THE JENNER INSTITUTE
DEVELOPING INNOVATIVE VACCINES

UNIVERSITY OF OXFORD

Viral Vectored Vaccines for Veterinary Vaccinology

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Synergies in Human and Livestock Vaccine Development

- Same or related diseases in two species
  - e.g. tuberculosis, influenza, RVF
- Rapid efficacy testing in large animal species
  - allowing biomarker identification
- Large animals better predictors of immunogenicity
- Common novel technology platforms
- Similar cost constraints for low income markets

Jenner Institute Core Facilities

- Viral vector core facility
  - Generates about 100 viral vector batches annually (60 new, 40 re-bulks) for 26 Jenner Investigators
- Transcriptomics facility
  - Primarily for human and large animal trials
- Adjuvant bank
  - > 50 adjuvants in house
- Flow cytometry core facility

Sanofi Pasteur Chimerivax

- Only licensed viral vectored vaccine for humans
- Live attenuated yellow fever virus vaccine strain YF17D expressing JEV membrane and envelope proteins
- Immunogenicity of a single dose is non-inferior to three doses of the inactivated JE vaccine
- Short-lived, asymptomatic low level viremia detected in some vaccinees
- Seroprotection estimated to last 10-20 years
- The same approach could be used for other flavivirus vaccines

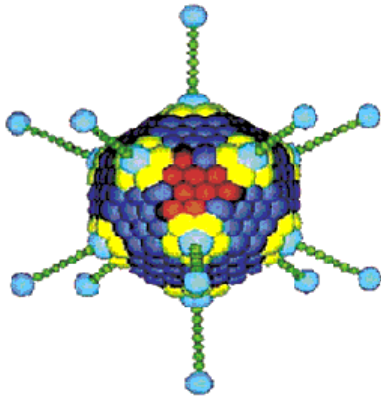
Human Vaccines Pipeline

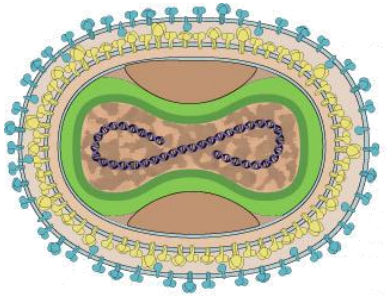
Disease Area	Number of GMP Vaccines	Preclinical	Phase I	Phase IIa	Phase Ib	Phase IIb	Phase III	Licensure
			Oxford		Patient Group /Endemic Area			
Malaria	15							
TB	3							
HCV	3							
HIV	5							
Pandemic Flu	2							
Meningitis	1							
RSV	3							
Ebola	1							
Staph aureus								
Prostate cancer								
Rift Valley Fever								

The busiest pipeline of any non-profit vaccine institute

Viral Vector Vaccines

to Maximise Cellular Immunogenicity





8 weeks

Adenovirus Prime → **MVA Boost**

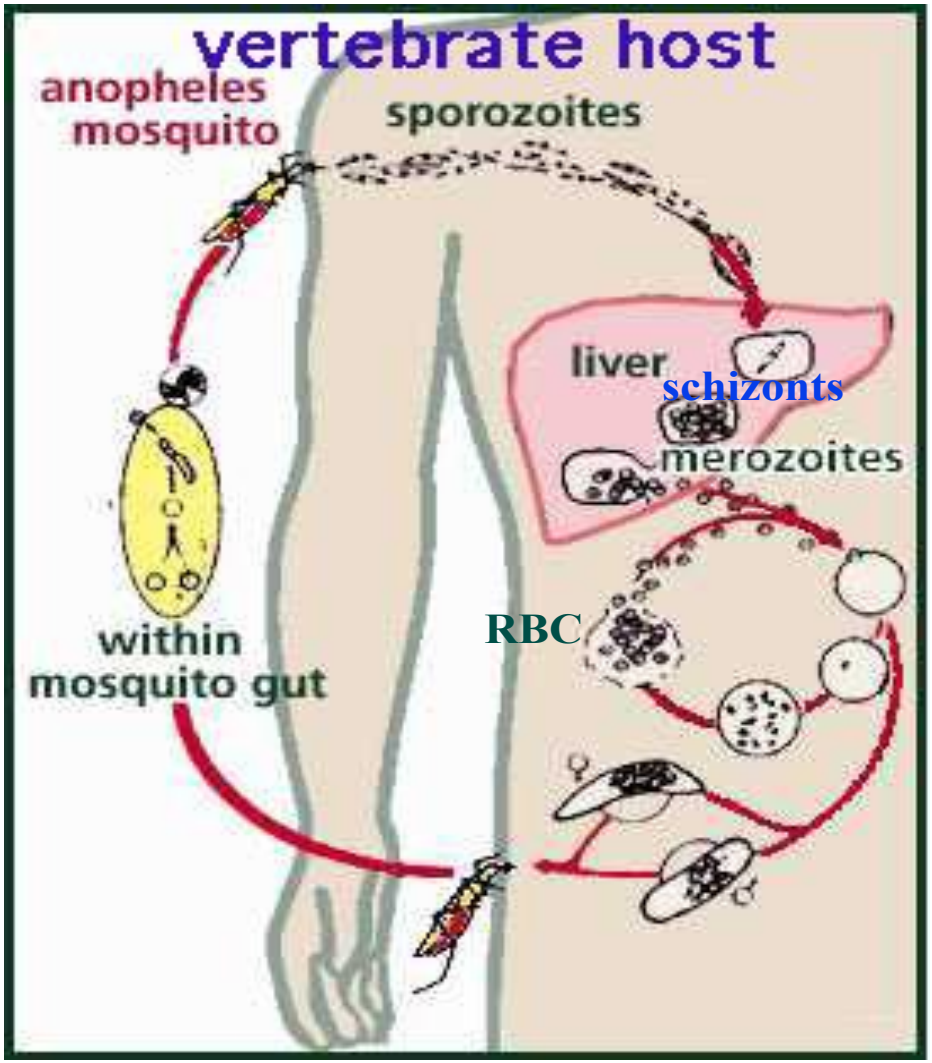
Malaria x 5, HCV, HIV, influenza, TB, RSV

