

**New human rabies  
vaccines in the pipeline  
- experimental use of a  
recombinant rabies-  
simian adenovirus  
vaccine**

H. Ertl, Wistar Institute,  
Philadelphia, PA, USA

# Rabies – a neglected fatal disease



Kills >55,000 humans each year



99% of cases are transmitted by dogs



40% of patients are children < 14 years of age



Efficacious vaccines for pre- or post-exposure vaccination are available but underutilized



More common pre-exposure vaccination especially of children in highly endemic areas would save lives (as shown in Peru) but is not cost-effective

## Cost-effectiveness of rabies pre-exposure vaccination



~ Current cost of post-exposure vaccination

USA: \$3,000 – \$40,000 (i.m. regimen + HRIG)

Developing countries: \$30 (i.d. regimen + ERIG)



~ Dog exposure rates (licks, bites per 100,000 residents per year)

Kenya: 336, Iran: 600, Uganda: 58, Thailand: 500, travelers to South East Asia: 4300

(caveat – data are outdated)



Pre-exposure vaccination of children would be cost-effective with an exposure incidence of 2-30% depending on the cost of the post-exposure vaccine regimen.



Pre-exposure vaccination of children would be cost-effective with a vaccine regimen that costs \$1-3 (taking the need for a boost after exposure into account).



# The 'ideal' rabies vaccine for pre-exposure vaccination of children

- As safe and efficacious as current vaccines
- Costs <\$3
- Single dose regimen
- Induces sustained titers virus neutralizing antibodies
- Induces a robust memory B cells response that can be recalled decades later by a single dose of the traditional vaccine

# New rabies vaccines – clinical trials

mRNA vaccine –  
multiple dose regimens –  
very poor efficacy

Pika vaccine – TLR-3  
agonist adjuvanted  
rabies vaccine: higher  
immunogenicity given 3x  
(2-2-1) IM regimen than  
Rabipur given IM 4 times

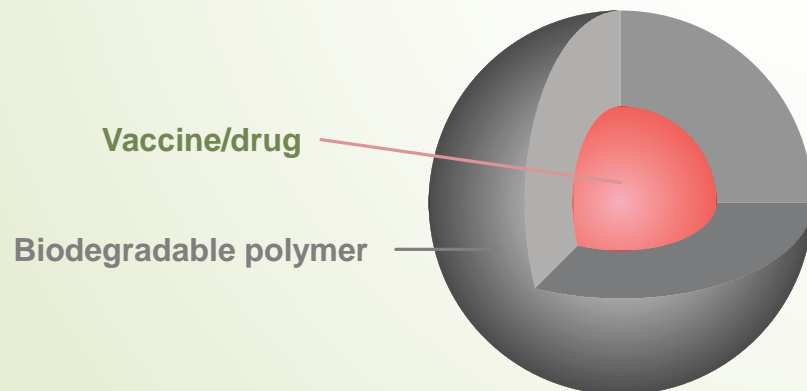
Glycoprotein  
nanoparticle vaccine –  
nothing has been  
published

