

**MODIFICATION OF AD5 HEXON  
HYPERVARIABLE REGIONS CIRCUMVENTS  
PRE-EXISTING AD5 NEUTRALIZING  
ANTIBODIES**

**Joe Bruder**

**ASGT 2007**

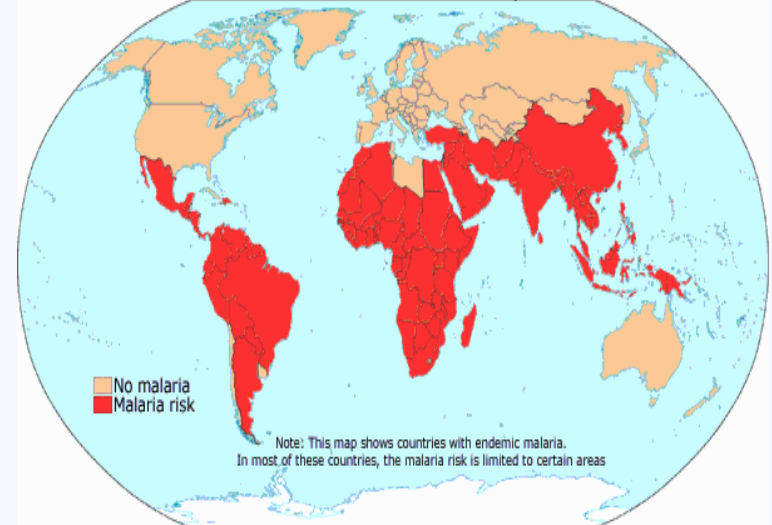
**GENVEC**

# MALARIA World Health Problem

**>1 million deaths/year**  
**No licensed malaria vaccine**  
**Drug resistance spreading**



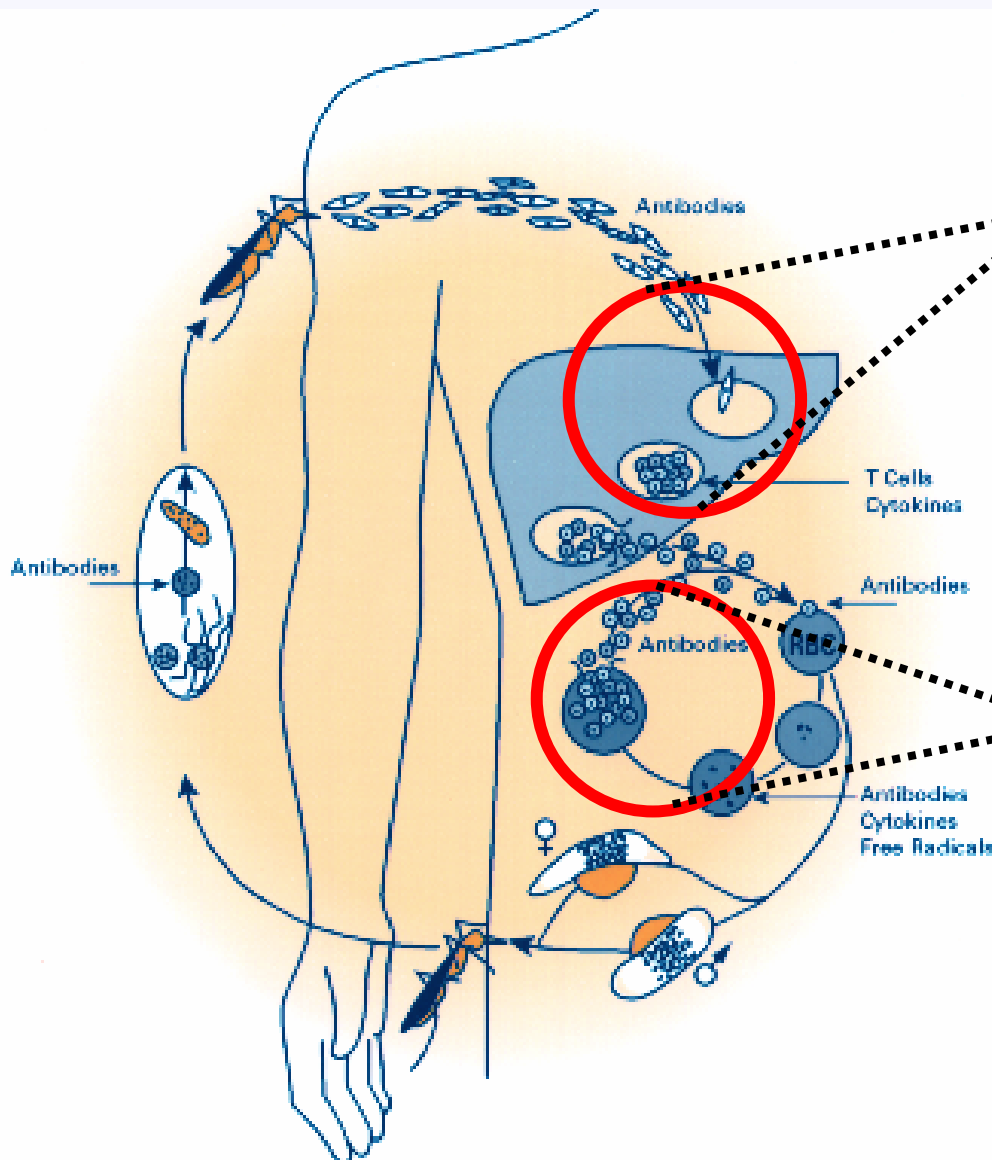
**Malaria Endemic Countries, 2000**



## **Product Opportunities**

- Military Vaccine
