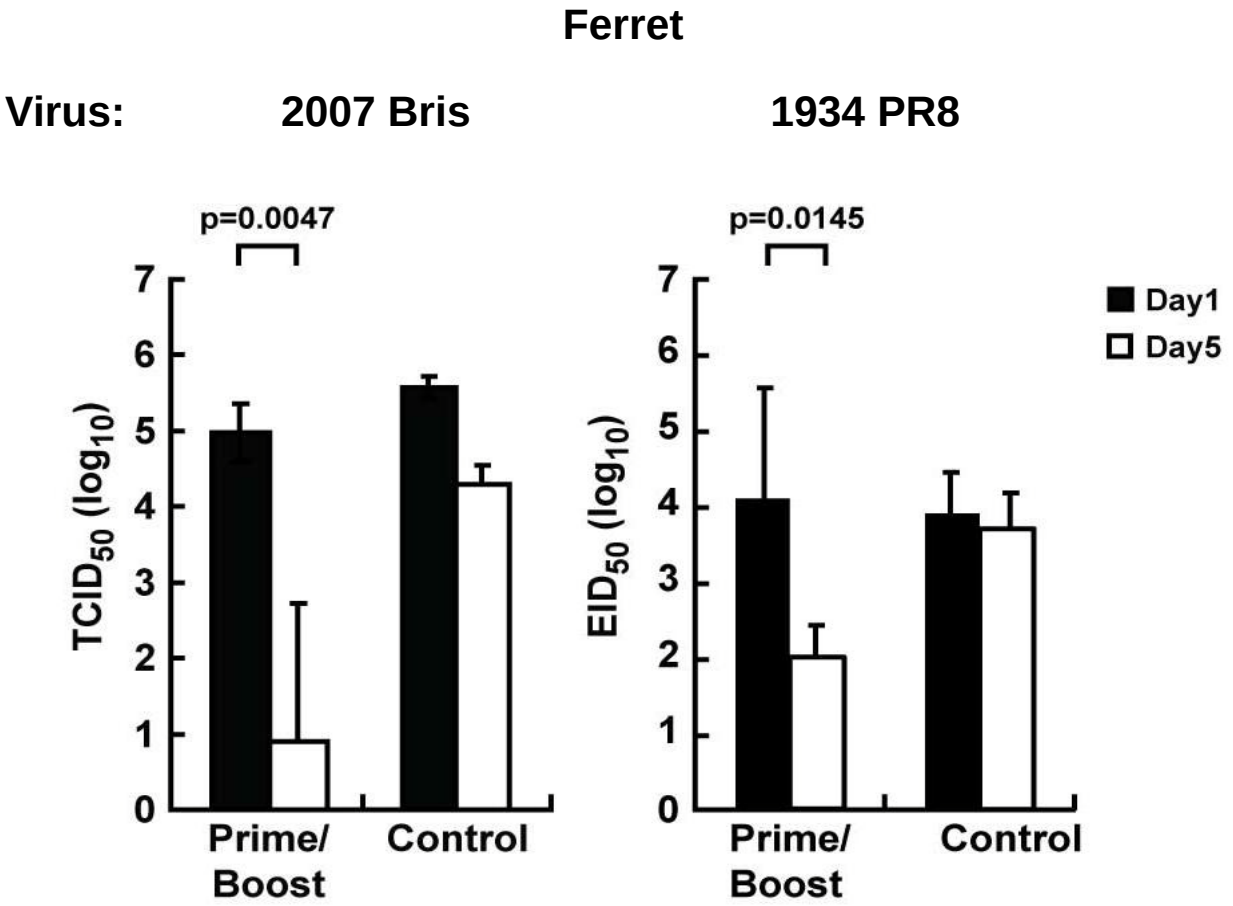
Mouse

Immunization \ Virus	1934 PR8	1986 Sing	1995 Bei	1999 NC	2006 SI	2007 Bris
DNA	0	0	631	879	<100	<100
Vaccine	0	693	677	330	574	0
Vaccine/Vaccine	<100	366	625	2778	851	728
DNA/Vaccine	574	735	3083	>12800	1808	1251