# New rabies – pre-clinical

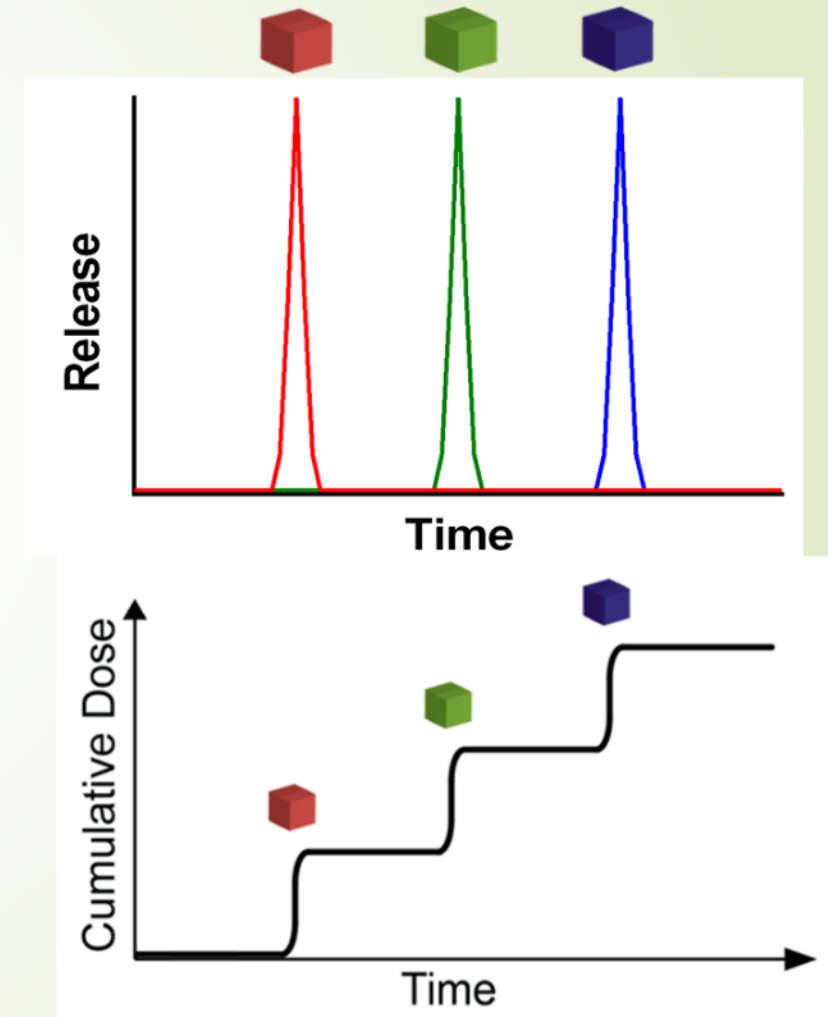
- Genetically attenuated rabies virus
- Inactivated genetically modified rabies virus
- Novel release systems
  
- Genetic vaccines – suited for pre but not post-exposure vaccination
  - DNA vaccines
  - Viral vector vaccines, e.g., poxvirus or replication-defective adenovirus vectors

# Single Injection Vaccine Technology by Particles for Humanity, PBC

- Developed at MIT's Langer Lab
- Particles molded from FDA-approved polymer
- Unique fabrication seals the vaccine in the core
- A single injection releases a series of vaccine doses at required timepoints
- Aims to match rabies dosing regimen with one shot



**Core-shell micromolded particles**



# Replication-defective chimpanzee adenovirus vectors



Based on chimpanzee serotype C68



Expressed the rabies virus glycoprotein of ERA



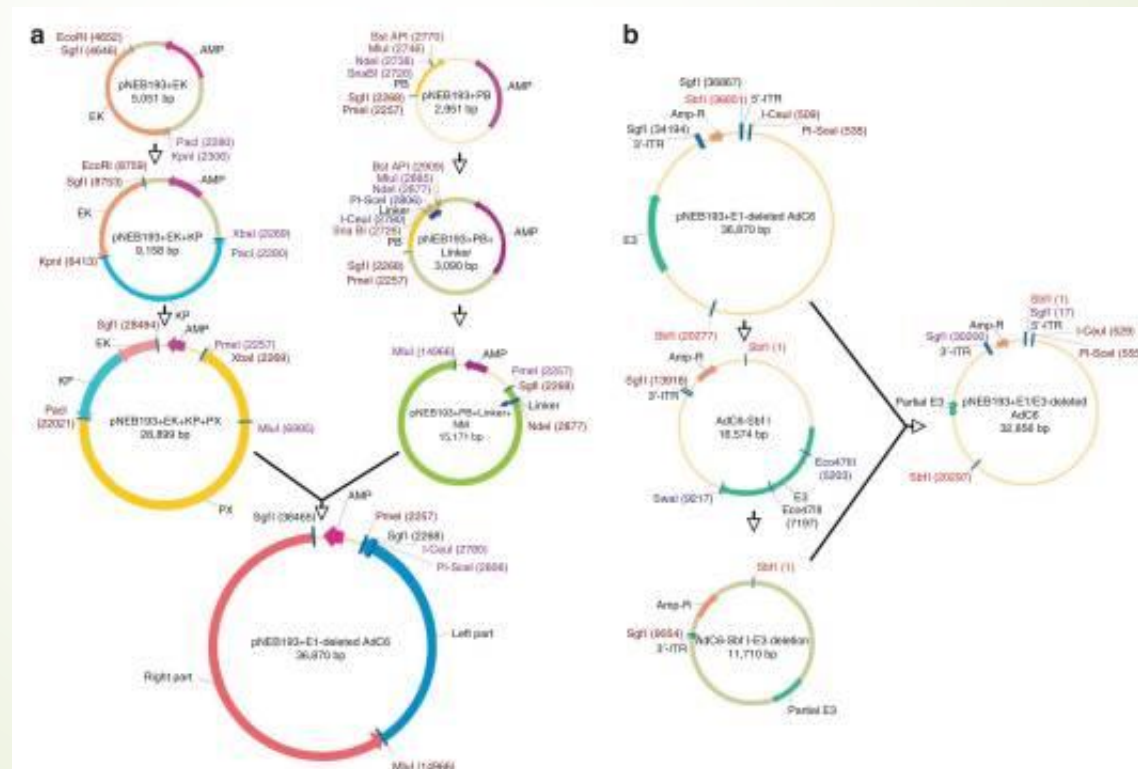
Testing in mice and nonhuman primates confirmed the vector's immunogenicity and efficacy after a single dose



