

Novel Adenovirus Vector-Based Vaccines for HIV-1

Dan Barouch

Beth Israel Deaconess Medical Center

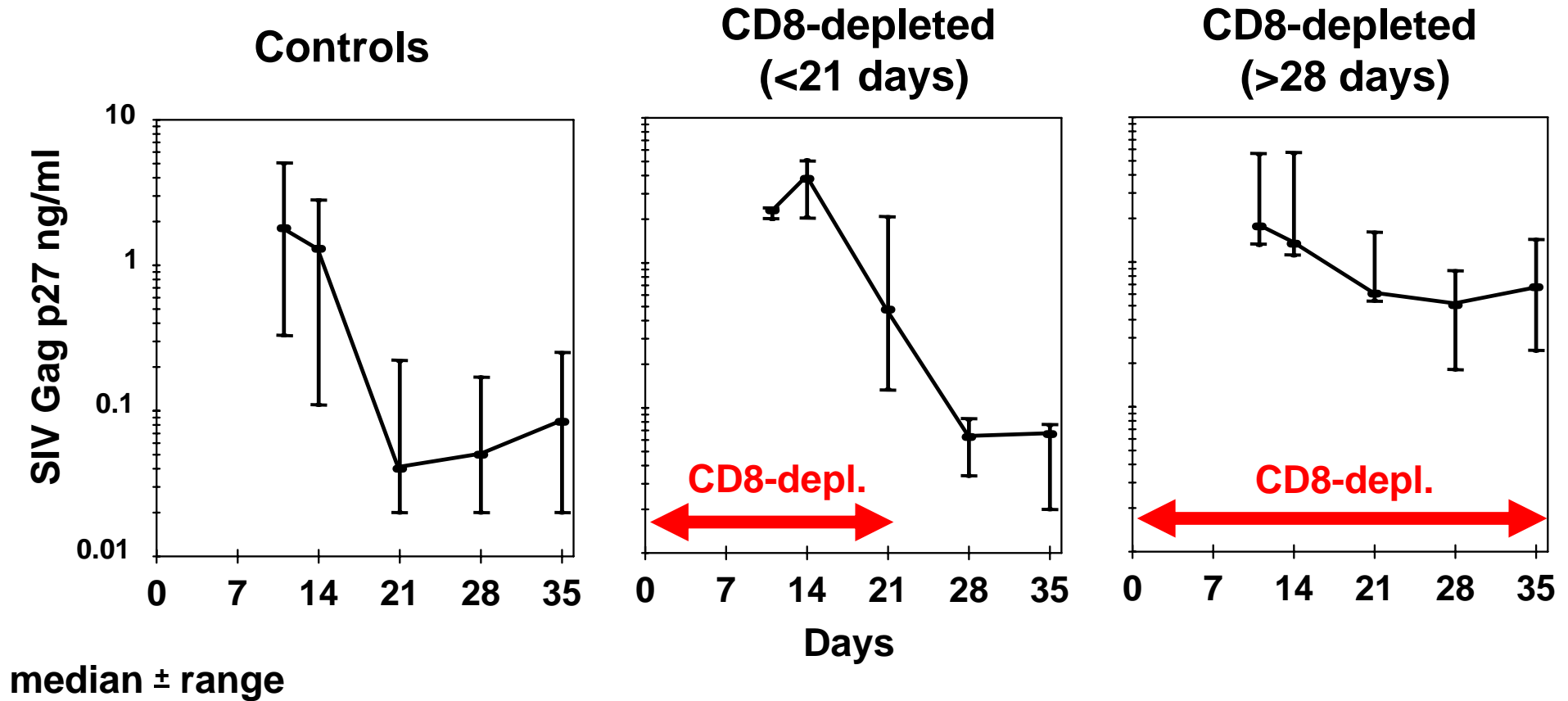
Harvard Medical School

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Current HIV Vaccine Strategies