Vaccine strain: H1 1999 New Caledonia HA

Wei et al. (2010)*Science* Epub July 15

Immune Protection Conferred against Viral Challenge in Ferrets



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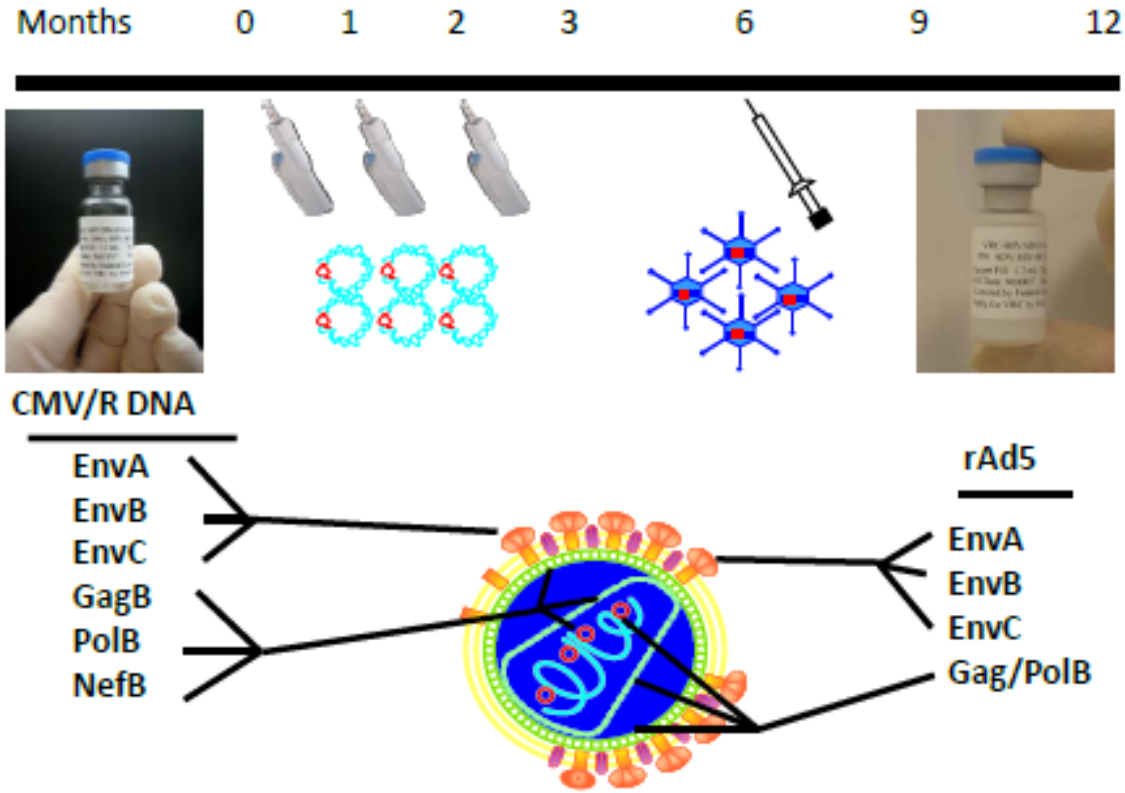
HVTN 505

Phase 2, randomized, placebo-controlled trial to evaluate the safety and effect on post-HIV acquisition viremia of a multiclade HIV-1 DNA plasmid vaccine followed by a multiclade HIV-1 recombinant adenoviral vector vaccine in HIV-uninfected, adenovirus type 5 neutralizing antibody negative, circumcised men and male-to-female (MTF) transgender persons, who have sex with men



HVTN 505: Schedule and Endpoints

		Prime			Boost
Study Groups	**N**	**Day 0**	**Wk 4**	**Wk 8**	**Wk 24**
Vaccine	**675**	**DNA**	**DNA**	**DNA**	**rAd5**
Placebo	**675**	**PBS**	**PBS**	**PBS**	**FFB**

What will we learn at primary analysis?

