MVA and (mainly) Malaria

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MVA: A Growing Safety Database

- 120,000 MVA vaccines during 1970s
- Poxvirus boosting for T cell response amplification discovered in malaria
  - Vaccinia then MVA (1996)
- First clinical trial of MVA boosting in 1999
- Since then over 100 clinical trials
  - 46 in malaria (six inserts), 35 in TB, HIV, influenza, HCV
  - >1000 vaccinees in malaria, > 2000 in TB, > 1000 others
  - Therapy: melanoma, renal cancer, prostate cancer, HIV, HCV, HPV (over 500 cancer patients for Trovax alone)
  - No myocarditis issue
MVA: some updates

• BAC recombineering technology has accelerated vector construction (Cottingham et al PLoS One, 2008)
  – as have flow sorting methods
  – Attempts to enhance immunogenicity further: limited success
  – Immunogenicity dependent on cross-presentation
  – Vector genetic and thermo-stability generally excellent

• Some differences from NYVAC reported
  – But appear minor

• Orthopox vectors being developed for diverse species
  – e.g. cattle (TB) and chickens (influenza)
  – Multiple avipox vectors widely used as veterinary vaccines
Malaria
A Complex Parasite Life-Cycle
The MeTRAP Vaccine Insert

Targets the Liver-Stage of *Plasmodium falciparum*

A Polyepitope-Protein Vaccine Construct

**ME:** Multiple malaria epitopes

**TRAP:** Thrombospondin-Related Adhesion Protein

TRAP strain is T9/96 in this vaccine
Why Use Viral Vectors in Prime-Boost Regimes?

• Best means of safely inducing T cells in humans

• 7 vaccines have induced >1500 SFU/ml
  – in malaria (x 3), HCV, HIV, tuberculosis and influenza
  – all used MVA viral vector boosting

• Adenovirus – MVA is the most potent approach
  – better than DNA – Adenovirus
  – better than Adenovirus - Heterologous Ad

Adenovirus Prime

8 weeks

MVA Boost
# 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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<tbody>
<tr>
<td>DNA x 3</td>
<td>48</td>
<td>ME-TRAP</td>
</tr>
<tr>
<td>Fowlpox x 2</td>
<td>50</td>
<td>ME-TRAP</td>
</tr>
<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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<tr>
<td>DNA x 2 - MVA</td>
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<td>Fowlpox x 2 - MVA</td>
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<tr>
<td>ChAd63-MVA</td>
<td>2800</td>
<td>ME-TRAP</td>
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</table>
Viral Vector Vaccines
to Maximise Cellular Immunogenicity

Adenovirus Prime

8 weeks

MVA Boost

Malaria, HCV, HIV, influenza, TB...
MVA Can Re-Boost at One Year
Gambian Data: FFM and DDM

Moorthy et al. 2004 J Inf Dis
ChAd-MVA Responses are Durable and Can Be Re-Boosted at 6-30 Months Post-MVA

O’Hara et al. 2012 J Inf Dis
ChAd63-MVA MeTRAP Efficacy correlates with CD8$^+$ T cells

57% (8/14) of volunteers show vaccine efficacy
21% (3/14) show sterile protection
3/3 showed efficacy at 8 months

CD8$^+$ T cells correlate with efficacy
specifically γ-interferon +ve cells

Ewer et al. submitted
MVA Boosts MSP1 & AMA1 Antibodies
ChAd63-MVA Phase Ia clinical trials

Sheehy SH et al. (2011) Mol Ther 19:2269-76
Sheehy SH et al. (2012) PLoS ONE 7:e31208
Sukuta Vaccine Clinic
The Gambia
MVA: Immunogenicity Summary

• MVA is a poor priming vector
  – but it remains the best boosting vector
• Generally MVA boosts what is primed
  – responses appear to broaden
• Mixtures of different vectors (Ad mixed with MVA)
  – are more potent than the individual vectors
  – both pre-clinically and clinically (Reyes-Sandoval et al. Mol Therapy 2012)
• Many adjuvants reduce MVA immunogenicity
  – IMX313 increases it as a carrier protein (Spencer et al. PLoS One 2012)
• Late re-boosting should be explored further
Why Might You Not Use MVA?

Three potential concerns

1. Cost of scale-up
   - Use cell lines (EB66, AGE1.CR)

2. Instability
   - Use the right promoter

3. IP
   - No longer an issue
3 Take Home Messages

• In nearly all cases MVA boosts pre-existing T cell responses by about 5 to 10 fold
  – to 1,000 - 10,000 SFU / million
  – significant efficacy in 6 phase II malaria trials required MVA boosting
  – also good antibody boosting, by about a 10 fold

• Safety has been very good in thousands of vaccinees
  – Malaria, TB, HIV, cancer, flu, HCV: > 4000 subjects
  – Europe, Africa, US

• Re-boosting with MVA vector after 6 months works
  – in mice and in humans
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