Review on vectored influenza vaccines

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Viral Vectored Influenza Vaccines

• Can be used to induce antibodies against HA
  – Will also boost CD4$^{+}$ T cell responses against HA
  – Developed as replacement to inactivated virion vaccines

• Can be used to boost T cell responses against internal antigens
  – Boost naturally acquired T cell responses in humans, which are biased towards CD8$^{+}$
  – Could be used with inactivated virion vaccines

• Could do both at the same time
Overview of pre-clinical studies

**HA** expressed from Ad, MVA, Vacc, fowlpox, canarypox, NDV, Herpes Virus of Turkeys, Equine Herpes Virus, Duck Enteritis Virus

**M2** expressed from Ad, Vacc

**M1** expressed from Ad, MVA, Vacc

**NP** expressed from Ad, MVA, Vacc

**NA** expressed from MVA
Pax Vax Oral Replication Competent AdHu4 H5HA

• 166 healthy volunteers aged 18-40
• Dose escalation from $10^7$ to $10^{11}$ vp plus placebo, 2 doses
• Boost with 90 $\mu$g inactivated parenteral H5N1
• 11% of vaccinees and 7% of placebo recipients seroconverted
  – Following boost, 100% of the high dose cohort seroconverted, 36% of placebo group
• Ad4 virus detected in rectal swabs from 46% of participants, with or without Ad4 seroconversion
  – Gurwith et al., Lancet ID 2013
VaxArt Oral Replication Deficient AdHu5 H5HA with a TLR3 ligand adjuvant (dsRNA)

- 54 healthy volunteers, dose escalation $10^8$ to $10^{10}$ vp or placebo
- No virus shedding detected
- No significant changes in anti-Ad5 responses
- No measureable HI titres, but IFN-γ and GrzB responses to HA increased
  - Peters et al., Vaccine 2013
- More recent clinical studies with seasonal HA resulted in increases in HI and neutralising antibody titres
T Cells Protect Against Influenza

- In animal studies, T cells against NP protect against flu challenge
- In clinical trials of flu virus challenge, in volunteers with naturally acquired immunity to flu, T cells protect against flu challenge
  - One third of volunteers protected, even if they did not have antibodies recognising the challenge virus
  - Some evidence of cross-subtype protection
T cell responses against influenza prevent illness after infection

People with strong T cell responses to influenza before the 2009 pandemic were less likely to become ill, have fever or sore throat, than those with low T cell responses.

Can we boost these responses with a vaccine?

Sridhar, Nature Medicine 2013
Can we boost T cell responses to influenza by vaccination?

LAIV increases T cell responses to influenza in children, but not in adults. Inactivated vaccine dose not boost T cell responses

He et al
J Virol 2006
Malaria vaccine development – ‘flu doesn’t boost’

- Recombinant flu expressing a P. yoelii epitope followed by recombinant vaccinia expressing the same CD8\(^+\) epitope, then P. yoelii challenge
  - Flu prime      Vacc boost      Protection
  - Vacc prime    Flu boost       No Protection
  - Li et al. PNAS 1993

- Repeated with cold adapted recombinant flu prime, MVA boost
  - CA prime/MVA boost more protective than CA prime/Vacc boost
  - No protection from Vacc or MVA alone
  - Flu not tested for ability to boost
  - González-Aseguinolaza et al., J Virol 2003
Safety as expected for MVA vaccination

T cell responses extremely high – only seen at this level post BCG priming and MVA 85A boosting for TB

The majority of the T cell response is CD8+ (before and after vaccination)

Berthoud et al., Clin Infect Dis. 2011 52: 1-7
Immunogenicity maintained in older adults

No significant difference in T cell responses to NP and M1 between young and older adults, either before or after vaccination. Antrobus, 2012 PLoS One
Clinical Efficacy

partial efficacy in a small influenza challenge trial

Volunteers vaccinated with $2.5 \times 10^{10}$ vp displayed 7x increase over baseline, with responses remaining elevated over baseline at D21.

Increased response in volunteers following MVA boost; well maintained to 8 weeks post boost.

Antrobus et al 2014.
Current Clinical Study

• 48 healthy volunteers, in 4 groups of 12
  – 18-50 years old
• Randomised to receive either the ChAdOx1 NP+M1 or MVA NP+M1 at Prime D0 followed by boost at either Week 8 or Week 52 with ChAdOx1 NP+M1 or MVA NP+M1
• 18 month follow up for all groups

<table>
<thead>
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<th>Group</th>
<th>Day 0</th>
<th>Week 8</th>
<th>Week 52</th>
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<tbody>
<tr>
<td>1</td>
<td>ChAdOx1 NP+M1</td>
<td>MVA NP+M1</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>ChAdOx1 NP+M1</td>
<td>-</td>
<td>MVA NP+M1</td>
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<tr>
<td>3</td>
<td>MVA NP+M1</td>
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<tr>
<td>4</td>
<td>MVA NP+M1</td>
<td>-</td>
<td>ChAdOx1 NP+M1</td>
</tr>
</tbody>
</table>
T cells AND antibodies: Co-administration of MVA-NP+M1 and TIV in mice

Mullarkey 2013 Eur J Immunol

* p<0.05
** p<0.01
*** p<0.001
Humoral responses following co-administration of MVA-NP+M1 and TIV in C57-B6 mice

• Peak antibody response seen at 8 wks post vaccination for all groups
• For intermediate (0.2 μg) and high dose (1 μg) groups Ab titers are significantly higher through 6 months

Stats: ELISA Mann-Whitney Test

* p<0.05
** p<0.01
*** p<0.001
‘Adjuvanting’ HA broadens the response

• DNA prime/Ad boost with H1H1 HA elicited a broadened pseudotype neutralization response within the H1 subtype and some cross-reactivity against H2N2 and H5N1 viruses: Wei 2010

• MVA H5HA, cross-clade neutralisation: Kreijtiz 2009

• MF59 adjuvanted H5HA, cross-clade responses: Galli 2009
Co-administration in humans

Adverse event profile was unchanged from giving only MVA-NP+M1

Mean fold increase in HI titre pre to post vaccination: response to H3N3 and H1N1 improved by co-administration

T cell response to NP and M1 boosted by MVA-NP+M1 alone, or co-administration

Antrobus 2014 Mol Ther.
How to apply this?

• MVA-NP+M1 does not need frequent updating
  – can be manufactured at scale, year round, ready to combine with HA protein (egg produced or cell line produced antigen, or recombinant protein)

• HA protein needs to be updated in response to genetic drift,
  – but as adjuvanted vaccines induce more cross-reactive responses, annual updates are not necessary

• Year-round manufacture and vaccination therefore becomes possible
  – Continue surveillance, update HA only after significant changes or introduction of a new subtype
How to vaccinate?

- In mice, we saw the same adjuvant effect when vaccines were mixed in the same syringe or given as two injections to the same limb. The adjuvant effect was reduced when the vaccines were given in opposite limbs.
- In clinical studies we gave two injections to the same limb approximately 1cm apart, within a few minutes. We do not believe precise spacing or timing is important.
- For maximum flexibility MVA-NP+M1 can be manufactured separately and then administered with any HA-containing vaccine (seasonal or pandemic). For an improved seasonal vaccine it could also be formulated with the HA.
Recommendations for WHO

• Support challenge studies
  – By assisting with making virus stocks for challenge available
  – These need to be updated frequently, but one GMP manufacture would be sufficient to challenge many individuals
  – Help to standardise screening assays for volunteers entering challenge studies
  – Work with CROs to standardise influenza challenge studies
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