okairos
from genes to vaccines

Malaria

A Complex Life Cycle

Mosquito Stage



Liver Stage

Blood Stage

Main Approaches to Malaria Vaccine Development

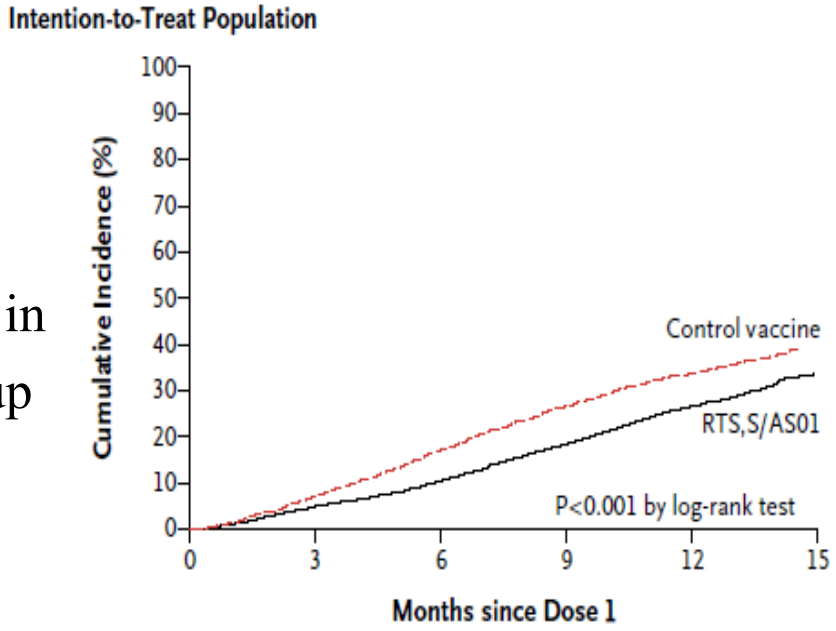
1. **Protein-adjuvant vaccines** — **antibodies**
   - RTS,S/AS01
   - AMA1/AS02
   - GMZ2/Alum
2. **Vectored vaccines** — **cellular immunity**
   - Fowlpox-MVA
   - Adenovirus-MVA
   - DNA-Adenovirus
3. **Whole parasite vaccines** — **both to multiple antigens**
   - Irradiated sporozoites
   - Genetically attenuated parasites

RTS,S Phase III trial Update

9 November 2012

- 15,000 infants at 11 African sites

- Less good news
  - 30% efficacy against clinical episodes in 6-12 week olds over 1 year of follow-up
    - this is the ideal target population



- Other findings
  - Safety findings satisfactory
  - Short time span of efficacy
  - 26% efficacy against severe malaria measured as 1-RR (ATP analysis)
  - Up to 600µg/ml of antibody, but this drops rapidly

Agnandji et al. NEJM 2012

Attempts at CD8+ T Cell Induction in Humans

- DNA
- RNA
- Peptides
- Lipopeptides
- Virus-like particles
- MAPs
- Dendritic cells + Ag
- MAbs to DC receptors

- Protein +
  - Alum
  - Montanide
  - AS01-15
  - TLR ligands
  - Emulsions
- Many viral vectors
  - ALVAC,
  - AAV
  - alphaviruses

More promising: Adenovirus & yellow fever vectors, orthopox boosting, peptide in IFA

Viral Vectors: some advantages

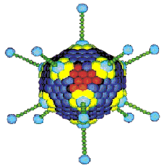
- Low cost of goods
  - Synergies with HIV, TB, cancer vaccine development
- Thermostable
  - 42^0 degrees for 6 - 12 months
- Intramuscular route
  - applicable to young infants
- Just two immunisations
- Rapid response potential

Viral Vectors: scalable manufacturing

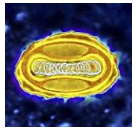
- Cell lines available for human and simian adenoviruses, or for MVA
- Cell lines grown in bioreactors or wave bags
- Chromatography purification process removes host cell DNA and host cell protein
- Tens of thousands of doses of Ebola vaccines have been manufactured (ChAd3 and MVA)
- A simplified process could be used for veterinary vaccines

Why Use Viral Vectors in Prime-Boost Regimes?