- Travelers Vaccine
- Vaccine for Developing World

# T Cells and Antibodies Can Provide Protection Against Malaria



## Liver-stage Vaccine

Vaccine Goal: Induce Protective

T-cell Response

Antigens: *PfCSP*, *PfLSA*, *PfAg2*

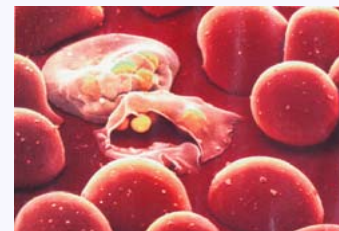


## Blood-stage Vaccine

Vaccine Goal: Induce Protective

Antibody Response

Antigens: *PfAMA1*, *PfMSP1-42*



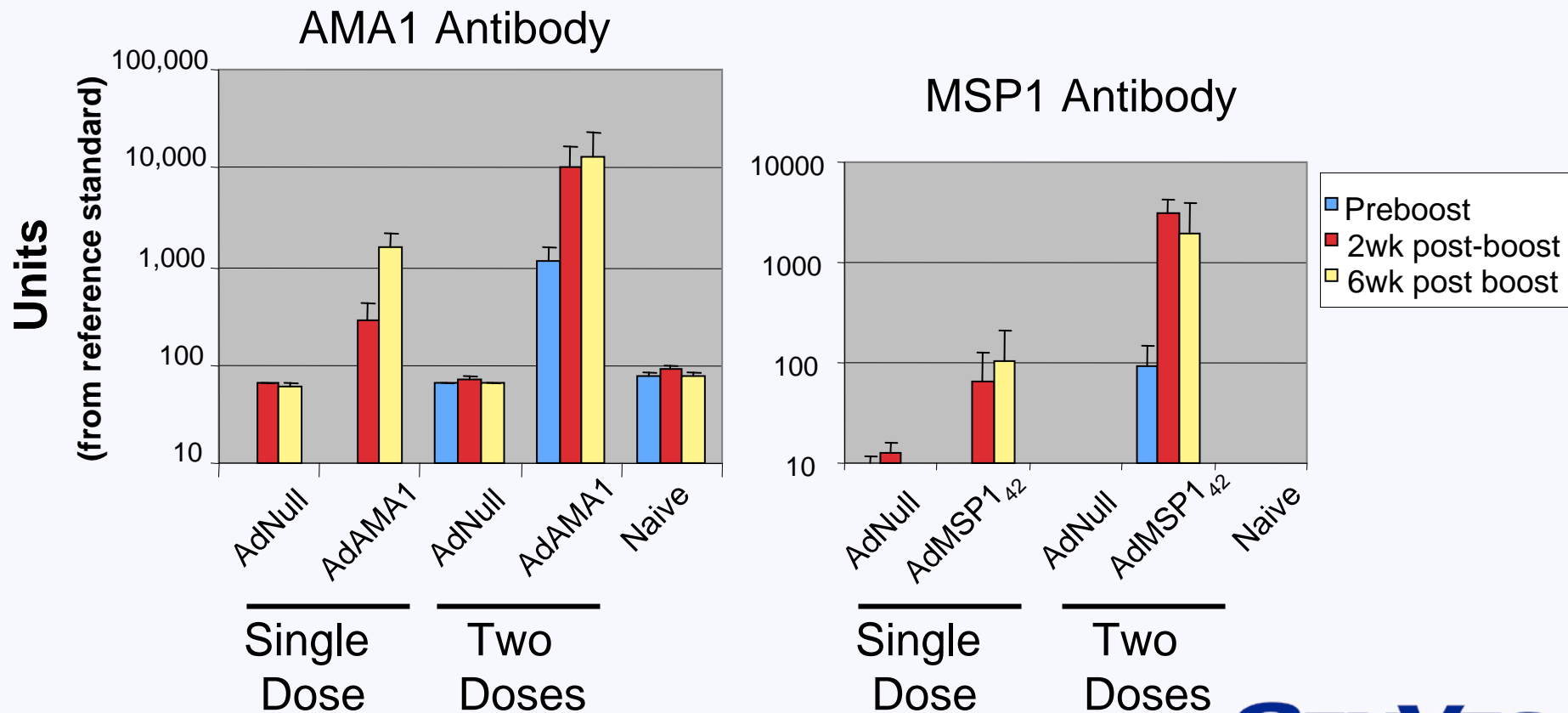
