MVA85A

Progress with phase I studies and some regulatory and safety aspects

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MVA85A

- **The first TB subunit vaccine candidate in clinical evaluation**
- **Currently in trials in UK and The Gambia**

- **MVA = modified virus Ankara, a viral vector vaccine**
- **A “boosting” vaccine**

Rationale for a Boosting Vaccine in Tuberculosis

- BCG has low efficacy in teenagers / adults in Asia and Africa
  - environmental bacteria both mask and inhibit BCG's effects
- A boosting vaccine that could build on pre-existing anti-mycobacterial T cell responses should benefit from these responses rather than be inhibited by them

Possible Aims of New TB Vaccines

- Prevent primary infection
  - lots of animal models
    - difficult to do better than BCG
- Prevent disease in those already infected
  - boosting immunity
    - Especially tennagers
    - ? MVA
- Improve treatment of disease
  - very difficult
    - e.g. *M. vaccae*

Heterologous Prime-Boost Immunisation

- 2 different vaccines, each encoding the same antigen, given several weeks apart.
  - Induces high levels of CD4+ and CD8+ T cells
  - Only poxviruses and adenoviruses boost T cell responses strongly
  - Several regimes tested in humans
    - DNA-MVA
    - FP9-MVA
    - DNA-adenovirus

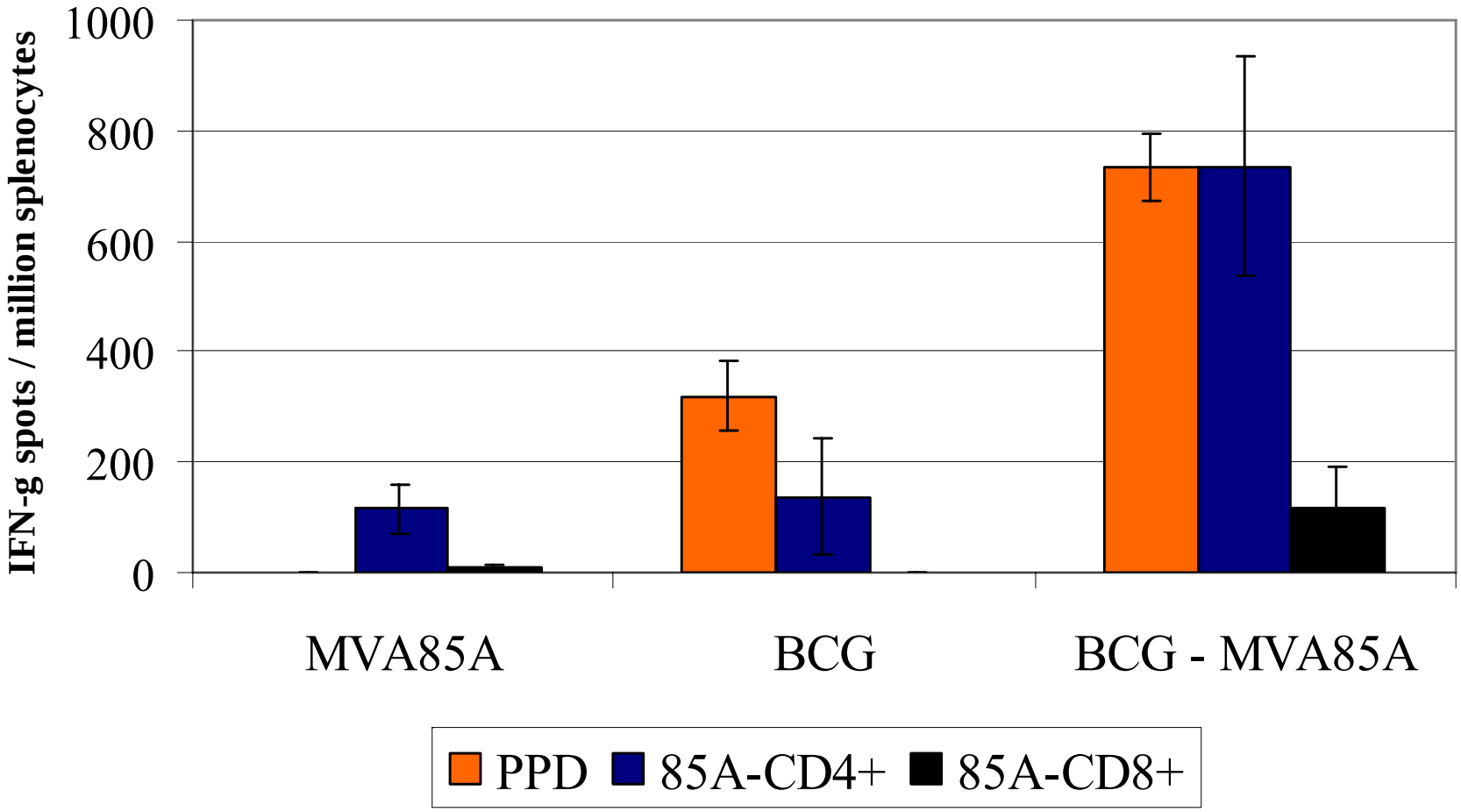
Modified Vaccinia Virus Ankara (MVA)

- A non-replicating vaccinia strain
  - Deletions in host range genes and cytokine receptor genes
- Safety
  - Over 120 000 people immunised against smallpox
  - Over 500 people safely immunised with recombinants
  - Mainly HIV-ve but also HIV +ve vaccinees
- Strong boosting of CD4 + & CD8+ T cells in humans (McConkey et al. *Nature Medicine* 2003)
  - In trials for malaria, HIV, melanoma, hepatitis, HPV