- Best means of safely inducing T cells in humans
- 8 vaccines have induced >1000 SFU/ ml blood
  - in malaria (x 4), HIV, HCV, tuberculosis and influenza
  - all used viral vector boosting
- Adenovirus – MVA is the most potent approach
  - better than DNA – Adenovirus
  - better than Adenovirus - Heterologous Ad



8 weeks



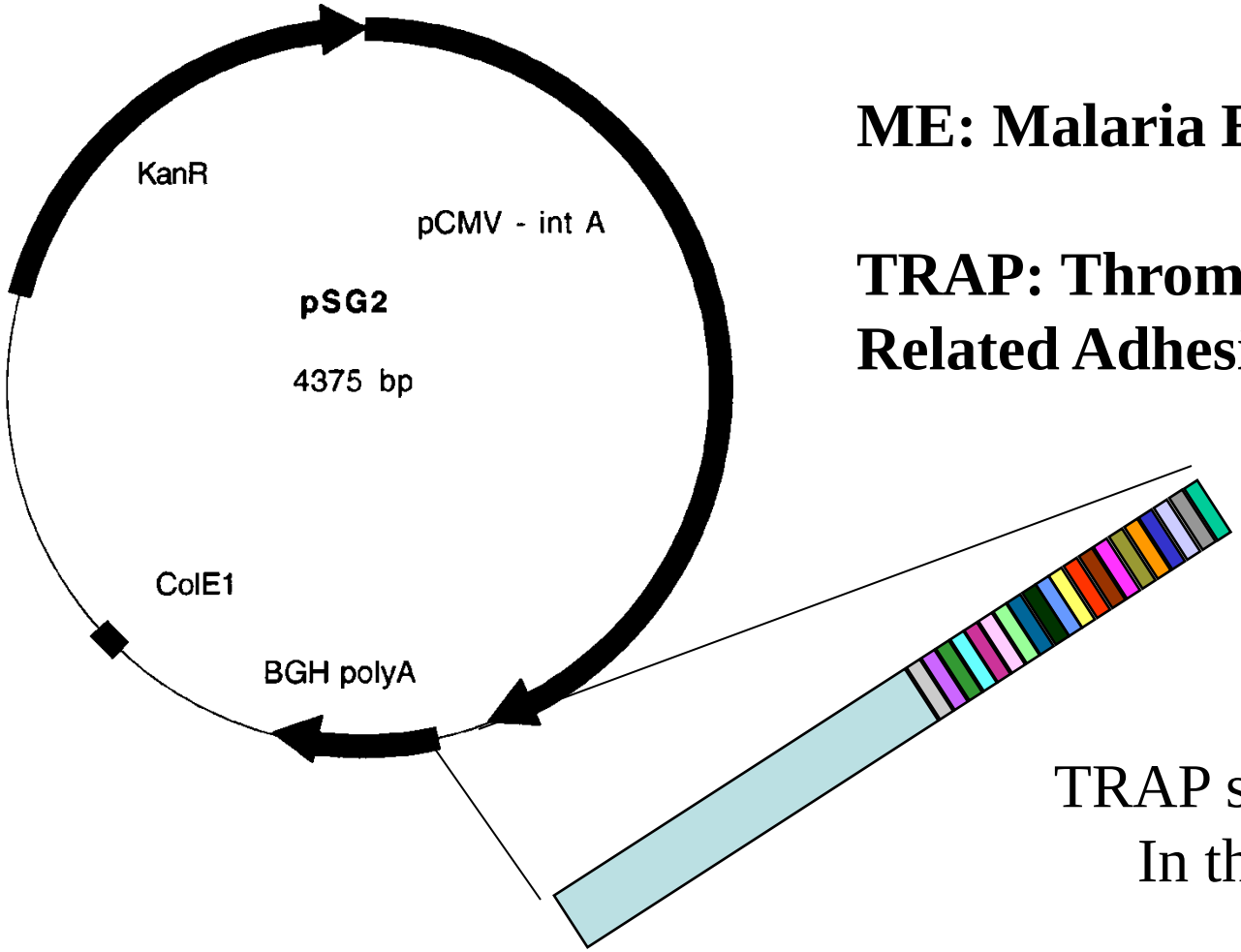
Adenovirus Prime **MVA Boost**

Clinical BioManufacturing Facility

University of Oxford

Vectored ME-TRAP

A PolyEpitope-Protein Construct



ME: Malaria Epitopes

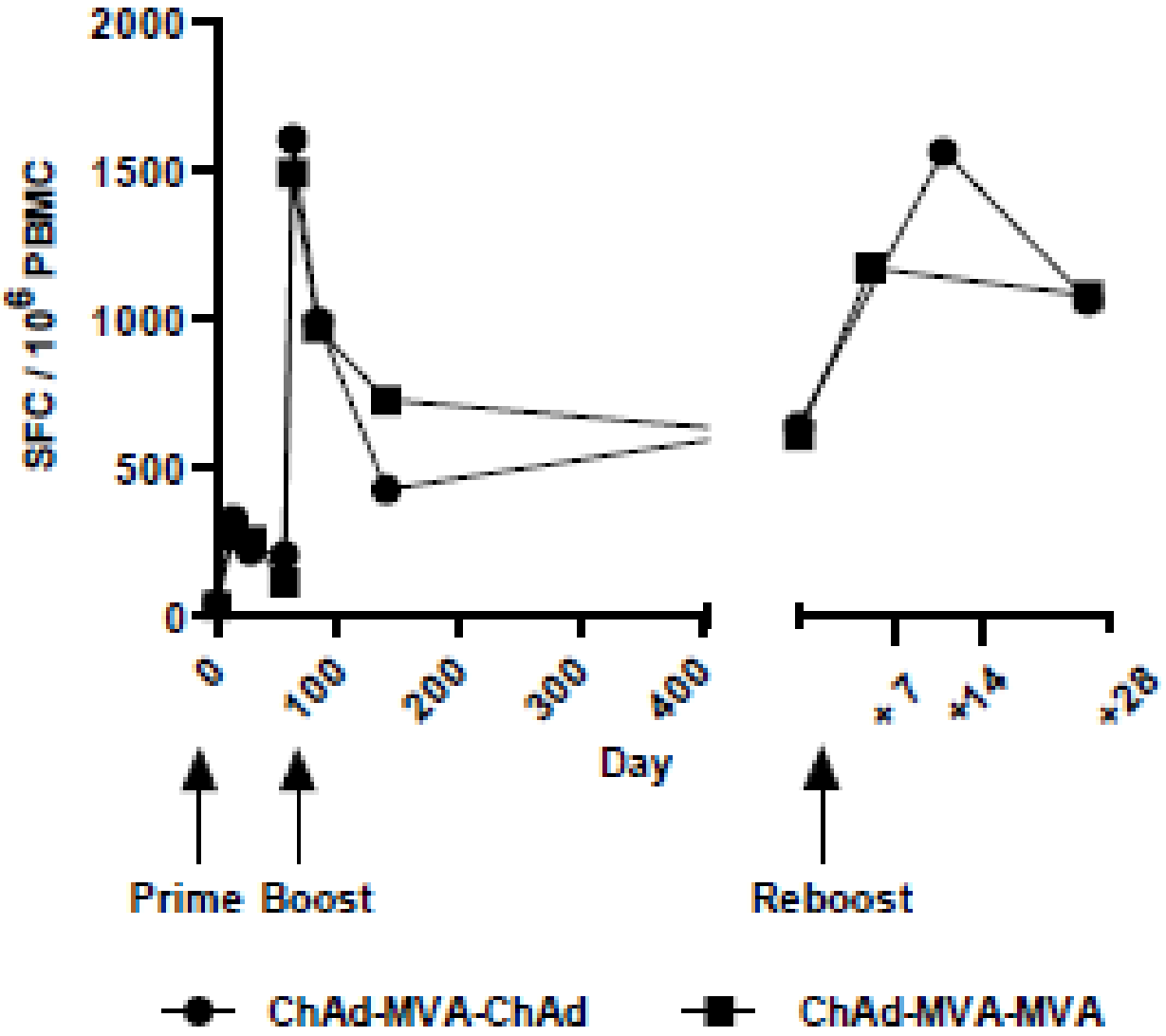
TRAP: Thrombospondin-Related Adhesion Protein