Oxford University (PI S. Douglas): Phase I trial to start in Q4 of 2019.

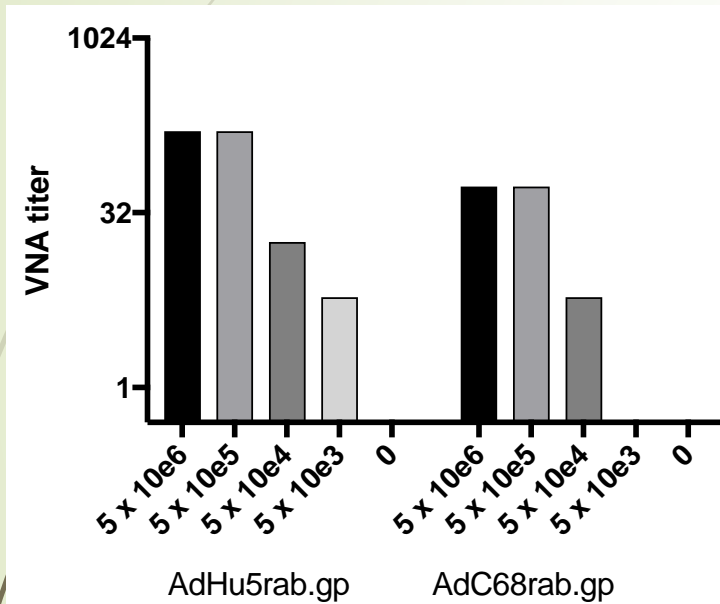


# Construction of adenovirus vectors

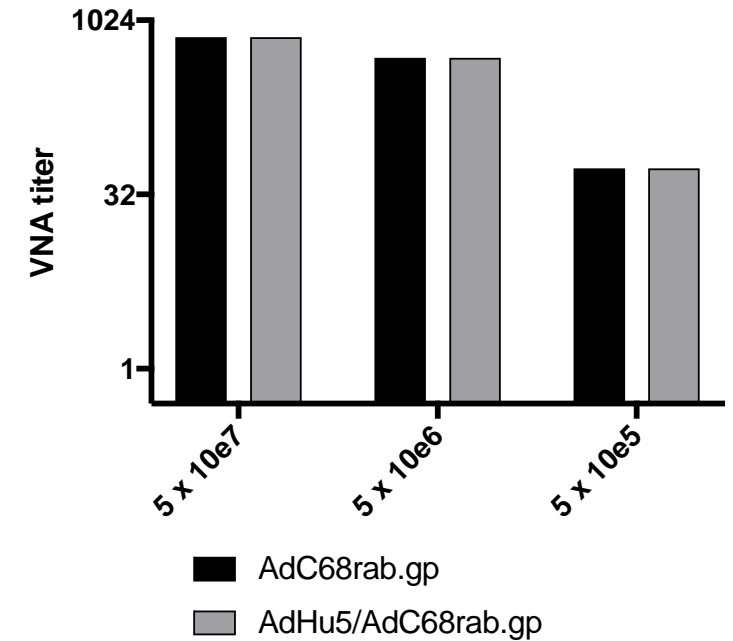
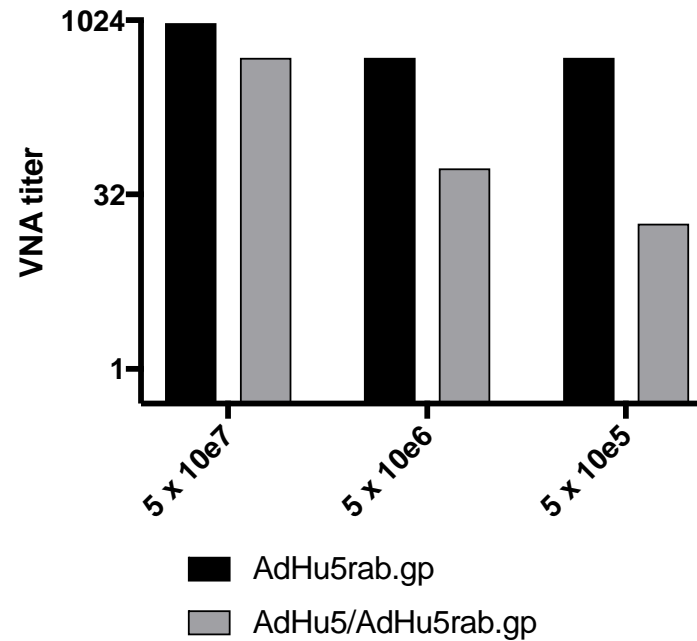