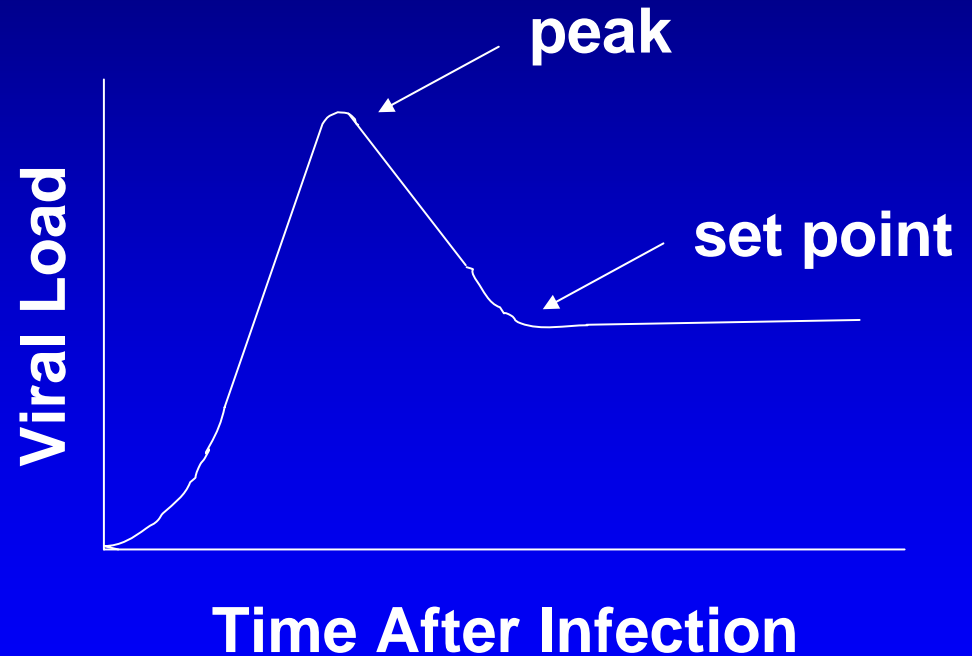
- **Traditional Strategies**
 - live attenuated virus
 - whole killed virus
 - protein subunit
- **Novel Strategies**
 - plasmid DNA vaccines
 - live recombinant vectors