TRAP strain is T9/96
In this vaccine

ME-TRAP T Cell Immunogenicity
in the Clinic

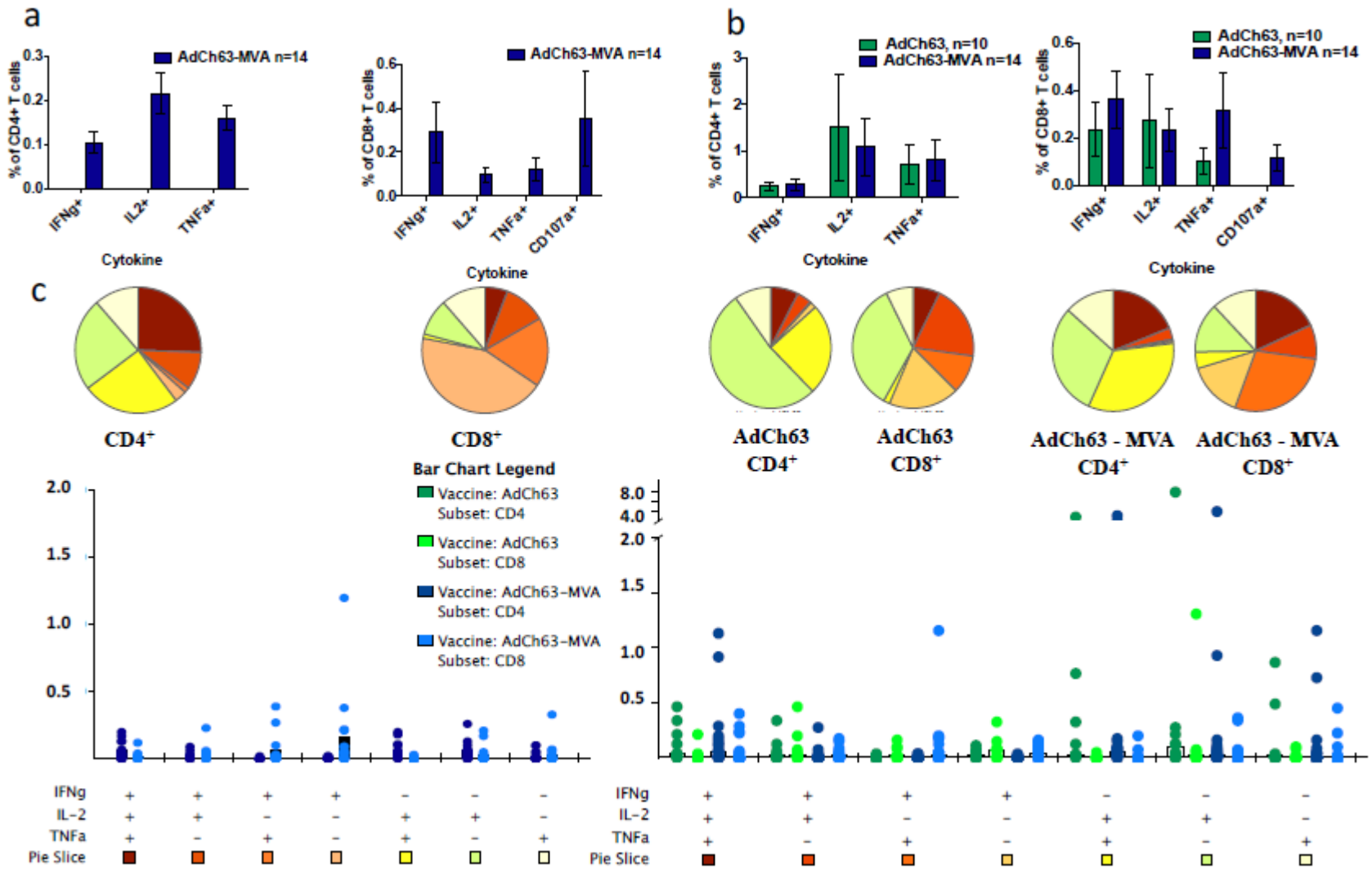
VACCINE	T CELL RESPONSE mean cells/ million PBMCs	ANTIGEN
DNA x3	48	ME-TRAP
FP9 x 2	50	ME-TRAP
MVA x 3	41	ME-TRAP
ChAd63 x 1	**850**	**ME-TRAP**