**GENVEC**

# Ad5-based Malaria Vaccine

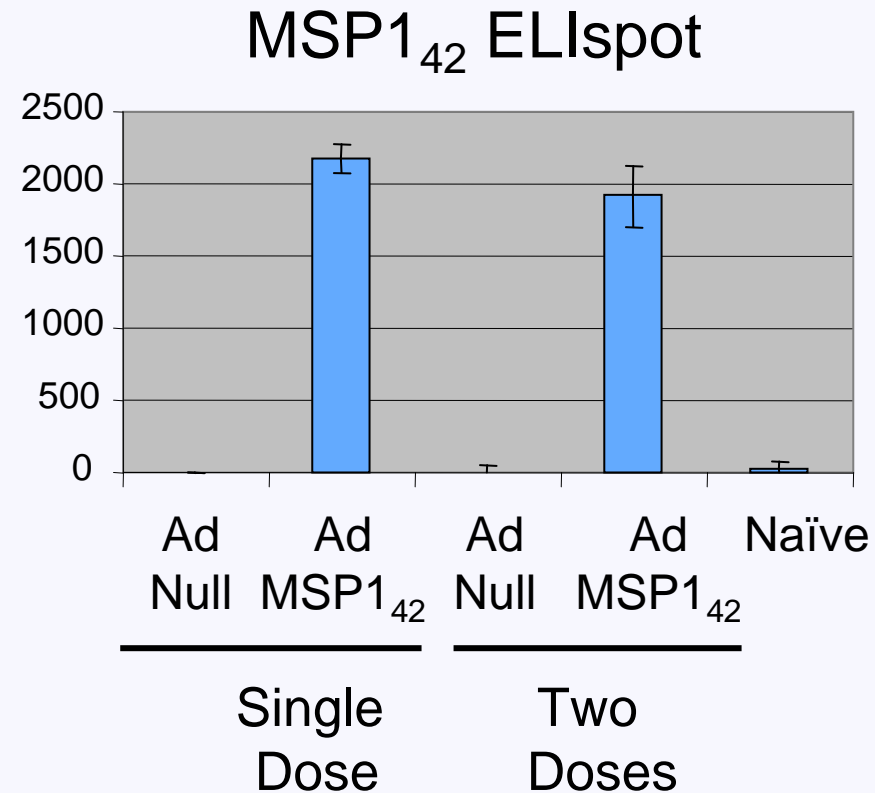
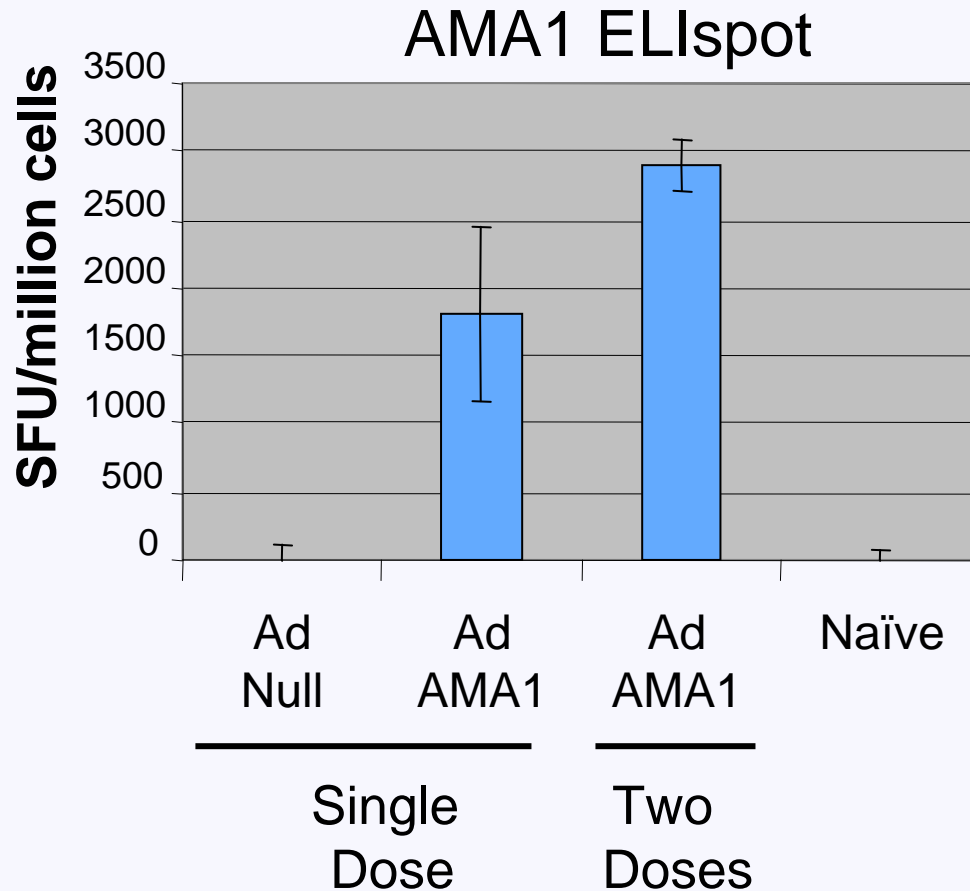
- Ad5 vectors induce potent immune responses to malaria antigens in animal models
  - Robust T cell responses in mice (Poster #153)
  - High titer functional antibody responses in rabbits (Poster #148)
- Phase 1/2a Clinical is trial under way
  - Safety
  - Immunogenicity
  - Ad5 prime- Ad5 boost
  - Protection from challenge



