



Viral Vectored Vaccines and Prime-Boost Approaches

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Viral Vectors

- In discovery / development since 1984
- Many licensed veterinary vaccines
 - Mainly poxviruses
- Recombinant yellow fever virus vector for JE at licensure
- Numerous other vectors in development
 - ALVAC, MVA, adenoviruses, flaviruses, AAV, VZV, Sindbis, VEE etc



Potential Benefits

- Rapid generation
- No need for protein expression and purification
- Potentially generic and low-cost manufacturing processes
- Thermostability
- Leading technology for T cell induction



Viral Vectored Vaccines in Clinical Development

- Malaria
- TB
- HIV
- HCV
- Dengue
- JE
- Influenza
- HBV
- Ebola
- EBV
- HPV
- West Nile
- Melanoma
- Colon cancer
- Renal cancer
- Prostate cancer
- Lung cancer



Recent Advances

- Induction of protective CD8 T cell responses with a vectored prime-boost regime
- Antibody induction by viral vectors
- Thermostability of viral vectors



CD8 T Cell Induction in Humans: approaches

- Peptides / adjuvants
- Lipopeptides
- Protein / adjuvants
- VLPs
- Salmonella
- Dendritic cells
- Prime-boost regimes
- Plasmid DNA
- Vaccinia
- ALVAC
- MVA
- NYVAC
- Adenoviruses
- AAV



Pre-Erythrocytic Vaccines: Background

- CD8 T cells to liver-stage antigens are protective in many pre-clinical models
 - Irradiated sporozoites
 - Vectored prime-boost regimes
- The leading candidate vaccine, RTS,S/AS01, induces no CD8 T cell response
 - Protection of 40% for 1 year through antibody induction