BCG In Prime-Boost Regimes

- Need common antigen to prime and boost
- Antigen 85A is immunodominant and conserved amongst all mycobacterial species and in all strains of BCG
- Enhanced efficacy of BCG-MVA Ag85A in BALB/c mice (Goonetilleke et al. *J. Immunol.* 171, 1602-1609, 2003)
- BCG-MVA-Fowlpox better than BCG in guinea pigs (Rawkins et al.)
- BCG-MVA-Fowlpox protective in macaques (Langermans et al. BPRC)

MVA-Antigen 85A Boosts BCG-Primed T Cell Responses in Mice



MVA85A:
Phase I Clinical Trials

3 small-scale phase I studies in Heaf-negative healthy adult (18 - 45 years) volunteers in the UK

- BCG alone
- MVA85A alone
- BCG prime-MVA85A boost

Immunogenicity Measures

- *Ex-vivo* IFN- γ ELISPOT assay using
  - Antigens
    - 85A (purified)
    - 85 B (Recombinant)
    - PPD
  - Peptides
    - 85A
    - ESAT6/CFP10

MVA85A: GMP Manufacturing

- Vaccine manufactured under cGMP conditions (IDT, Germany)
  - 1983 seed stock
  - MSV and WSV
  - grown on chick embryo fibroblasts
  - Sucrose cushion purification
  - Titre at IDT
  - EP release assays: especially microbiological
  - Filling at IDT
  - Low cost!

Toxicology

- GLP Toxicology studies (on clinical lot)
  - single species, two dose, scaled dose
- Tissue distribution studies
  - Culture and PCR
- Potency and stability studies
  - Virus stability on repeated passage
  - ELISPOT
- Sequencing of insert

Insert Design

- Ag85A conserved sequence
- Not codon optimised
- tPA leader sequence
- PK antibody tag at C terminus
- Murine T cell epitopes in Balb/c used for potency testing
- Beta-galactosidase insert under late vaccinia promoter

Regulatory Reviews

- Local Ethical Committee approval
  - often multiple
- Medicines Control Agency (MHRA) review

  - DDX / CTX submission (CTA in 2004)
- Department of the Environment
  - MVA approval for contained use (Category 1)
- Gene Therapy Advisory Committee Review
  - No committee presentation
- Health and Safety Executive use approval
  - GMO issues in the UK

Some General Issues

- What is required vs what is recommended?
  - consultants advise companies
- What are the requirements for phase I vs those for licensure?
- Separate regulatory filings for multiple vaccines in prime-boost protocols
- No “combined” product toxicology for prime-boost vaccines
- Almost all malaria, TB and HIV vaccines in phase I trials will not reach licensure

MVA85A Vaccinations

- 14 volunteers immunised with 5 x 10^7pfu id
  - 11 immunised x 2 with MVA85A
  - 3 immunised x 1 with MVA85A
- Schedule:
  - Screen + Heaf test;
  - 1st immunisation at week 1,
  - 2nd immunisation at week 4;
  - reviewed at 1w; 4w; 8w; 12w; 24w

MVA85A Induced Responses

Why Such Strong Immunogenicity?

- Strikingly strong T cell responses to Ag85A induced by a single immunisation with MVA85A
- 5-10 fold higher responses than with other MVA constructs tested to date
- Suggests that these volunteers may have pre-existing memory T cell responses to a cross-reactive antigen (cf Weir et al.)

MVA85A Trials Summary

- Good safety of MVA85A
- Unexpectedly strong T cell immunogenicity of MVA85A in Oxford volunteers
- Studies in Gambian volunteers underway
- BCG-MVA85A immunogenicity appears even stronger than MVA85A alone

Next Steps

- Complete current phase I studies in Oxford and The Gambia
- Evaluate further immunological responses
  - Cultured ELISPOT, FACS
- Phase I trials in *M. tuberculosis* infected healthy volunteers – now approved
- Evaluate Fowlpox-Ag85A immunisation regimes
- Phase I studies in HIV+ves
- "Challenge" with BCG as possible efficacy model

Safety / Regulatory Issues: **Koch Phenomenon**

- Hyper-responsiveness to mycobacterial antigens in vaccinated subjects with tuberculosis disease
- Similar reactivity seen with some therapeutic vaccines in some animal models
- Could similar reactogenicity be observed in non-diseased vaccinees administered new generation TB vaccines?

Avoiding the Koch Phenomenon: an approach

- Vaccinate sequentially:-
  - Mycobacterially naïve: skin test + ELISPOT negative
  - BCG +ve, not *M. tuberculosis*-infected
  - *M. tuberculosis*-infected but healthy
  - Tuberculosis patients (post-chemotherapy)

- Monitor for "mild Koch reactions"
  - CRP, CXR, ?CT

Some Future Issues

Live Vectors in HIV +ves

- Distinguish replicating BCG from non-replicating viral vectors: MVA, FP9
- MVA safe in severely immunosuppressed macaques
- MVA used in HIV immunotherapy
- Several ongoing trials of MVA and other non-replicating poxviruses in HIV+ves

High-Risk Individuals in Vaccine Trials

- Efficacy trials of new TB vaccines require samples of thousands followed for years even at moderate incidence rates
- High risk populations allow smaller (safer) more rapid trials
  - e.g. Household contacts; HIV+ves
- But how high a risk is allowable without requiring chemoprophylaxis?

Post-Exposure Vaccines

- A new concept
- Risk of immunopathology?
  - e.g. Vaccination of the skin test positives
  - is further toxicology required / useful?
- Very high incidence rates in recent skin-test convertors
  - At what incidence rate should chemoprophylaxis be used?
  - Is careful follow-up an ethical alternative?

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