# Antibody Responses are Increased by Homologous Ad5 Boost in Mice



# Inefficient Boosting of T Cell Responses by Homologous Ad5 Boost in Mice

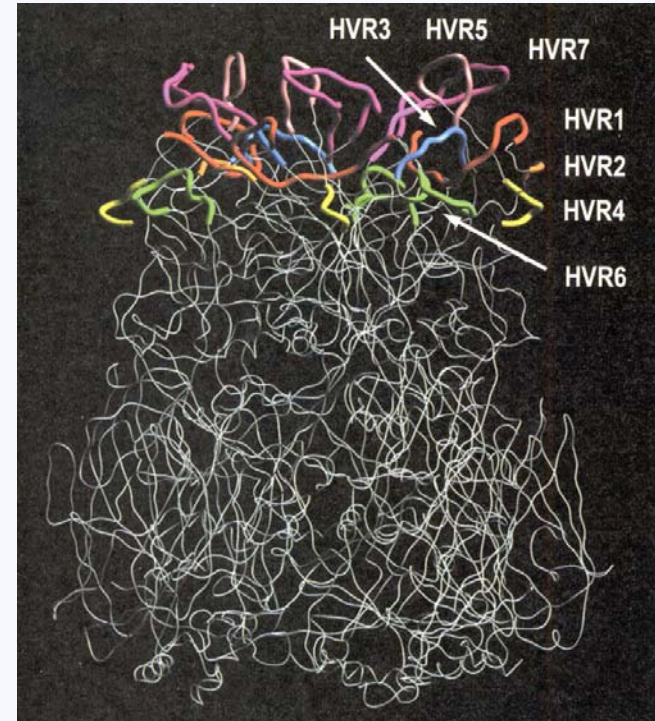
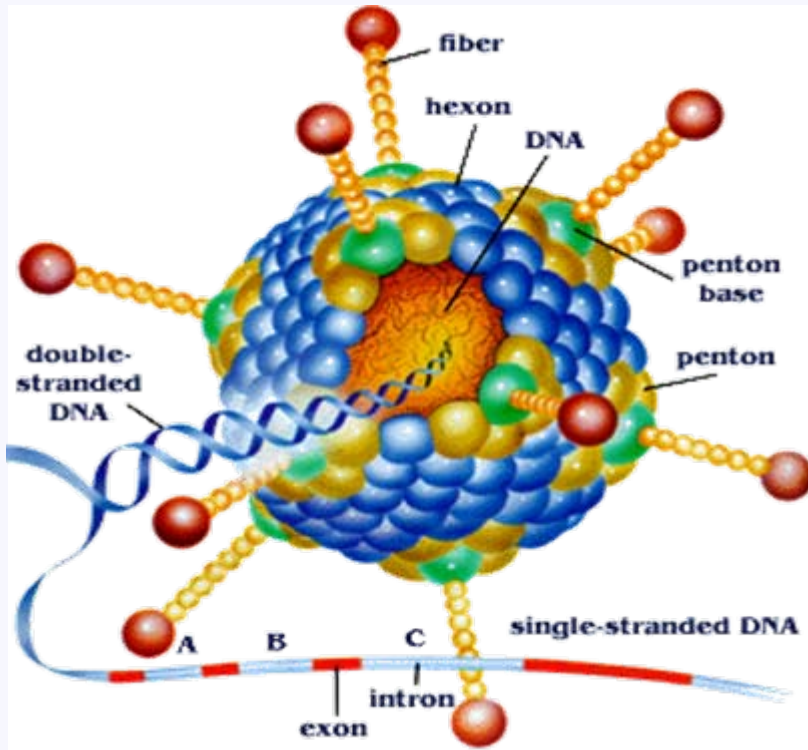


