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

<table>
<thead>
<tr>
<th>Disease Area</th>
<th>Number of GMP Vaccines</th>
<th>Preclinical</th>
<th>Phase I</th>
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<th>Phase Ib</th>
<th>Phase IIb</th>
<th>Phase III</th>
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<td>Rift Valley Fever</td>
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</tbody>
</table>

The busiest pipeline of any non-profit vaccine institute
Viral Vector Vaccines
to Maximise Cellular Immunogenicity

Adenovirus Prime 8 weeks MVA Boost

Malaria x 5, HCV, HIV, influenza, TB, RSV
Malaria
A Complex Life Cycle

Mosquito Stage

Liver Stage

Blood Stage
Main Approaches to Malaria Vaccine Development

1. **Protein-adjuvant vaccines**
   - RTS,S/AS01
   - AMA1/AS02
   - GMZ2/Alum

2. **Vectored vaccines**
   - Fowlpox-MVA
   - Adenovirus-MVA
   - DNA-Adenovirus

3. **Whole parasite vaccines**
   - Irradiated sporozoites
   - Genetically attenuated parasites

antibodies

cellular immunity

both to multiple antigens
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
  – $42^\circ$ 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
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

<table>
<thead>
<tr>
<th>VACCINE</th>
<th>T CELL RESPONSE</th>
<th>ANTIGEN</th>
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<tr>
<td>DNA x3</td>
<td>48</td>
<td>ME-TRAP</td>
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<tr>
<td>FP9 x 2</td>
<td>50</td>
<td>ME-TRAP</td>
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<tr>
<td>MVA x 3</td>
<td>41</td>
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<tr>
<td>ChAd63 x 1</td>
<td>850</td>
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<td>DNA-MVA</td>
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<tr>
<td>FP9-MVA</td>
<td>475</td>
<td>ME-TRAP</td>
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<tr>
<td>ChAd63-MVA</td>
<td>2800</td>
<td>ME-TRAP</td>
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</table>
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 ME+TRAP ELISpot Response

<table>
<thead>
<tr>
<th>Day</th>
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<th>T996+ME</th>
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<td>105</td>
<td>690</td>
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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

THE Pirbright INSTITUTE
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
# Licensed viral vectored veterinary vaccines

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

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)
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
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

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