DNA-MVA	430	ME-TRAP
FP9-MVA	475	ME-TRAP
ChAd63-MVA	**2800**	**ME-TRAP**

Responses are Durable and Can Be Re-Boosted at 6-30 Months Post-MVA



O'Hara JID 2012

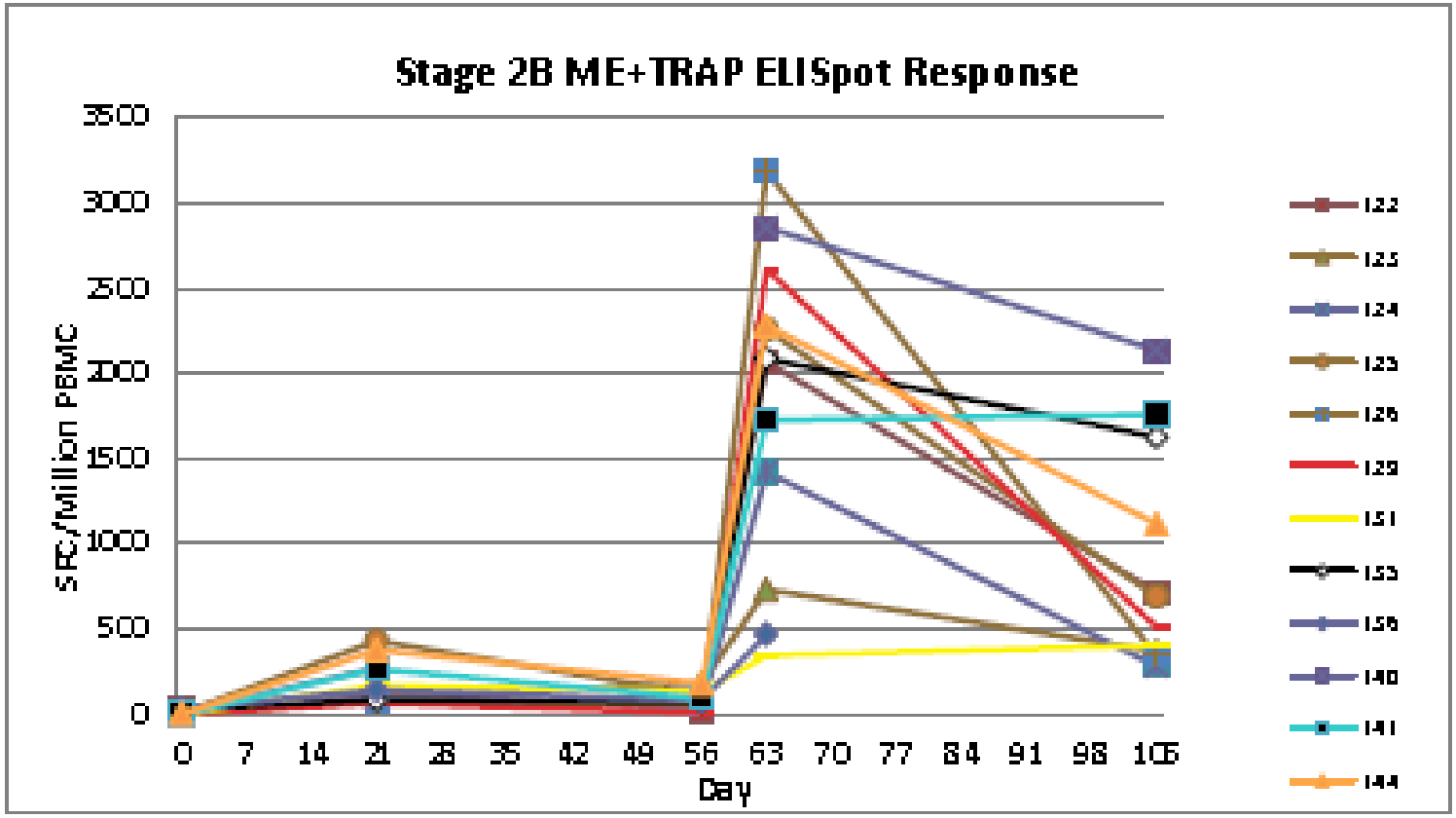
Induced CD8 and CD4 Cells to TRAP Show Substantial Polyfunctionality