# **Ad5 Neutralizing Antibodies**

## **Do They Limit Ad5-based Vaccines?**

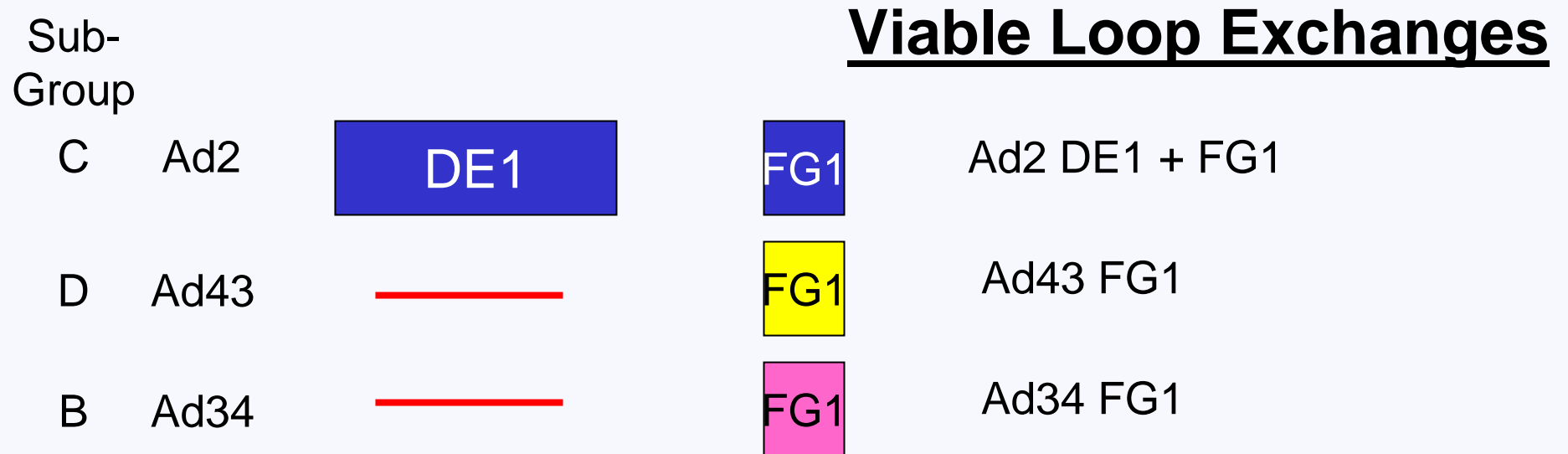
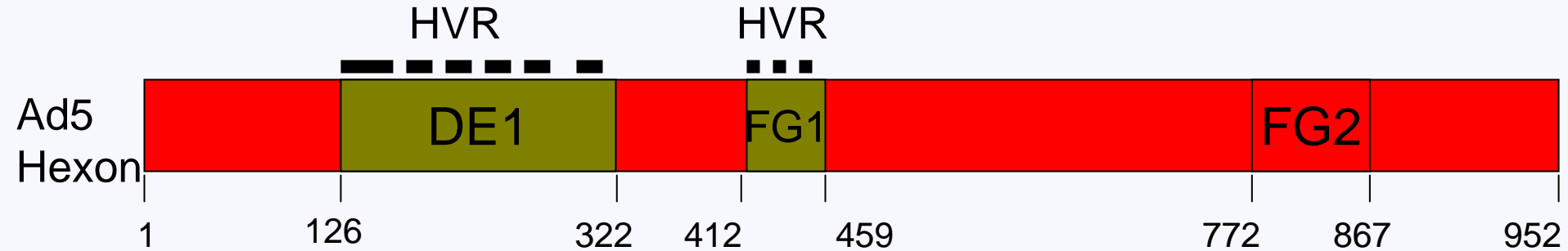
- **Pre-existing Ad5 NAB (a perceived problem)**
  - Prevalent in human populations
  - Reduced T cell responses in animal models
- **Human data from HIV trials**
  - Robust T cell and antibody responses even in volunteers with high titers of Ad5 NAB, especially in DNA prime adenovector boost
  - Trend toward a reduction in T cell responses in volunteers with high titers of Ad5 NAB, in single dose Ad5 trial