In Vivo Depletion of CD8⁺ T Lymphocytes Prolongs SIV Viremia in Rhesus Monkeys



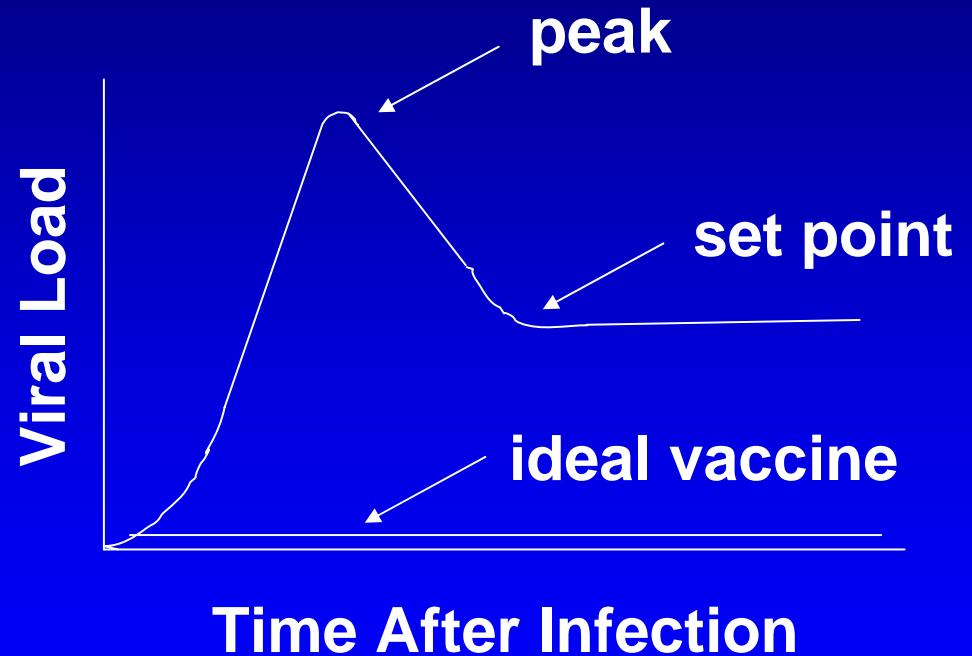
Goals of an HIV-1 Vaccine

- **Protection from infection**
 - Sterilizing immunity
- **Protection from disease**
 - Reduction in setpoint viral loads



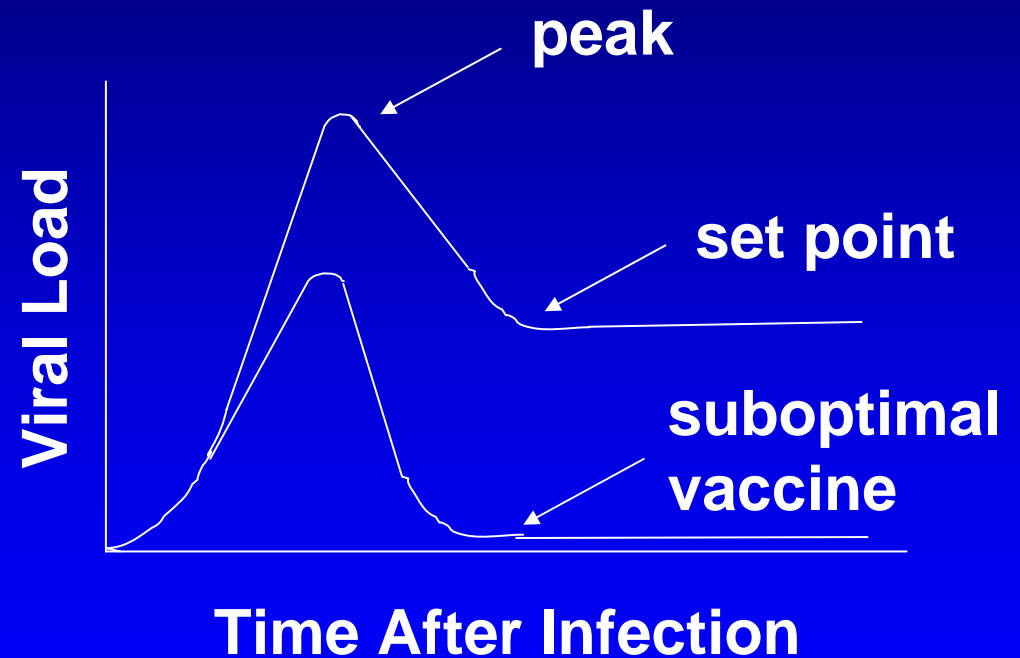
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Replication-Incompetent Recombinant Adenovirus Serotype 5 (rAd5) Vectors

- **Vector comparisons in rhesus monkeys have shown that rAd5 is one of the most immunogenic vaccine vectors for eliciting antigen-specific cellular immune responses**
- **rAd5 vector-based vaccines for HIV-1:**
 - **Elicit potent and durable immune responses**
 - **Induce both systemic and mucosal immune responses**
 - **Pharmaceutical-scale manufacturing capacity**
 - **Lead vaccine candidate currently in phase II trials (Merck, NIH/VRC, HVTN)**

Ongoing Phase II Trials of Recombinant Ad5 Vector-Based Vaccines for HIV-1

- **Merck V520-023 / HVTN 502**
 - Phase IIb study, 3000 participants
 - Manufacturer: Merck Research Laboratories
 - Endpoint: Limited vaccine efficacy
 - rAd5 single modality regimen
 - Clade B Gag, Pol, Nef
- **HVTN 204**
 - Phase IIa study, 480 participants
 - Manufacturer: NIH Vaccine Research Center (VRC)
 - Endpoints: Safety and immunogenicity
 - DNA prime, rAd5 boost regimen
 - Clade A/B/C Env, clade B Gag-Pol