ChAd63-MVA ME-TRAP Efficacy

- 21% sterile efficacy in CHMI studies
  - but a further 30% of vaccinees show a 2 day delay in time to patency
    - Corresponding to a >90% reduction in liver parasite load
    - Against 5 bites of heavily infected mosquitoes
- The efficacy is against heterologous strain challenge
- Efficacy of ChAd-MVA is repeatable
  - In two further challenge trials (Vac45 and Vac52)

ChAd63-MVA MeTRAP
in Gambian 10 week olds



Stage 2B	Median	Mean
Day	T996+ME	T996 +ME
SCREEN	12	12
21	135	182
56	82	89
63	2077	1837
105	690	905

Current Animal Virus Vaccine Research

FMD

BRSV

Bluetongue

BVDV

Marek's Disease

Avian Influenza

IBV

IBD

African swine fever

FMD

Swine Influenza

CSF

Bluetongue

PPR

FMD

Nairobi sheep disease

African horse sickness

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Livestock Vaccine Programmes

- Foot and mouth disease
- **African swine fever**
- **Bovine tuberculosis**
- **Peste des petites ruminants**
- **Respiratory syncytial virus**
- **Rift valley fever**
- **Avian and swine influenza**
- Marek's disease
- **African horse sickness**
- Bluetongue

AHVLA
Animal Health and Veterinary Laboratories Agency

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Licensed viral vectored veterinary vaccines

Recombinant viral vector	Target pathogen	Target species	Target antigen	Brand name	Distributor
ALVAC (plus tetanus toxoid and Carbopol adjuvant)	Equine influenza virus	Horses	HA (Kentucky and Newmarket strains)	ProteqFlu-Te (Europe) Recombitek (USA)	Merial
ALVAC	West Nile Virus (WNV)	Horses	PreM–Env	Recombitek Equine WNV	Merial
ALVAC	Rabies virus	Cats	Glycoprotein G	Purevax Feline Rabies	Merial
ALVAC	Feline leukaemia virus (FeLV)	Cats	Env, Gag–Pol	Purevax FeLV	Merial
ALVAC	Canine distemper virus	Dogs	HA and F	RECOMBITEK rDistemper	Merial
ALVAC	Canine distemper virus	Ferrets	HA and F	Purevax Ferret Distemper	Merial
Fowlpox virus (FPV)	Avian influenza virus and FPV	Poultry	H5 HA	Trovac AI H5	Merial
FPV	Newcastle disease virus (NDV) and FPV	Poultry	HN and F	Vectormune FP-N	Biomune
Vaccinia virus	Rabies virus	Wildlife	Glycoprotein G	Raboral	Merial
NDV (LaSota strain)	Avian influenza virus and NDV	Poultry	H5 HA	NewH5	Avimex
Flavivirus YFV-17D (live chimeric virus)	WNV	Horses	preM-Env of WNV in YFV-17D backbone	PreveNile	Intervet
HVT (live chimeric virus)	IBDV and Marek's disease virus	Poultry	VP2 of IBDV in HVT backbone	Vaxxitek HVT + IBD	Merial

ALVAC, attenuated canarypox virus; Env, envelope protein; Gag, group-specific antigen; F, fusion antigen; H5 HA, HA from influenza virus H5; HA, haemagglutinin; HN, haemagglutinin–neuraminidase protein; HVT, Turkey herpesvirus; IBDV, infectious bursal disease virus; Pol, polymerase; preM, pre-membrane protein; VP2, viral protein 2; YFV-17D, attenuated yellow fever virus strain 17D.