Two Correlates of Vaccine Induced Protection in Humans

- High level antibodies to CSP
- High level T cells to TRAP

Neither occurs naturally



Prime-Boost Approaches in Malaria

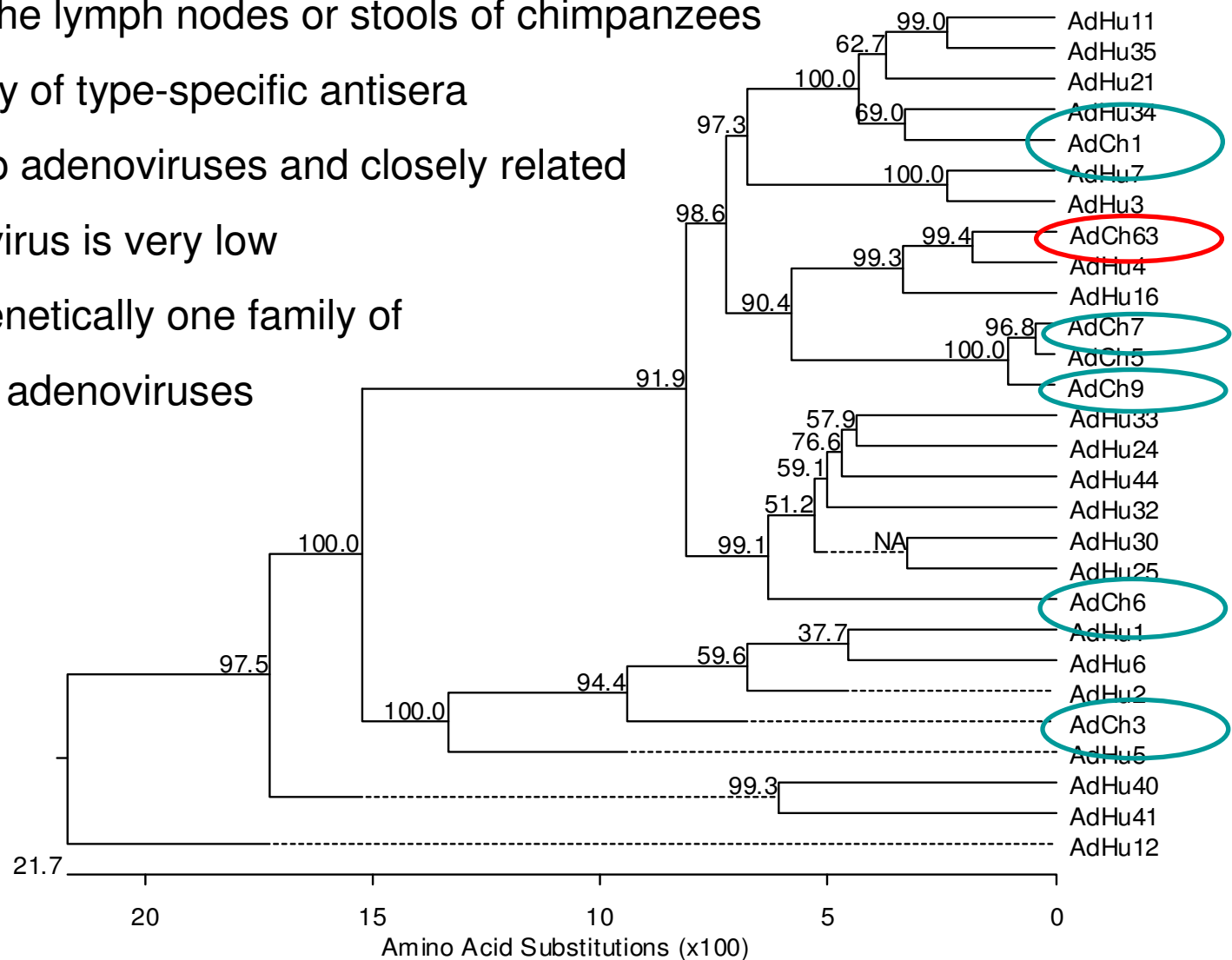
- DNA-MVA and Fowlpox-MVA regimes have induced detectable protective efficacy in the sporozoite challenge model
 - with a TRAP but not a CSP insert
 - protection correlated with CD4 T cell induction
 - but only 5-12% of volunteers sterilely protected
- Pre-clinical results then showed better CD8 T cell induction with adenoviral vectors



Human and Chimp Adenoviruses

Phylogenetic tree of hexons

- Isolated from the lymph nodes or stools of chimpanzees
- Cross-reactivity of type-specific antisera between chimp adenoviruses and closely related human adenovirus is very low
- Really phylogenetically one family of higher primate adenoviruses





Why Use Simian Adenoviral Vectors?

- A high % of individuals have been exposed to the adenovirus AdHu5

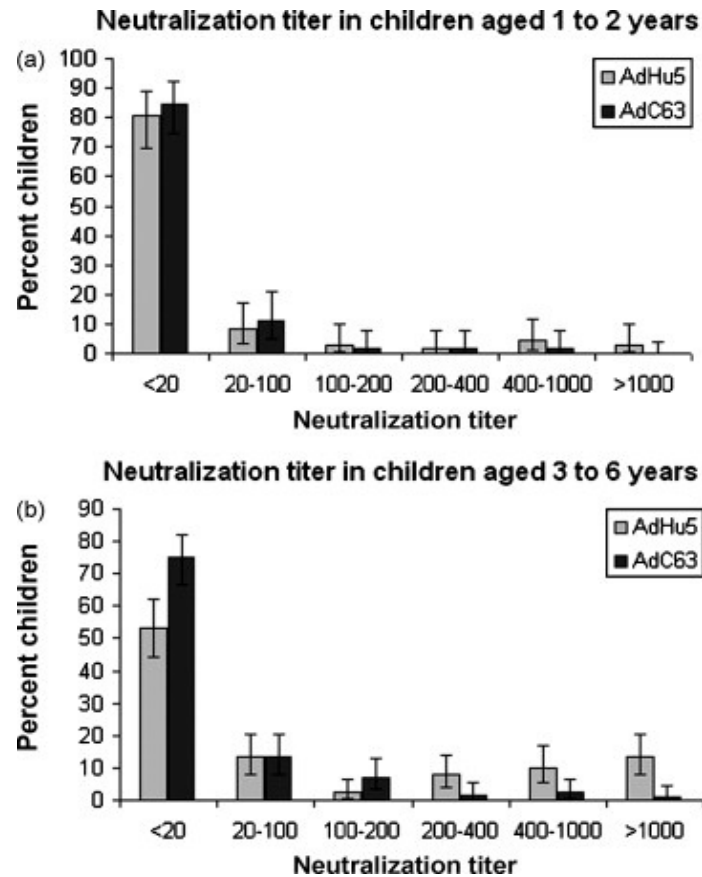
	% People with	neutralizing	antibodies
Origin	AdHu5	AdC68	AdC6
United States	34%	2%	4%
Thailand	76.5%	1.5%	3%
Cameroon	55.8%	1.7%	7.9%
Côte d'Ivoire	95.8%	9.5%	10.7%