# IMMUNOGENICITY IN MICE

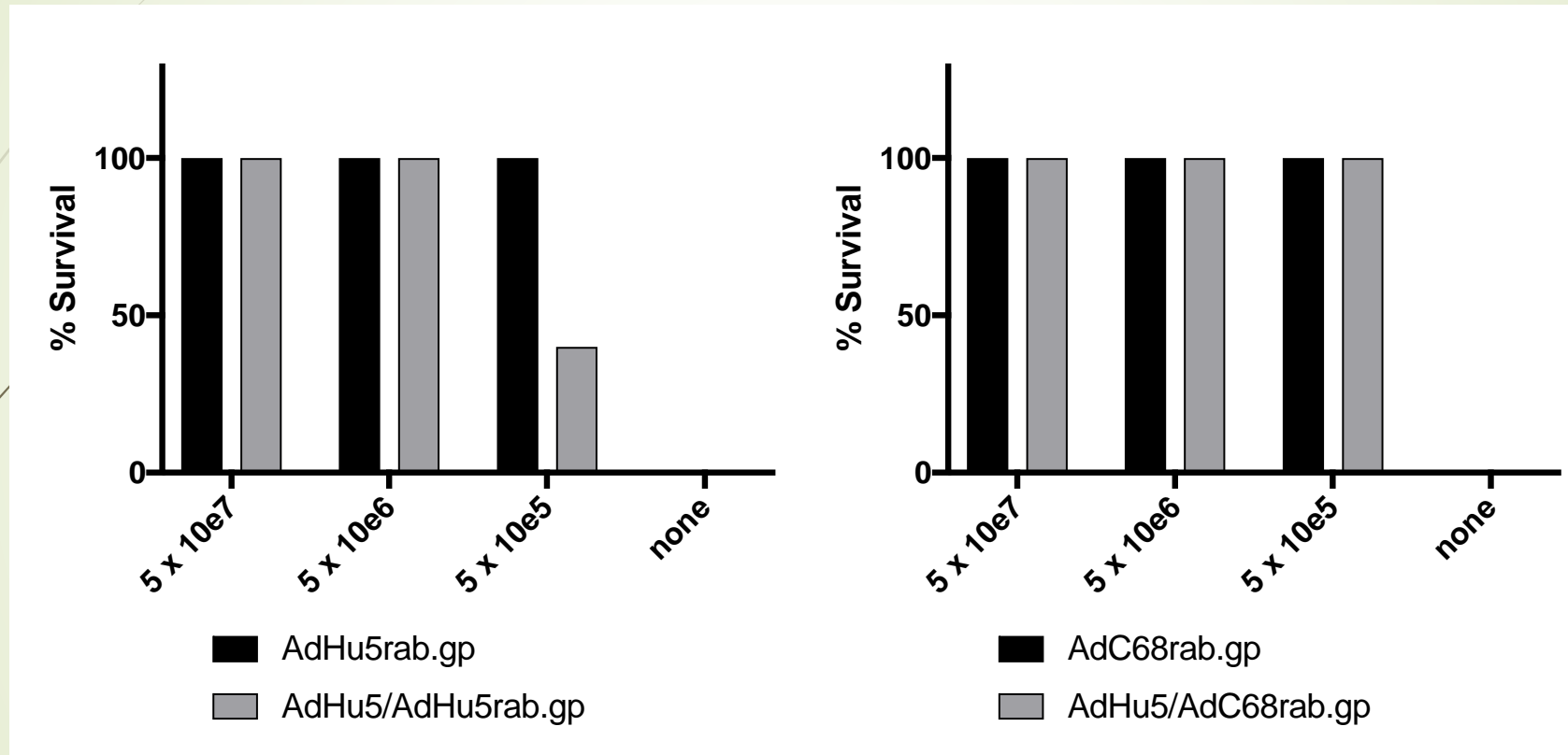
Naïve mice



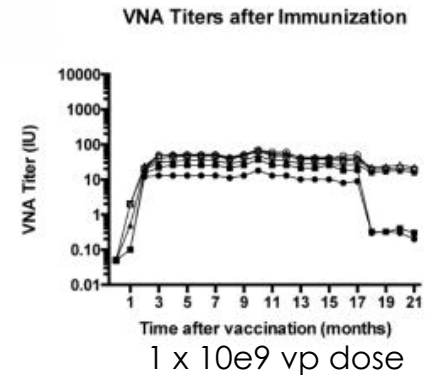
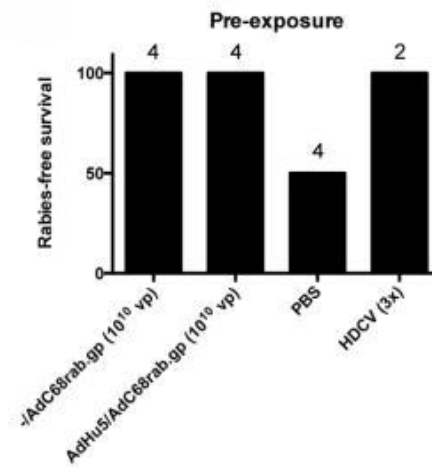
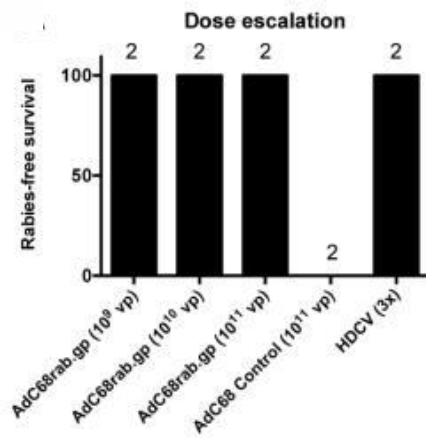
AdHu5-pre-exposed mice