45 HIV infection endpoints

- 90% power to detect 1.0 $\log_{10}$ reduction in plasma VL
- 80% power to detect 57% reduction in acquisition

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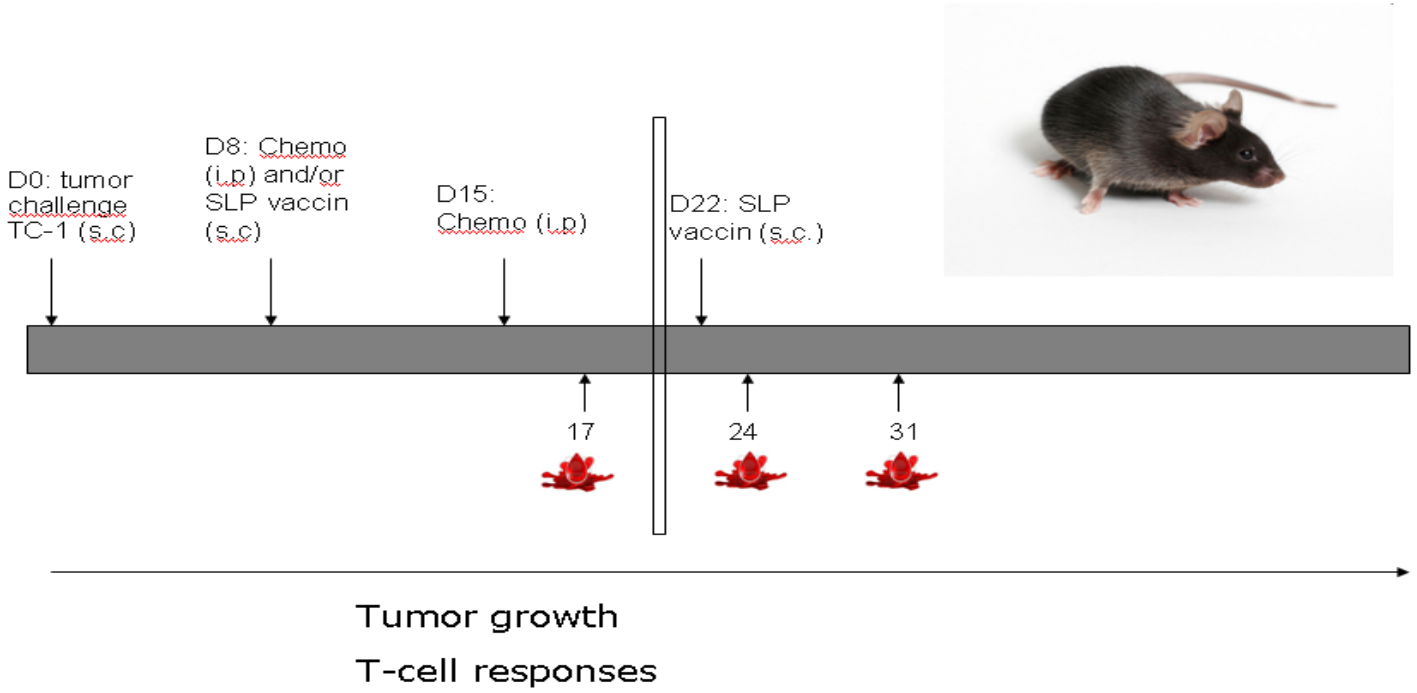
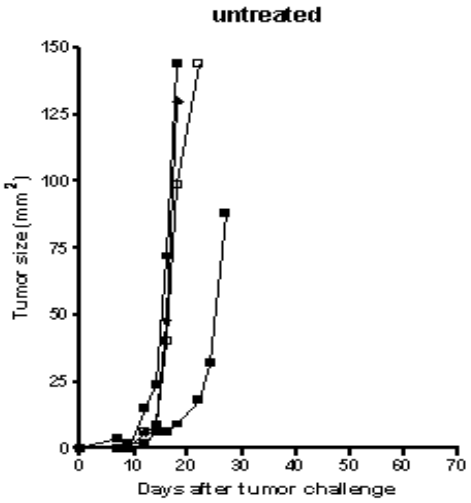
Chemo-immunotherapy model in B6 mice bearing HPV-16+ TC-1 tumors (C. Melief- Amsterdam)

