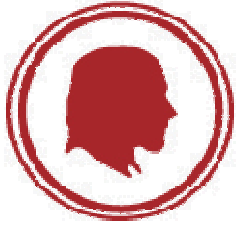




Improving BCG with MVA85A: An update on clinical trials

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The Jenner Institute
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MVA85A

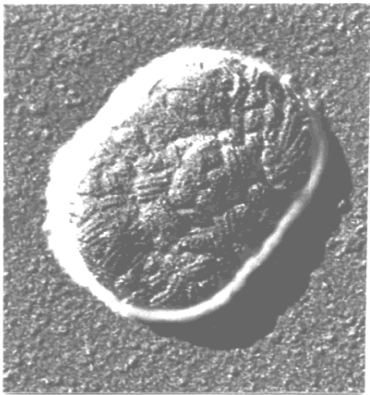
Modified vaccinia Ankara (MVA)

Poxvirus

No replication in mammalian tissues

Good T cell enhancing vector

Excellent safety record



M.tb antigen 85A

Mycolyl transferase

Major target antigen

Protective in small animals

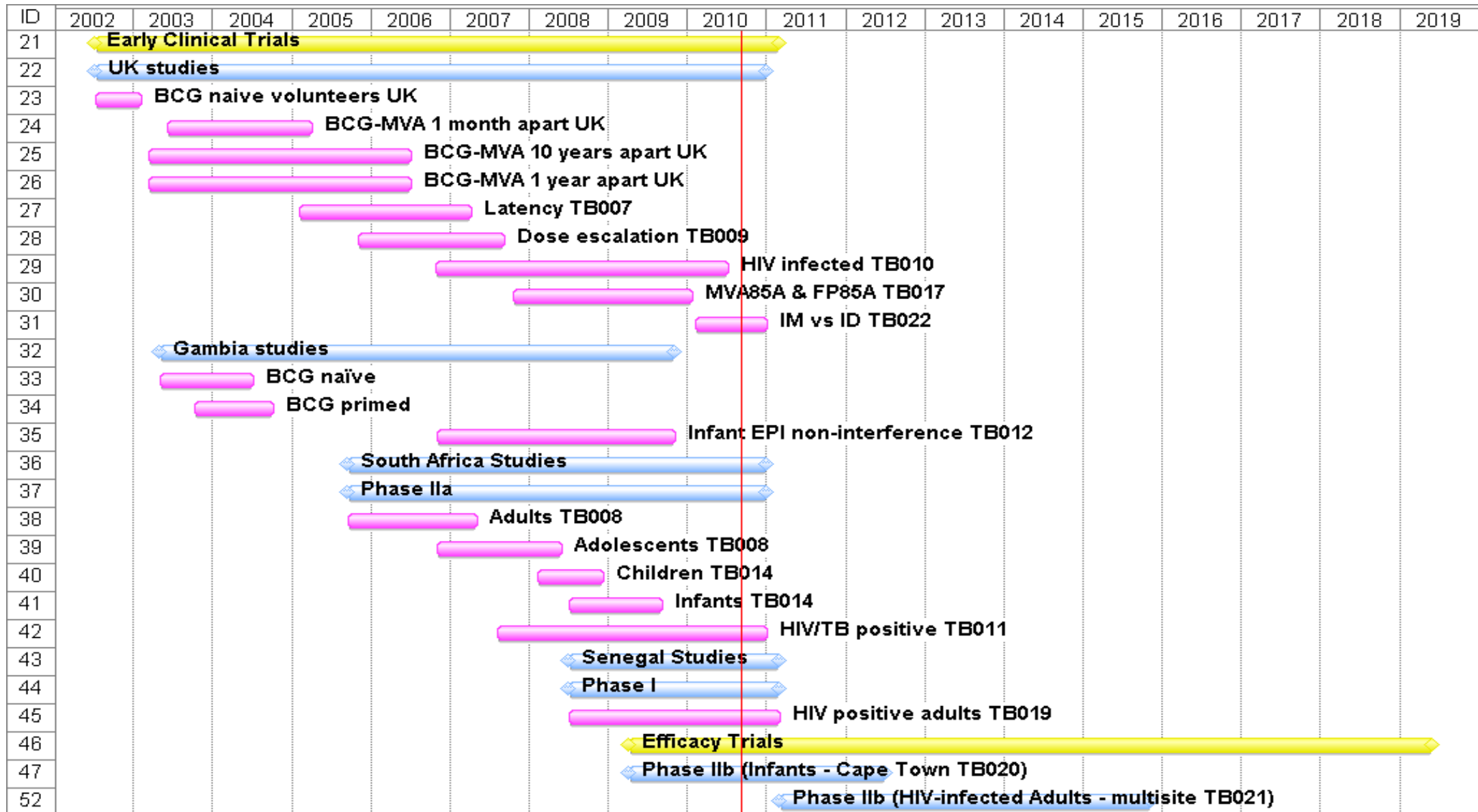
In all environmental
mycobacteria

Doesn't interfere with new
diagnostic tests

BCG - MVA85A regimen



Summary of clinical trials with MVA85A since 2002





Outcome measures in all trials

- Safety
- Immunogenicity
 - Ex-vivo IFN- γ Elispot assay
 - 18 hour incubation
 - More detailed immunological analysis
 - Multi-parameter flow cytometry
 - Proliferation
 - TReg/IL17 analysis
 - Gene expression studies
- Efficacy (Phase IIb trials)