# Efficacy in mice

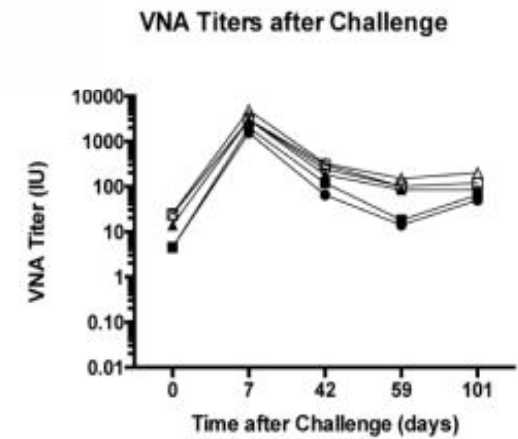
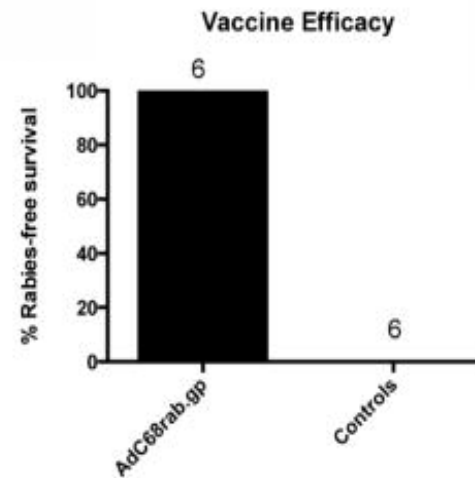