Xiang, Z et al. Emerg Inf Dis. 12(10):1596-9.2006.

- Pre-existing anti-vector immunity makes the vaccine ineffective
- Use alternative Ad vectors that do not circulate in human populations
 - ✓ Chimpanzee adenoviral vectors
 - ✓ AdCh63, AdC3, AdC6, AdC7, AdC68
 - ✓ Aim: to select the best chimpanzee adenoviral vector to be used in humans as a liver-stage vaccine



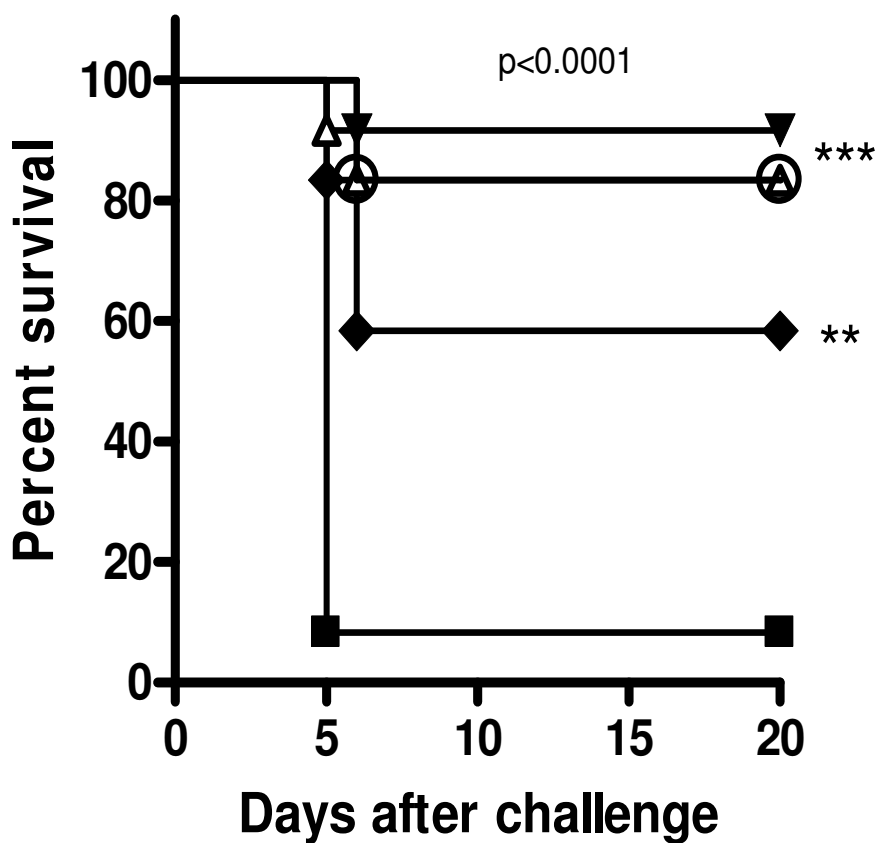
Low Anti-AdCh63 Antibody Prevalence in Target Groups