# Hexon Modifications to Avoid Pre-existing Neutralizing Antibody

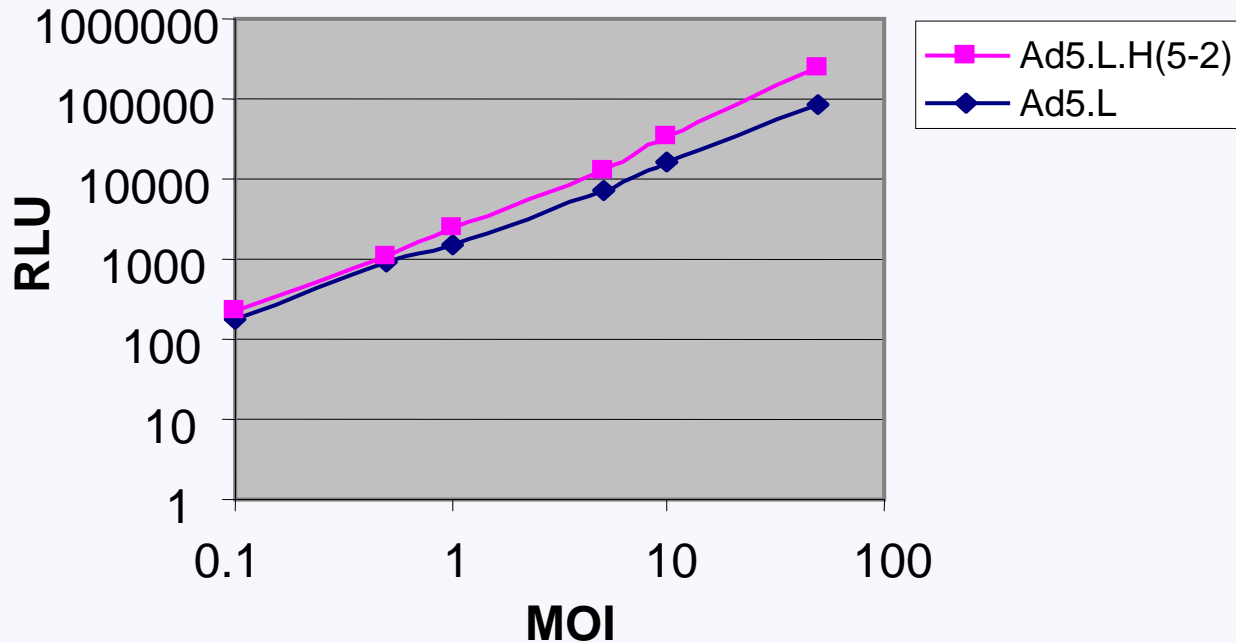
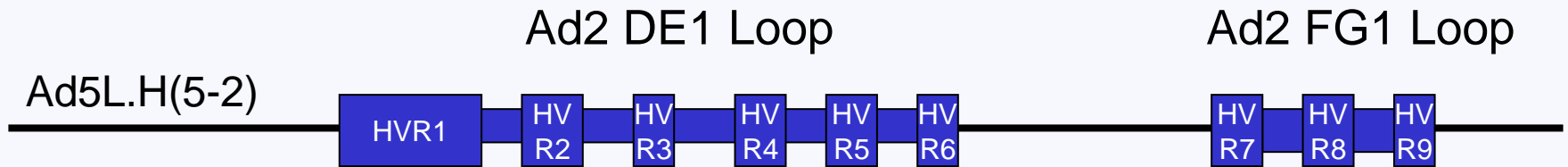


- The HVR on hexon are the main determinants of NAB
- The HVR can be modified to circumvent pre-existing NAB

