Development and evaluation of influenza vaccines based on adenovirus and MVA as vectors
Sarah C Gilbert
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, plus some evidence of cross-subtype protection, McMichael NEJM 1983
  – Pre-existing influenza-specific CD4+ T cells responding to internal proteins correlate with disease protection against influenza challenge in humans, Wilkinson Nat Med 2012
T cells also recognise H5N1 peptides even in the UK population

Cross-reactive responses recognise Matrix (red) and NP (blue) most frequently
Lee et al. JCI 2008 118:3478-90
T Cell Responses Decline After Natural Infection

The half life of CD8+ T cells recognising flu is 2-3 years.

A T cell boosting vaccine could potentially achieve protective levels in anyone previously exposed to ‘flu.

Boosting to higher levels mean protection lasts longer.

MVA-NP+M1

- Antigen: NP:M1 fusion protein.
- H3N2 sequences used
- Flexible linker between NP and M1, total coding sequence 758 aa
- Inserted at TK locus of MVA, Vaccinia P7.5 promoter, no marker
- Single intramuscular injection
Safety and Immunogenicity in Phase I

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
The response is mainly CD8$^+$

CD8$^+$ and CD4$^+$ T cells that secrete IFN-γ before and after MVA-NP+M1 immunisation.

Data from group receiving 2.5 x 10$^8$ pfu i.m.

Berthoud et al., Clin Infect Dis. 2011 52: 1-7
Vaccinees Aged 50 plus

Clonality studies indicated that MVA-NP+M1 expanded pre-existing memory CD8\(^+\) T cells. The observed CD27\(^+\)CD45RO\(^+\)CD57\(^-\)CCR7\(^-\) phenotype indicates a lack of terminal differentiation and senescence.

Phase IIa Flu A Challenge

• Screen volunteers for low HI titre
  – Volunteers recruited at Oxford CCVTM and Southampton WTCRF, age 18-45 years

• Challenge with well characterised drug-sensitive flu A

• Volunteers remain in containment for 7-10 days, monitor symptoms and virus shedding (nasal washes) daily
  – Challenge and quarantine phase conducted by Retroscreen Virology Ltd., London

• Measure T cell responses before and after vaccination and challenge.
Clinical Outcome

Challenge virus was H3N2 A/Wisconsin/67/2005

Influenza challenge study:
Three volunteers shed virus on more than one day but did not seroconvert.
Not associated with more severe symptoms

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<th>Symptom severity</th>
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Immunogenicity for co-administration of MVA-NP+M1 and TIV in mice

*** $p<0.0001$

Mullarkey et al., submitted
‘Adjuvanting’ HA broadens the response

• DNA prime/Ad boost with H1HA 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: Kreijtz 2009

• MF59 adjuvanted H5HA, cross-clade responses: Galli 2009
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 (inactivated or recombinant)
• 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
Clinical Study FLU003

• Adults aged 50 years or over randomised to receive TIV or TIV + MVA-NP+M1
• Measure T cell responses to NP and M1, HI titres to all three TIV components
• Further assays to assess the breadth of humoral responses
• Manuscript now in preparation
ChAdOx1 NP+M1

- Novel simian adenovirus ChAdOx1 expressing the same NP+M1 insert has now completed dose escalation studies in preparation for

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In Summary

- MVA-NP+M1 boosts T cell responses to conserved antigens of influenza to levels that can protect against disease and virus shedding.
- Co-administration of MVA-NP+M1 with a protein HA vaccine additionally results in increased humoral responses to HA.
- This provides a rapidly deployable solution to inducing broad immunity to influenza.
- ChAdOx1 NP+M1 dose escalation studies completed, Phase I studies to start Q2 2013.
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