Pre-Existing Immunity to Adenovirus Serotype 5

- **High prevalence of pre-existing immunity to Ad5 in human populations, particularly in the developing world**
- **Major limitation of current rAd5 vector-based vaccines**
- **Ad5 Seroprevalence:**
 - **U.S., Western Europe: 30-50% (low to moderate titers)**
 - **Sub-Saharan Africa, Southeast Asia: 80-95% (high titers)**
- **Blunts rAd5 vaccine immunogenicity in both preclinical and clinical studies and may limit their clinical utility**

Development of Novel Adenovirus Vectors

- **Goal is to develop novel rAd vectors with:**
 - **Immunogenicity of rAd5 vectors**
 - **Serologic profile of rare Ad serotypes**
 - **Large-scale manufacturability**
- **Two key strategies identified:**
 - **Novel serotype rAd vectors**
 - **Novel chimeric rAd vectors**

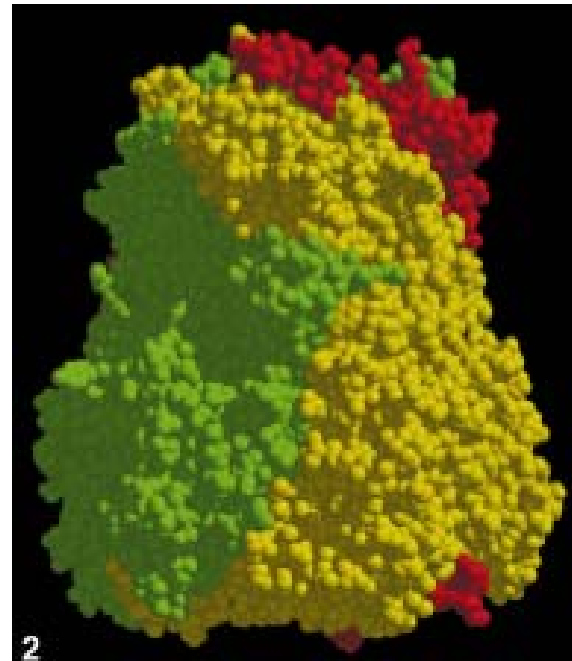
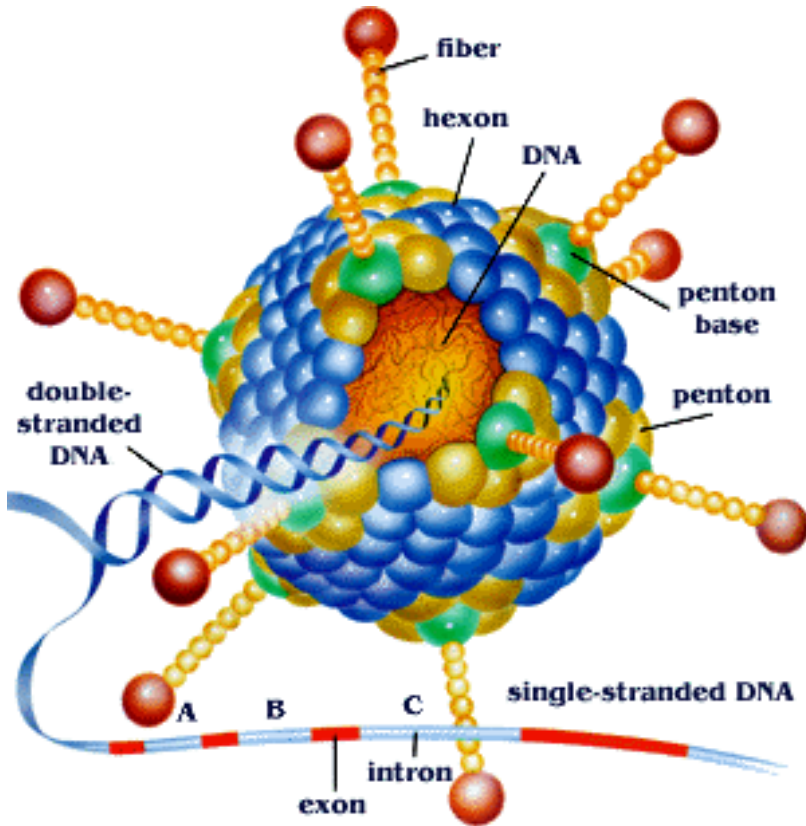
Development of Modified rAd5 Vectors Engineered to Evade Pre-Existing Anti-Ad5 Immunity