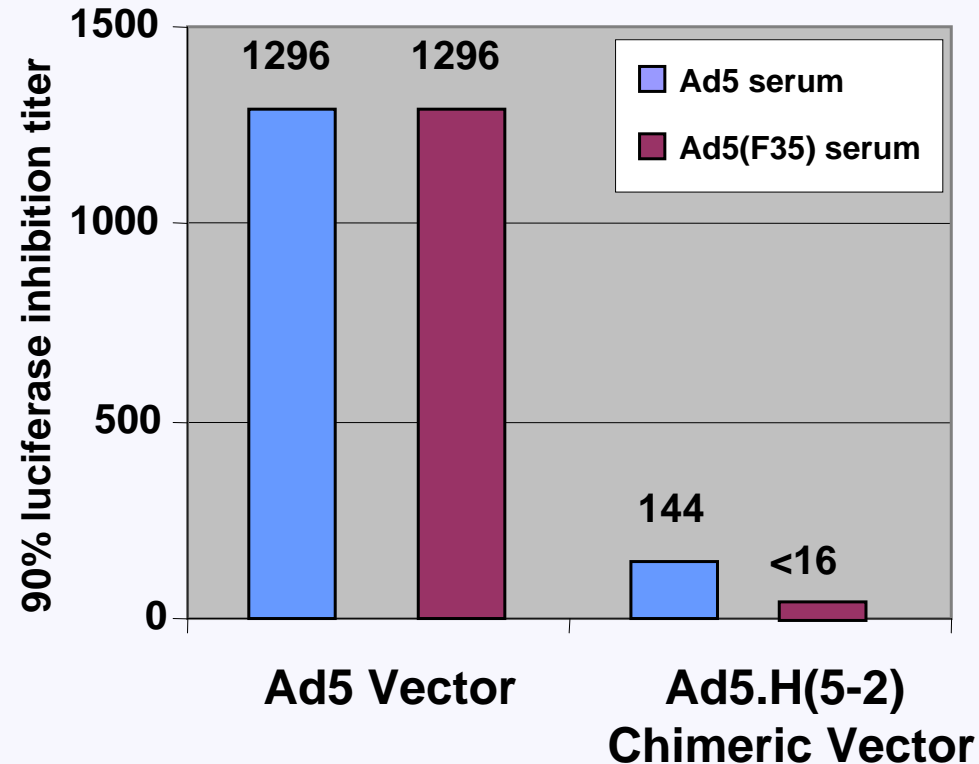
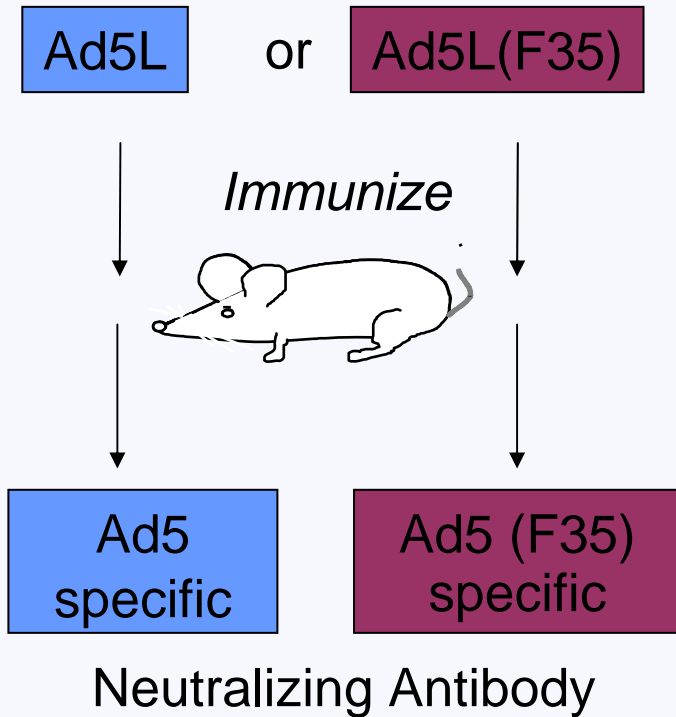
# Generation of Ad5 Vectors with Chimeric Hexons



# Good Transgene Expression by Chimeric Ad5.H(5-2) Vector

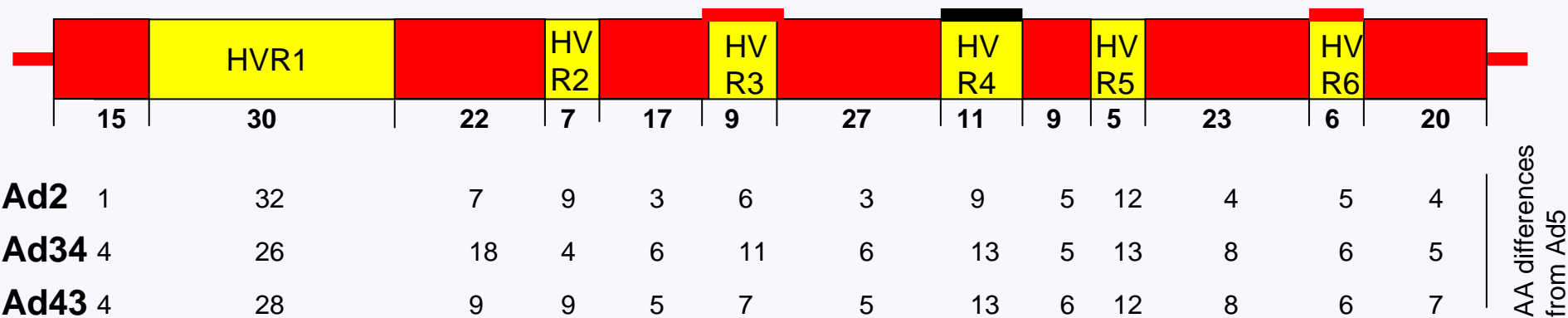


# Chimeric Ad5.H(5-2) Vector is Not Efficiently Neutralized by Ad5 NAB



**POC that a hexon-modified vector can avoid Ad5 NAB**

# Why was the Ad2 DE1 Loop Substitution Tolerated and the Ad43 and Ad34 Substitutions Not Viable?



- HVR are similarly divergent among serotypes
- Regions flanking HVR are more similar between Ad2 and Ad5 than they are between Ad34 or Ad43 and Ad5
- Hypothesis – HVR flanking regions are necessary for the assembly of viable capsids

# Generation of Ad5 Vectors Containing the Ad43 Hexon Hypervariable Regions

Vector  
Viability

DE1 Loop

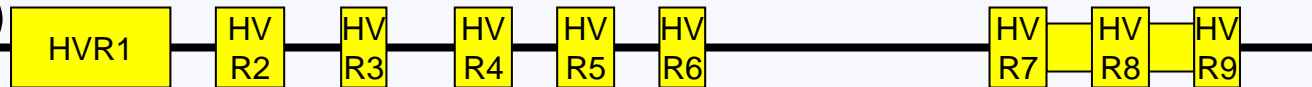
FG1 Loop

AdH(5-43)