Draper & Heeney Nat Rev Microbiol 2010

Viral Vectored Vaccines against PPR

BBSRC-CIDLID: Development of a DIVA vaccine against PPR

- PPRV is a morbillivirus which causes disease characterised by fever, nasal discharge, bronchopneumonia, necrotic stomatitis and diarrhoea in sheep and goats
- Mortality varies from 20% to 60%
- Current live attenuated vaccines are effective but require a cold-chain for distribution and do not distinguish infected from vaccinated animals (DIVA)
- Aim to develop a DIVA vaccine using replication-defective Ad5 expressing PPRV H and/or F proteins

(Herbert, Baron , Baron & Taylor *Vet Research* 2014)

BBSRC bioscience for the future

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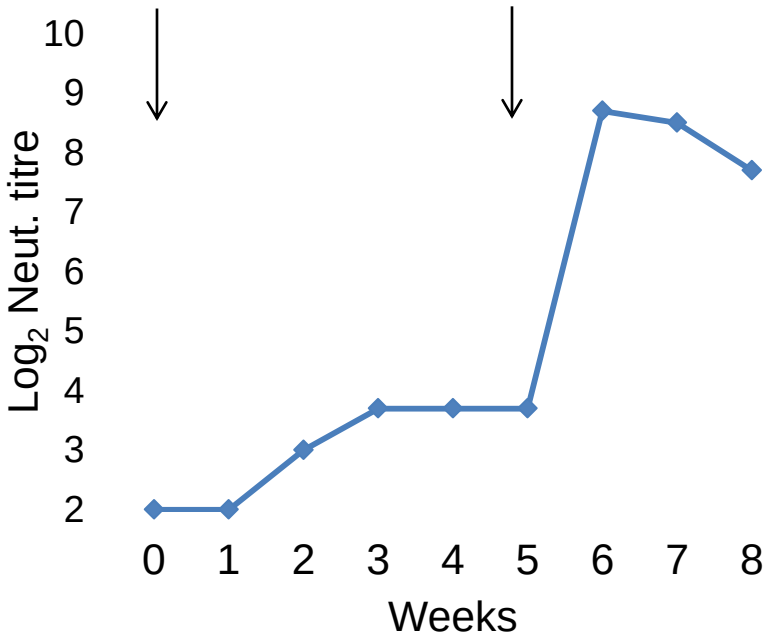
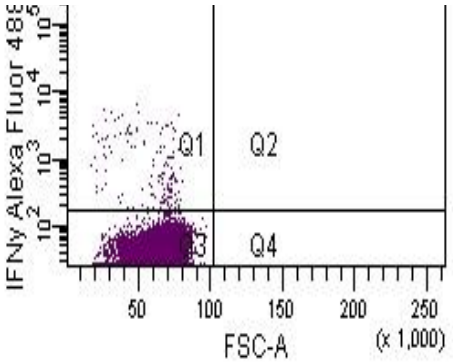
Ad5/PPRV H + F in goats

Neutralising Ab response

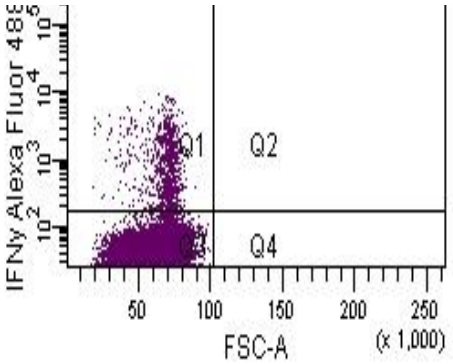


- Goats inoculated i.m. with 1 x 10^9 i.u. of each AdV

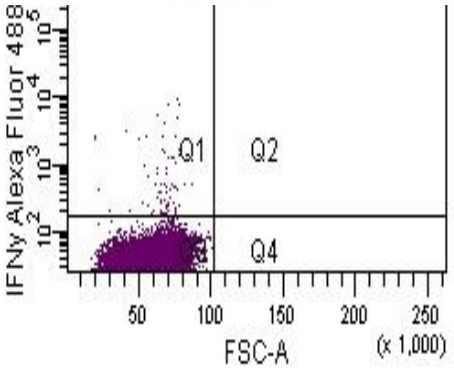
F-specific CD8 T cells



H-specific CD8 T cells



Control



Priming of F & H specific $CD8^+$ T cells by Ad5/F+H

PPR challenge in goats

- **A single immunisation of Ad5-F** protected goats against infectious PPR challenge four months after immunisation
- Neutralising antibody and $CD8^+$ T cells were primed
- No virus shedding after challenge
- No pre-existing immunity to the viral vector (unlike capripox vectored vaccines)
- DIVA compatible, only one PPR antigen is required in the vaccine