- Apart from pre-existing immunity, rAd5 appears to be an excellent vaccine vector (stability, yield, immunogenicity, manufacturability, regulatory affairs, safety profile)
- Objective:
 - To make the minimal changes in rAd5 required to evade pre-existing anti-Ad5 immunity
- Strategy:
 - Map targets of dominant Ad5-specific NABs
 - Replace dominant NAb epitopes with corresponding regions from rare Ad serotypes
 - Produce and characterize novel chimeric rAd vectors

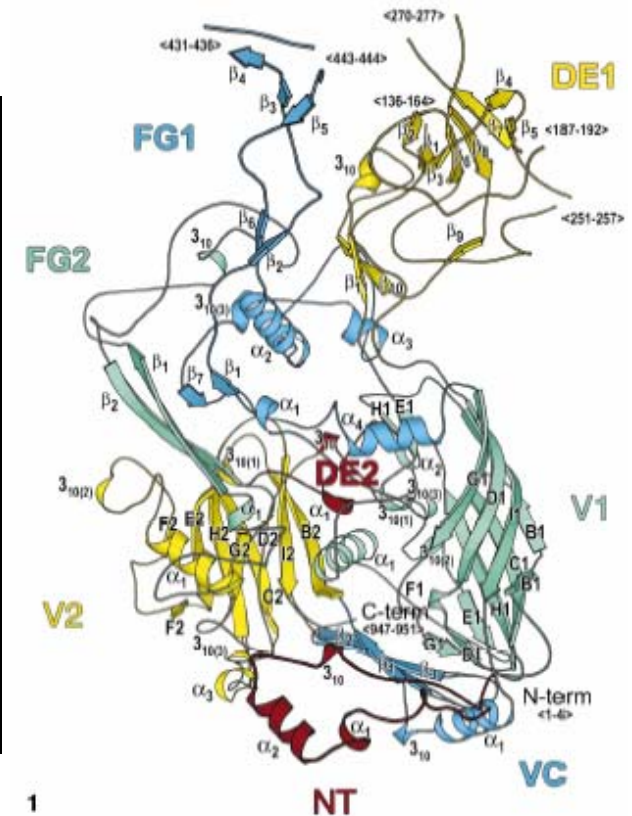
Construction of Hexon-Chimeric rAd5 Vectors

- **Dominant Ad5 NAbs are directed primarily against the Ad5 hexon major capsid protein**
- **However, complete hexon swaps between Ads from different subgroups have proven limited by viral structural constraints**
- **Interestingly, hexon sequence variability among Ad serotypes concentrated in 7 short hypervariable regions (HVRs)**
- **Aim: To assess the virologic and immunologic properties of a chimeric rAd5 vector containing the hexon HVRs of Ad48**