-

AdH(5-43m)



+

AdH(5-43s)

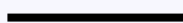


+

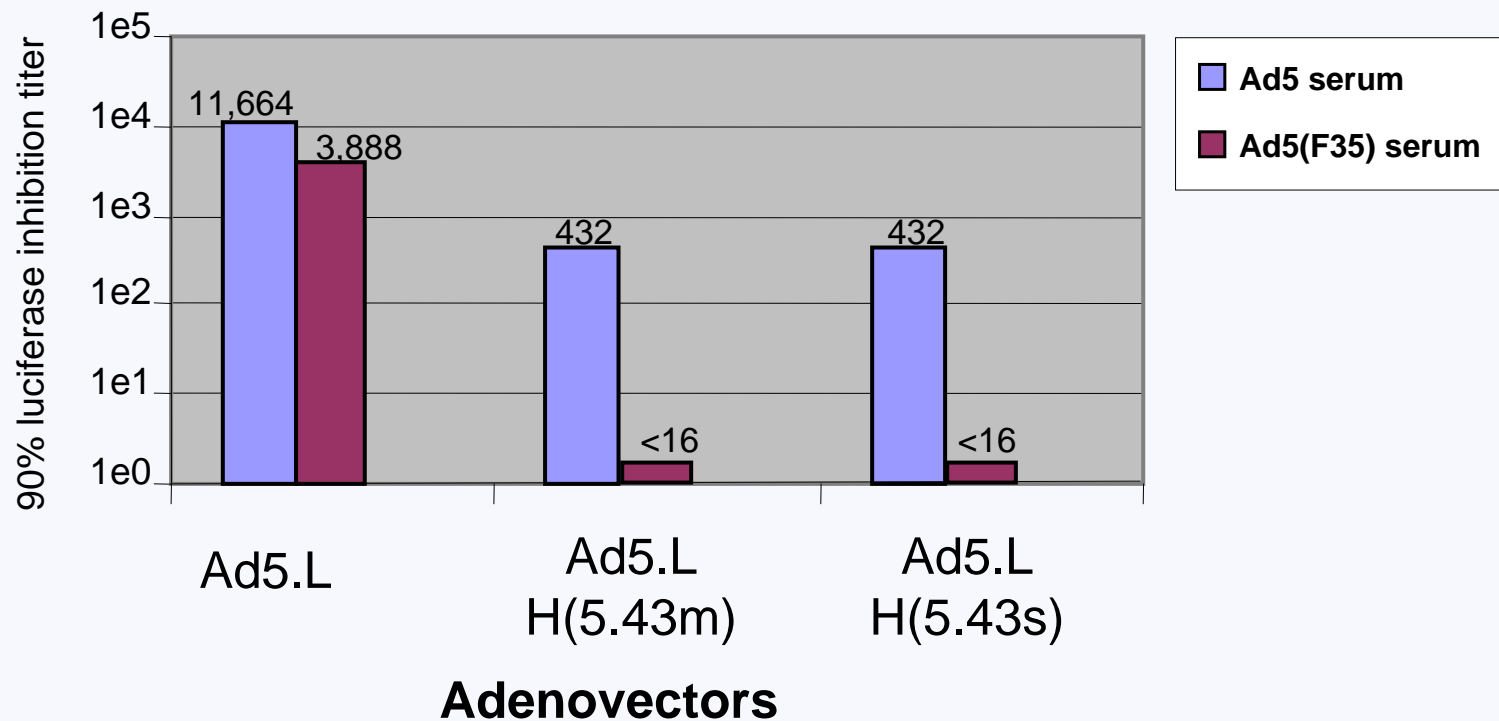
Ad43



Ad5



# AdH(5-43) Chimeric Vectors Are Not Neutralized Efficiently by Ad5 NAB



# Conclusions

- **Ad5-Ad5 prime-boost regimen**
  - Clinical data are expected later this year for malaria vaccine
  - Good boosting of antibody responses in mice
  - Poor boosting of T cell responses in mice
- **Hexon-modified vectors**
  - We have generated vectors with HVR from Ad43 and they are not neutralized efficiently by Ad5 NAB
  - These vectors are expected to have Ad5 like vaccine capability and to circumvent preexisting Ad5 NAB
  - They may have advantages in prime-boost regimens

# Key Contributors



- Elena Semenova
- Charlie Thomas
- Jennifer Tseng
- Jason Gall
- Rick King



- Denise Doolan
- Noelle Patterson
- Jennifer Cockrill
- Maureen Stefaniak
- Keith Limbach
- Tom Richie



- Emily Long
- Sheng Lee
- Walter Brandt
- Filip Dubovsky