Safety data

- 12 clinical trials completed; 4 ongoing
- Over 1000 subjects vaccinated, including
 - 47 latently infected
 - 80 HIV infected
 - 24 children
 - 1056 infants
- Well tolerated
- Mild local reactions common (>90%)
- Mild systemic side effects common
- No signs of immunopathology



EPI non-interference study in Gambian infants

- 3 groups (16/52 old infants):
 - EPI alone
 - EPI + MVA85A
 - MVA85A alone; 3rd EPI deferred
- Status
 - Study complete
- Safety profile is excellent
- No effect of MVA85A on EPI immunogenicity





Trials in HIV-infected adults

	TB010	TB011	TB019
Location	Oxford, UK	Worcester, South Africa	Dakar, Senegal
Dose	10 with 5×10^7 pfu 10 with 1×10^8 pfu	5×10^7 pfu	1×10^8 pfu
Participants	20	36	24
<i>M. tb</i> coinfectd	4	15	17
CD4 count	>350	>300	>300
Viral load	<100,000	Not specified	<100,000
ARV treatment?	No	24 – No 12 – Yes	Group 1 (n=12) : No Group 2 (n=12) : Yes
Second dose?	No	No	Group 1 at 12 months Group 2 at 6 months



HIV safety data

- No effect on HIV RNA load
- No effect on CD4 count
- AE profile as in HIV- subjects
- No evidence of immune activation



Summary

- MVA85A safe and immunogenic in all clinical trials to date including:
 - *M.tb* infected adults (UK and South Africa)
 - HIV infected adults (UK and South Africa)
 - Infants (The Gambia and South Africa)
 - Adolescents (South Africa)
- MVA85A induces highly polyfunctional CD4+ T cells, which proliferate and have a non-terminally differentiated phenotype; MVA85A induces IL-17+ and IFN γ + CD4+ T cells, and induces CD8+ T cells
- MVA85A can improve BCG induced protection in mice, guinea pigs, non-human primates and cows
- **Clinically the most advanced new TB vaccine**



Does it work?

- Challenges in evaluating efficacy of a new TB vaccine
 - No perfect immunological correlate of protection
 - No perfect animal model

 - Efficacy trials with large numbers of subjects and long periods of follow up needed
 - 3 target populations
 - Infants
 - Adolescents
 - HIV infected adults



Infant Phase IIb efficacy trial

- Objectives:

- Safety
- Immunogenicity
- Efficacy (against disease & infection)
- Immune correlates

- Design:

- BCG vaccinated infants in Worcester, South Africa
- Randomised at 18-26 weeks to receive either:
 - MVA85A (1×10^8 pfu)
 - placebo (Candin)
- Sample size = 2784 (1392/arm)
 - Cumulative TB incidence of 3%
 - 90% power to detect 60% improvement over BCG alone

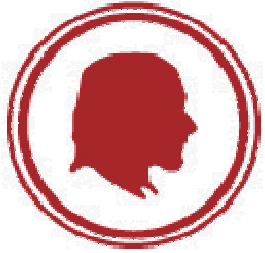




Infant Phase IIb efficacy trial

- Status:
 - Study sponsored by Aeras
 - Study commenced in April 09
 - Dosing commenced 15th July 2009
 - As of 15th September:
 - 3723 consented to date
 - 1673 randomised
- Collaborators:
 - SATVI
 - Aeras
 - Wellcome Trust
 - OETC





Phase IIb trial in HIV+ adults

- Proof of concept study in HIV+ adults
 - protection against TB disease
 - protection against *M. tb* infection
 - safety & immunogenicity
- Two sites
 - South Africa: Cape Town with Rob Wilkinson
 - Senegal: Dakar with Souleymane Mboup
- Sponsored by Aeras
- Funded by EDCTP, MRC and Aeras
- Due to start in Q1 2011



HIV efficacy trial design

- HIV-infected adults
 - +/- ARV
 - 1400 subjects randomised to receive either:
 - 2 doses of MVA85A, 6-9 months apart or
 - Placebo (candin)
 - Annual incidence assumed to be 2.5%
 - 80% power to detect 60% improvement
 - Follow-up for 2 years



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