Homotrimeric Double Barrel Structure of Ad5 Hexon



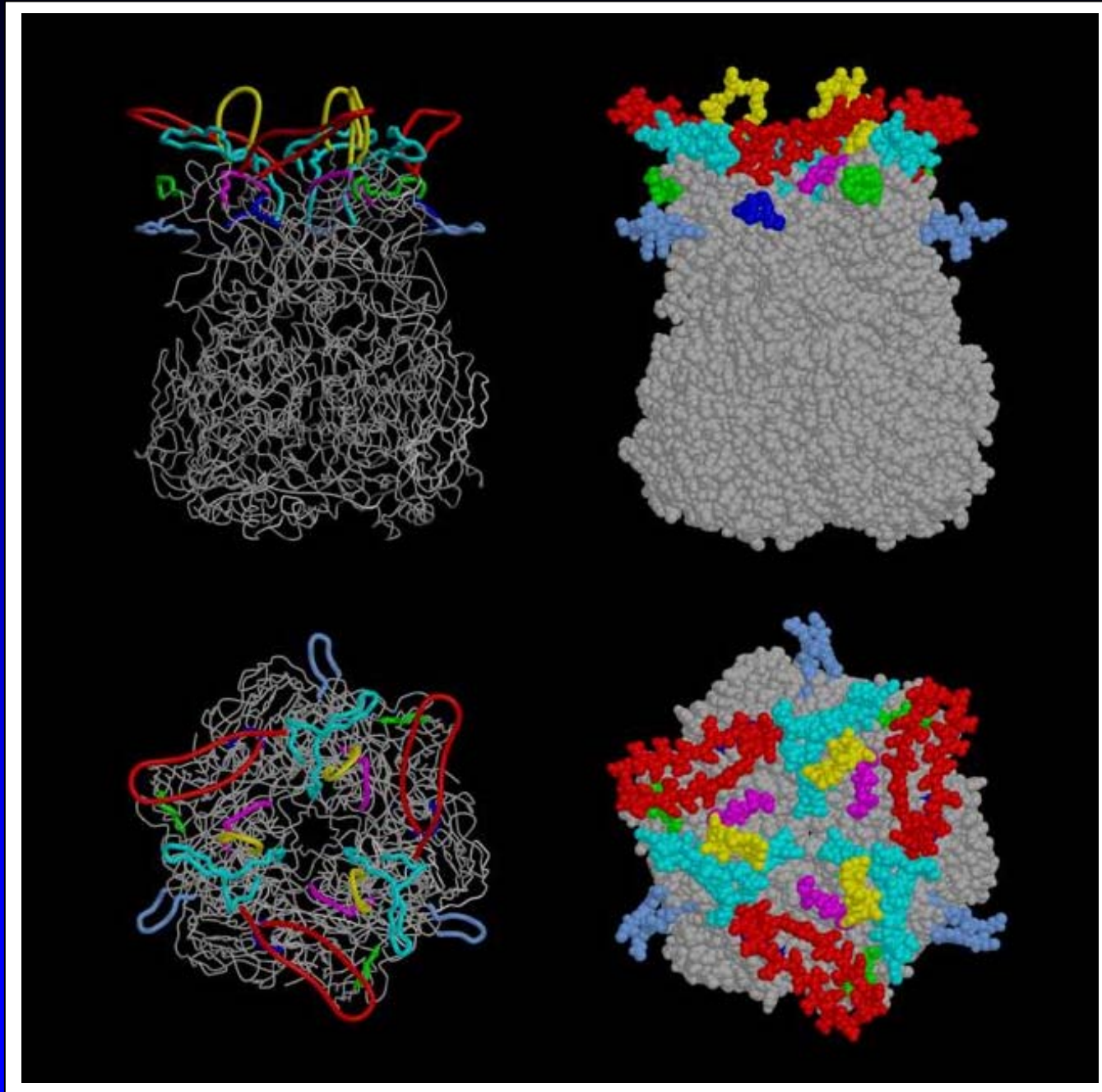
Hexon Trimer



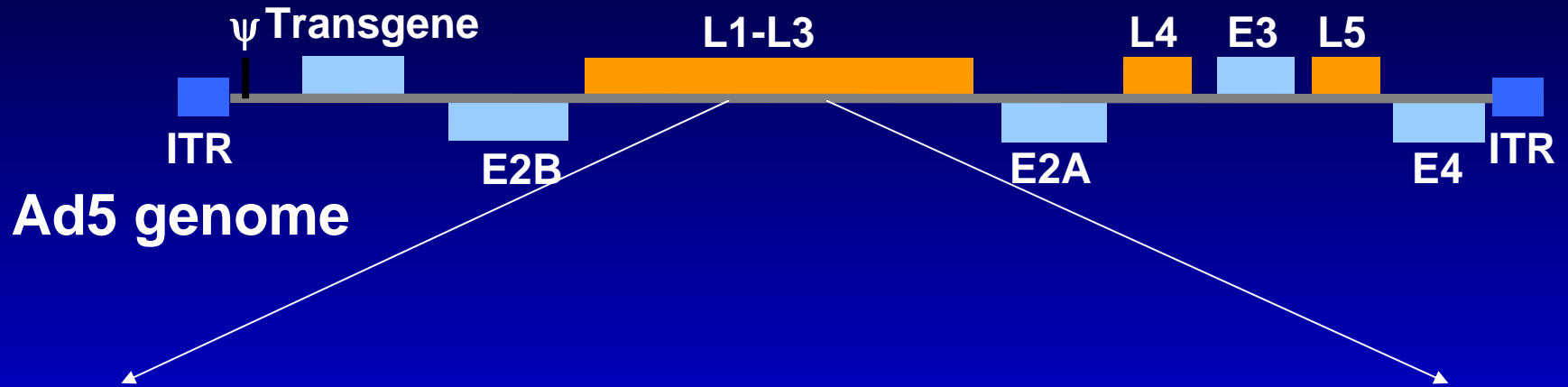
Hexon Monomer

**The 7 Hexon
HVRs (Color)
Form the Majority
of the Solvent-
Exposed Surface
of the Ad5 Hexon
Capsid Protein**

- HVR1 = Red**
- HVR2 = Green**
- HVR3 = Magenta**
- HVR4 = Light Blue**
- HVR5 = Yellow**
- HVR6 = Blue**
- HVR7 = Cyan**