Single Dose Protection against *P. berghei* with Adenoviral Vectors encoding ME-TRAP

protection mediated by pb9-specific CD8 T cells



Vector	Efficacy
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AdH5	83 %
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AdC6	67
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AdC7	83
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AdC9	92
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FP9	0
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MVA	0
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MAL 34 – Trial Outline

3 Groups:

- Group 1:** AdCh63 ME-TRAP - MVA ME-TRAP - malaria challenge (n=8)
Group 2: AdCh63 ME-TRAP - malaria challenge (n=10)
Controls: no vaccination - malaria challenge (n=6)

23rd March

11th May 18th May

8th June

←----- 8 weeks -----> ←----- 3 weeks ----->

←----- 4 weeks ----->

AdCh63 ME-TRAP
Group 1

MVA ME-TRAP
Group 1

Malaria Challenge
Groups 1, 2 & 3

AdCh63 ME-TRAP
Group 2



Blood-Stage Vaccines

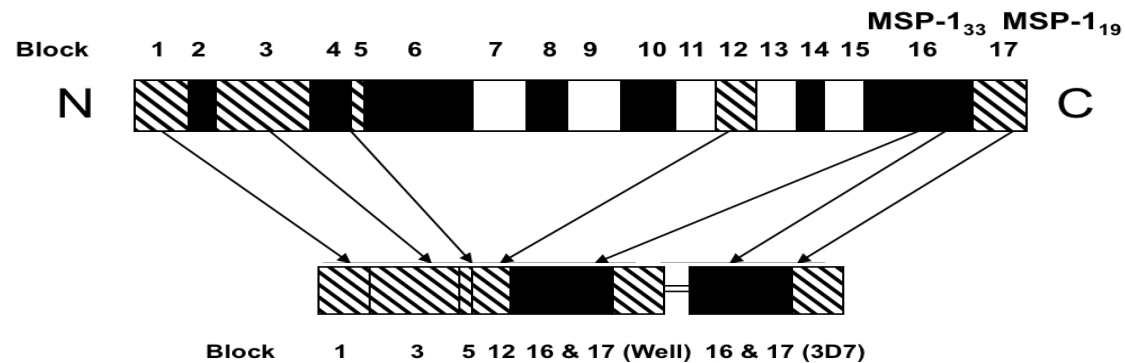
A New Vectored Approach

- Aims to induce both protective antibodies and effector T cells
 - efficacy of low dose blood-stage infections in humans
- Potential for activity against liver-stage and for combination with pre-erythrocytic vectors
- Ad-MVA found to be the most protective regime
 - MSP-1₄₂

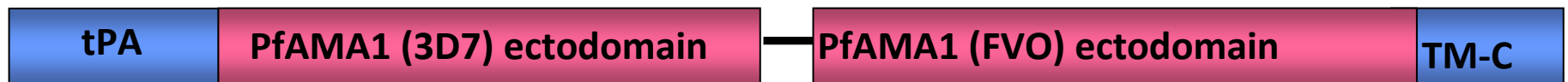


New AdCh63 and MVA Vectors with Blood-Stage Antigens

Pf MSP1 Bi-Allelic Insert



Pf AMA1 Bi-Allelic Insert





Time Line for Four Malaria Vaccines

Liver-Stage

- ME-TRAP
 - **Phase IIa Challenge mid-June 2009**
 - African trials to start January 2010
- CSP
 - Phase I and phase IIa 2010

Blood-Stage

- MSP1
 - **Phase I started November 2009**
 - Challenge mid - 2010
- AMA1
 - Phase I Q1 2010
 - Challenge mid - 2010



Conclusions

- A new Adenovirus-MVA prime-boost regime shows good safety in humans and very promising immunogenicity and efficacy
 - one phase IIa challenge study with ME.TRAP completed with another in progress
 - a further phase I trial with a blood-stage insert initiated
- Viral vectors are the only approach to have induced very high level effector T cell responses in humans
 - in malaria, TB and flu



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