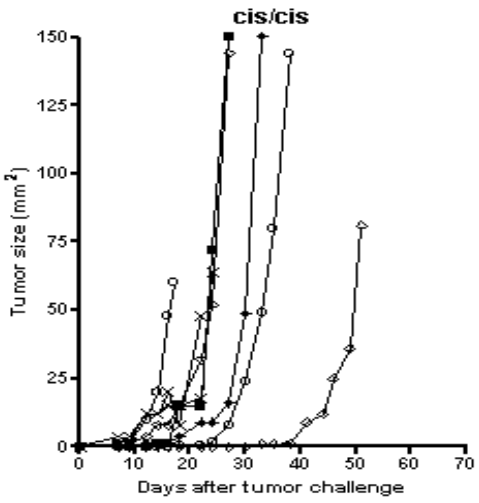


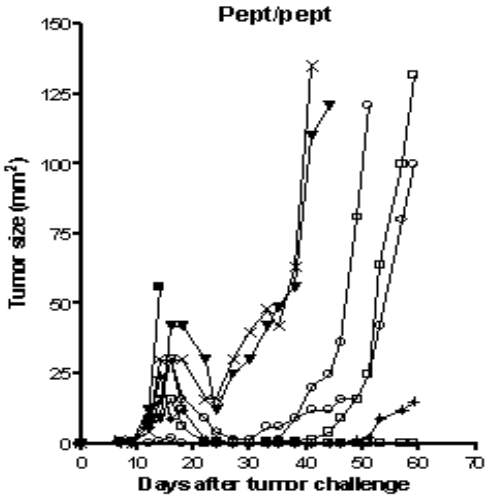
- TC-1 tumor → C57BL/6 tumor cell line expressing HPV-16 E6 and E7 protein
- SLP vaccine → 35-mer long peptide (E7 43-77) containing a Tc-epitope and a Th-epitope
  - Provided in Montanide ISA-51 (slow release)
  - Prime-boost
- Use of a well-tolerated dose of chemotherapy (no weight loss)

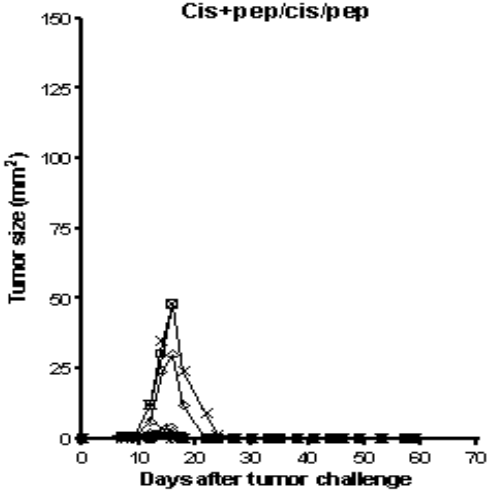
Results - tumor growth

(C. Melief- Amsterdam)









Combination Components in Vaccines

1. **Vectors/Delivery Platforms**

   --heterologous prime-boost immunization elicits qualitatively different immune responses that enhance efficacy.

Such regimens with combination vectors stimulate qualitatively different immune response for experimental AIDS and influenza vaccines

2. **Inserts/Genes**

   --combinations of inserts in the same or different vector platforms increase the breadth of coverage in vaccines.

This approach allows increase breadth of response that improves protection against diverse viral strains.

3. **Combination drug/ab treatment with immune stimulation**

   --confers protection/efficacy not otherwise seen with either agent alone.

Such combinations show efficacy not seen with either one alone.