Hexon HVR-Chimeric rAd5 Vectors



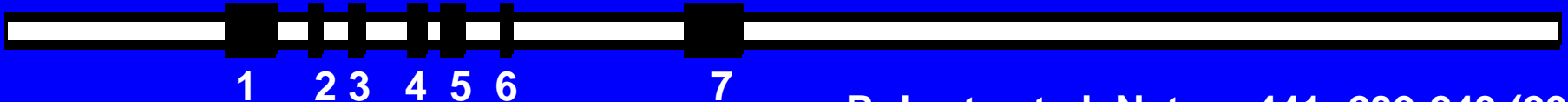
Ad5 Hexon



Ad5HVR48(1) Hexon

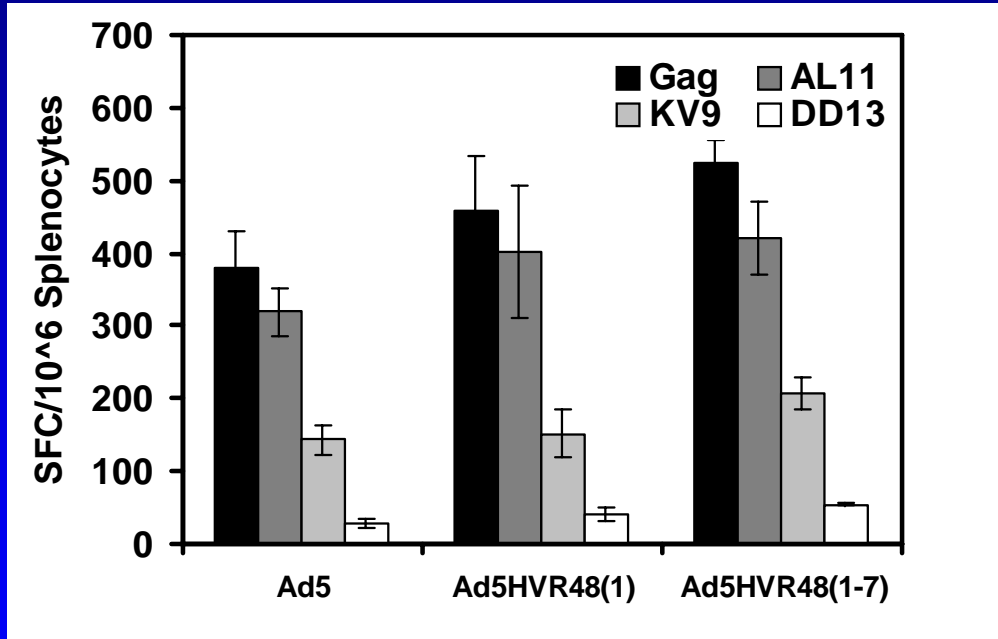


Ad5HVR48(1-7) Hexon

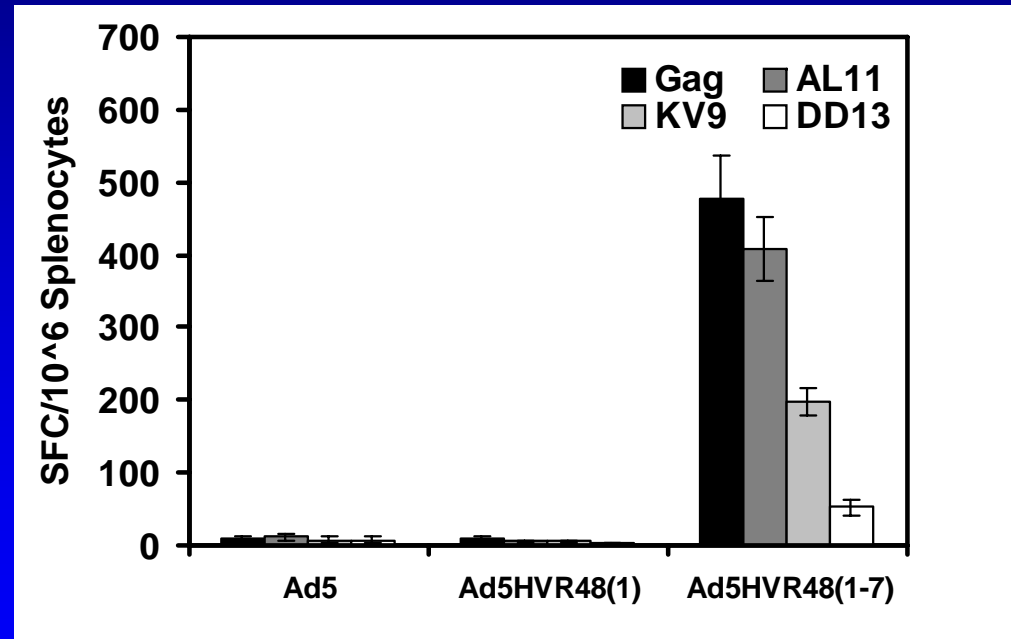


Chimeric rAd5HVR48(1-7)-Gag Vector Effectively Circumvents Anti-Ad5 Immunity in Mice

Naive



Anti-Ad5 Immunity



Conclusions

- **rAd5 vectors may be limited by high levels of anti-Ad5 immunity in the developing world**
- **Novel serotype/chimeric rAd vectors can be constructed with:**
 - **Immunogenicity of rAd5 vectors**
 - **Capacity to circumvent anti-Ad5 immunity**
 - **Large-scale manufacturability**
- **We propose that novel rAd vectors should be advanced into clinical trials as candidate HIV-1 vaccines:**
 - **To replace rAd5 vectors as single modality vaccines**
 - **To be used with rAd5 vectors in prime-boost regimens**

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