Herbert et al. Veterinary Research 2014

BBSRC bioscience for the future

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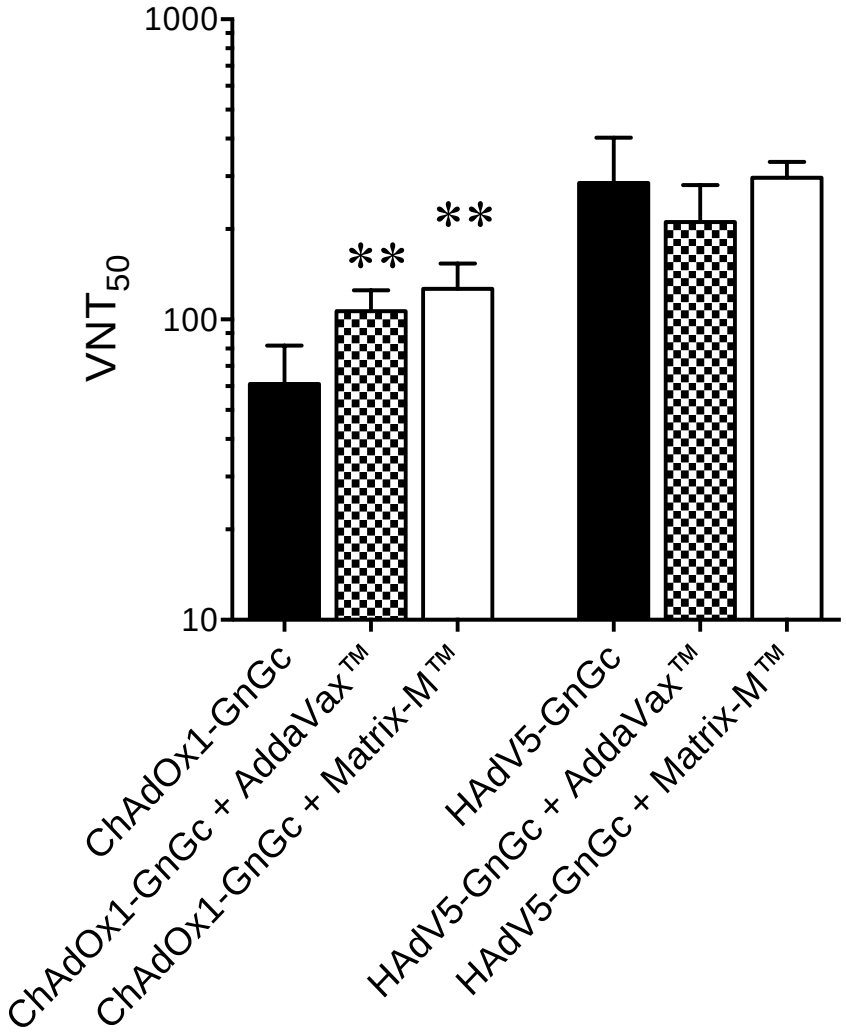
Immunogenicity and efficacy against RVF viral challenge in mice 8 weeks post-vaccination



- ✓ 100% protective efficacy by all regimens in BALB/c mice
- ✓ ChAdOx1-GnGc +/- Matrix-Q™ selected for ruminant trials

Warimwe et al. Virol J. 2013;10:349

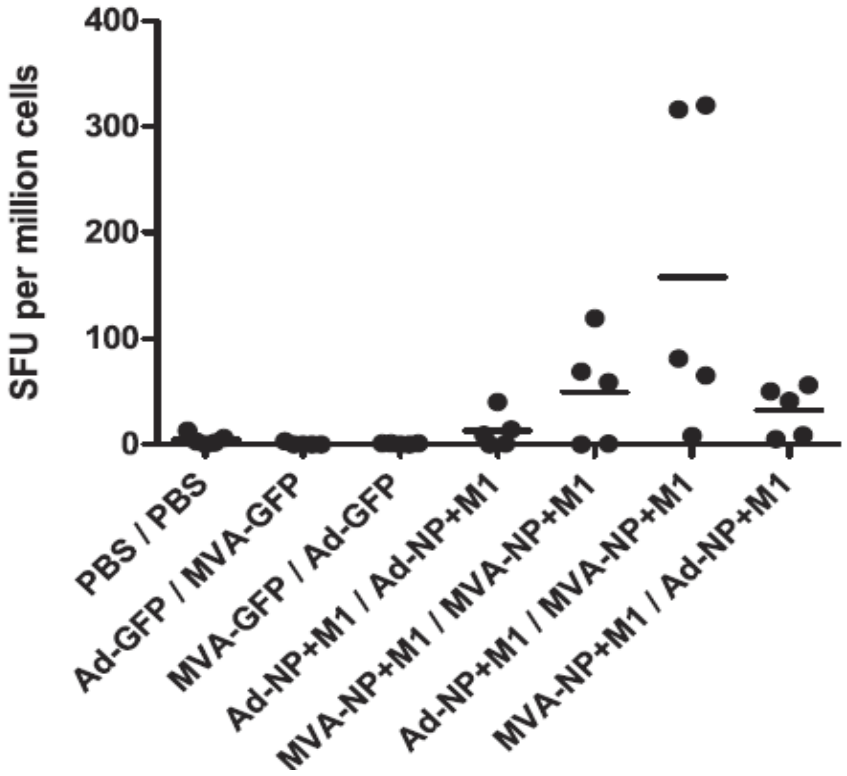
Jenner Human Influenza Vaccine

- MVA encoding NP+M1 in phase II trials
  - Boosts CD8+ and CD4+ T cells very strongly
    - in adults including older adults
  - Preliminary efficacy against challenge
  - Being compared clinically to ChAdOx1 vector
  - Co-administration with trivalent flu vaccine beneficial
    - Enhances antibodies to standard trivalent influenza vaccine

- Development options
  - Stockpiling for emergency pre-pandemic use
  - Mixture with standard flu vaccines for higher efficacy

Influenza Adenovirus-MVA Prime-Boost Regimes in chickens

prime *in ovo*, boost the hatchlings



Ad-MVA NP+M1 group showed reduced cloacal shedding measured by plaque assay at 7 days post infection

Boyd et al 2013

Funding Acknowledgements