# Immunogenicity in nonhuman primates (NHP studies conducted at CDC with C. Rupprecht)

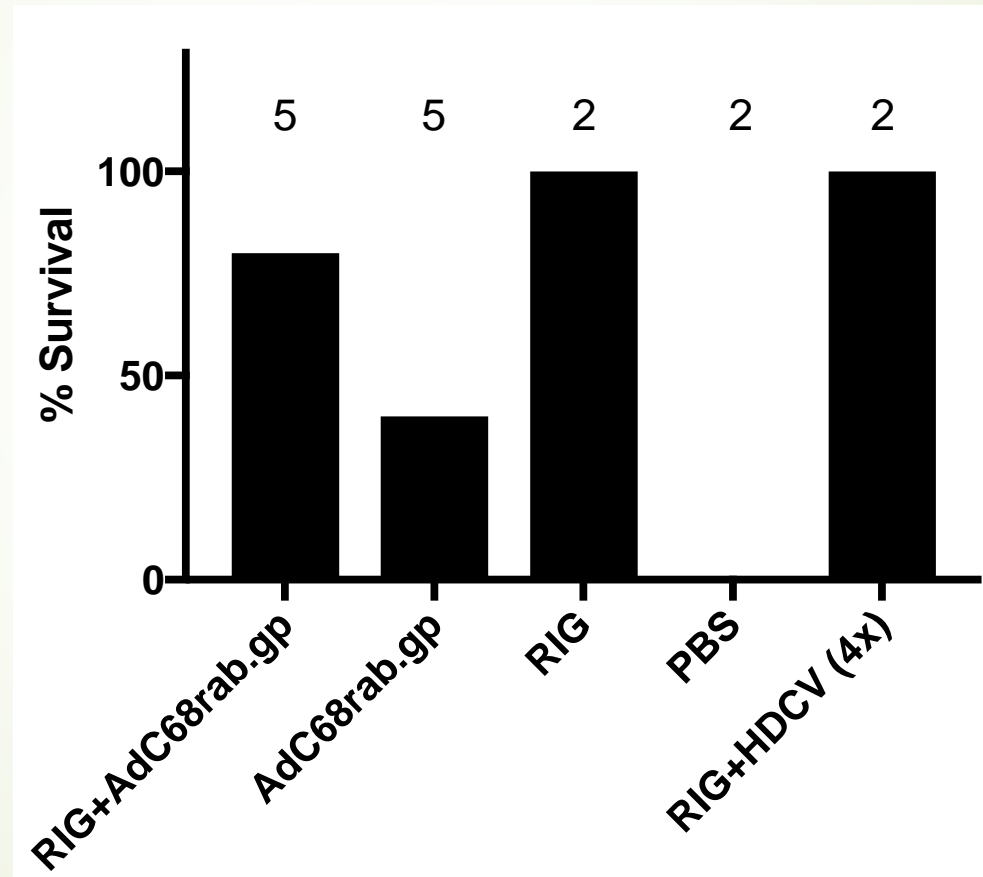


# Efficacy in PrEP nonhuman primates

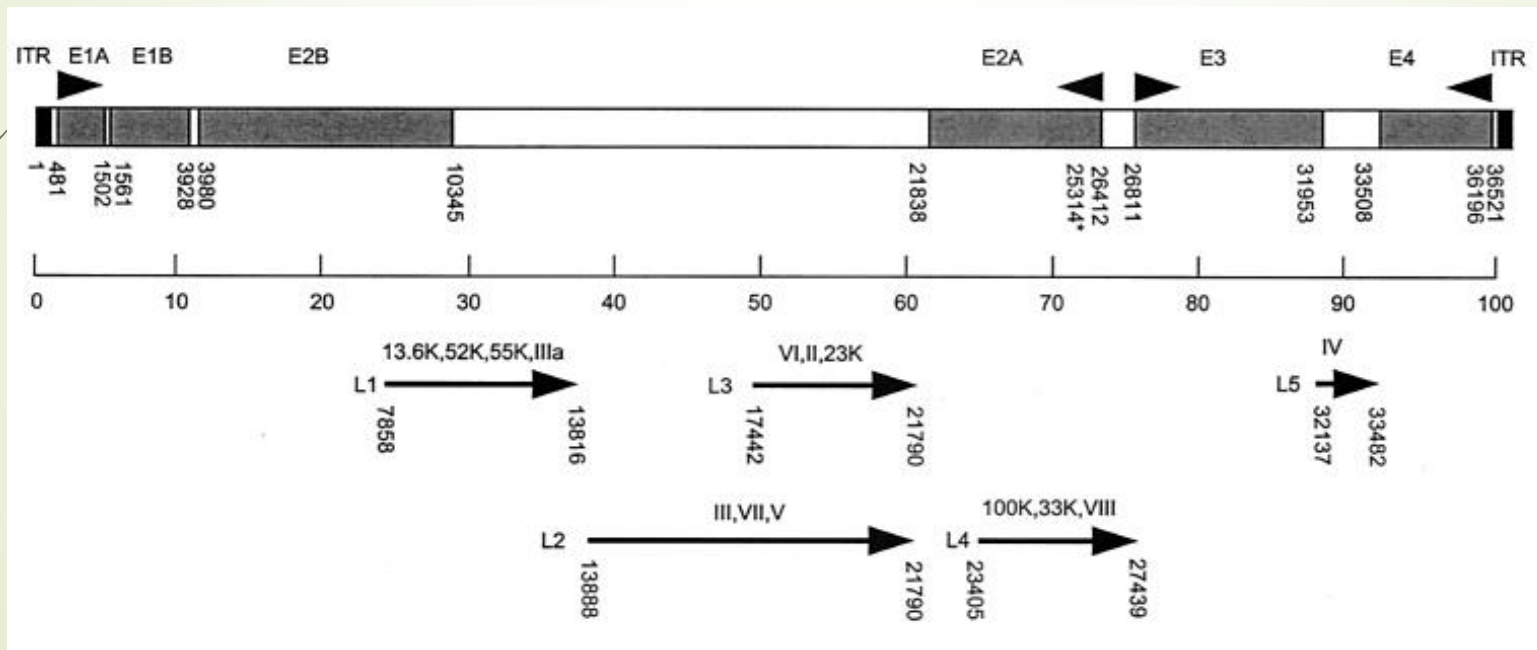
6 NHPs in the vaccine and the control groups, challenged with a coyote derived rabies virus ~ 21 months after a single vaccination with  $10^9$  vp of the AdC68rab.gp vector



# Efficacy in PEP nonhuman primates



# Clinical trial vaccine – ChAdOx2 RabG AdC68rab.gp with an E4ORF replacement






# Phase I trial in adults in the UK

- ▶ Vaccine given once IM at two different doses in comparison to a 3 dose IM regimen of a traditional rabies vaccine. To assess memory responses 2 doses of the traditional vaccine will be given ~ 1 year later.
- ▶ End-points
  - ▶ Safety
  - ▶ Induction of VNAs >0.5 IU





# Phase II trials in adults and children in Tanzania

- ▶ Compare vaccine with an without adjuvant
- 

# Acknowledgements

## Ertl Lab

Z. Xiang

X. Zhou

D. Zhou

W. Giles-Davis

C. Rupprecht



S. Douglas

