



Boosting BCG with MVA85A: Results of clinical trials

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MVA85A

- MVA
 - Attenuated vaccinia strain
 - Safe
 - Good at boosting T cell responses
- Antigen 85A
 - Leading antigen for inclusion in TB subunit vaccine
 - Protective in mice and guinea pigs
 - Immunodominant in animal and human studies
 - Up to 40% of PPD response is Ag 85 complex
 - Highly conserved amongst all mycobacteria
 - Present in all strains of environmental mycobacteria
 - Present in all strains of BCG and *M.tuberculosis*

Design of clinical studies with MVA85A

- Gradually increasing mycobacterial load:
 - BCG naïve, TST negative adults
 - BCG primed adults
 - Latently infected adults
- Studies conducted:
 - First in a country with low mycobacterial exposure (UK) first,
 - Subsequently conducted in a country with higher mycobacterial exposure (The Gambia & South Africa)
- Aim to minimise risk of a Koch reaction

MVA85A: Summary of trials: 2002-2006

Trial Number	Vaccination	Volunteer Type	Total number to be recruited	Location	Status
002	MVA85A	BCG naive adults	14	Oxford	Completed
004	BCG-MVA85A (1 MONTH APART)	BCG naive adults	10	Oxford	Completed
005	MVA85A (>10 YEARS APART)	BCG vaccinated adults	12	Oxford	Completed
007	MVA85A	Latent TB infection	12	Oxford	Enrolment complete
008	MVA85A	Adults Adolescents	36	Cape Town	Adult enrolment complete Adolescents ongoing
009	MVA85A	Dose-finding	24	Oxford	Enrolment complete
010	MVA85A	HIV infected	20	Oxford	Recruitment underway
002G	MVA85A	BCG naïve	11	The Gambia	Completed
005G	BCG-MVA85A	BCG vaccinated >10 years ago	10	The Gambia	Completed
011	MVA85A	HIV/M.tb infection	36	Cape Town	Awaiting approval
012	MVA85A	Infants	471	The Gambia	Recruitment underway

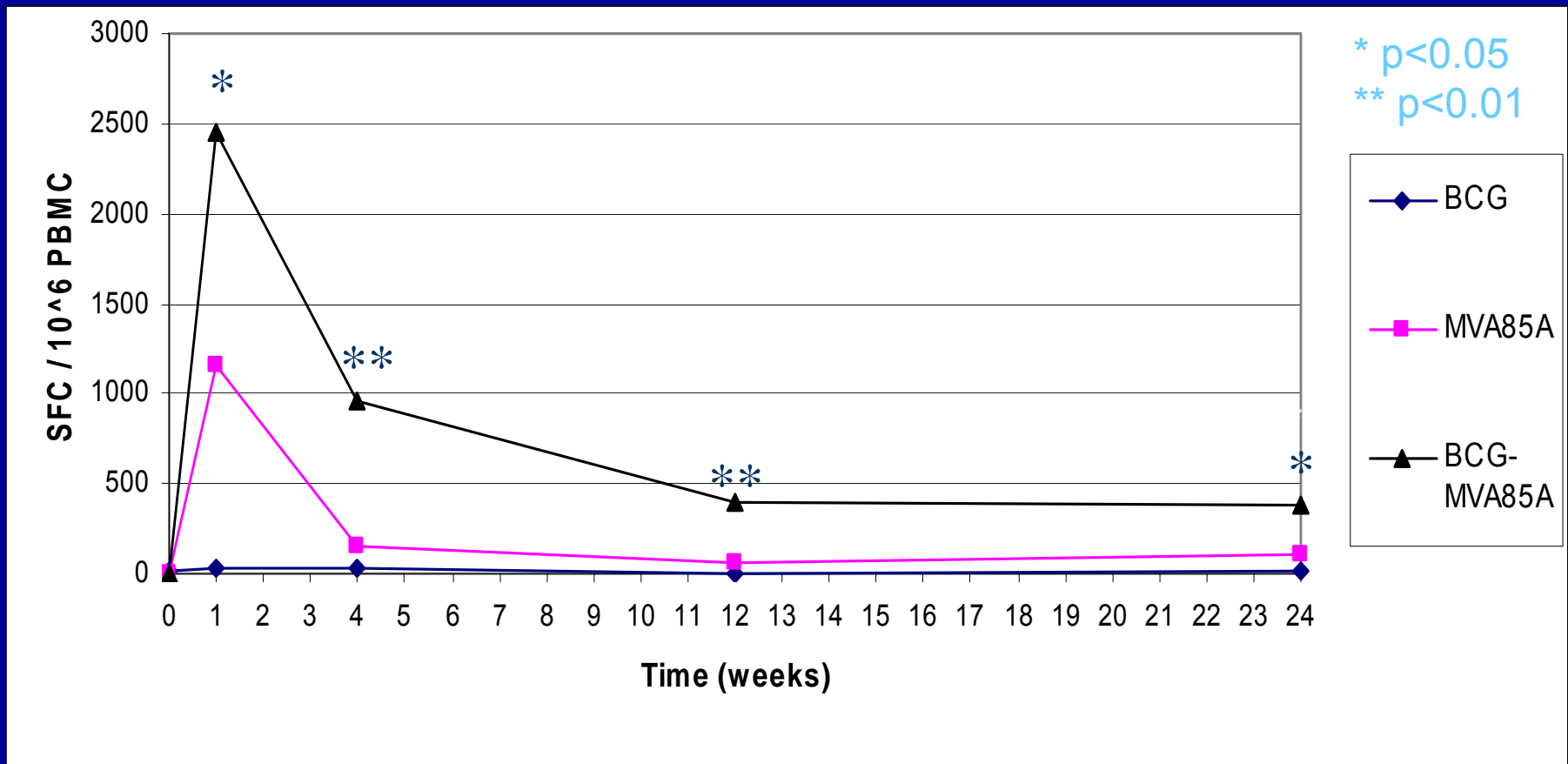
Outcome measures in all trials

- Safety
- Immunogenicity
 - Ex-vivo IFN- γ Elispot assay
 - More detailed immunological analysis

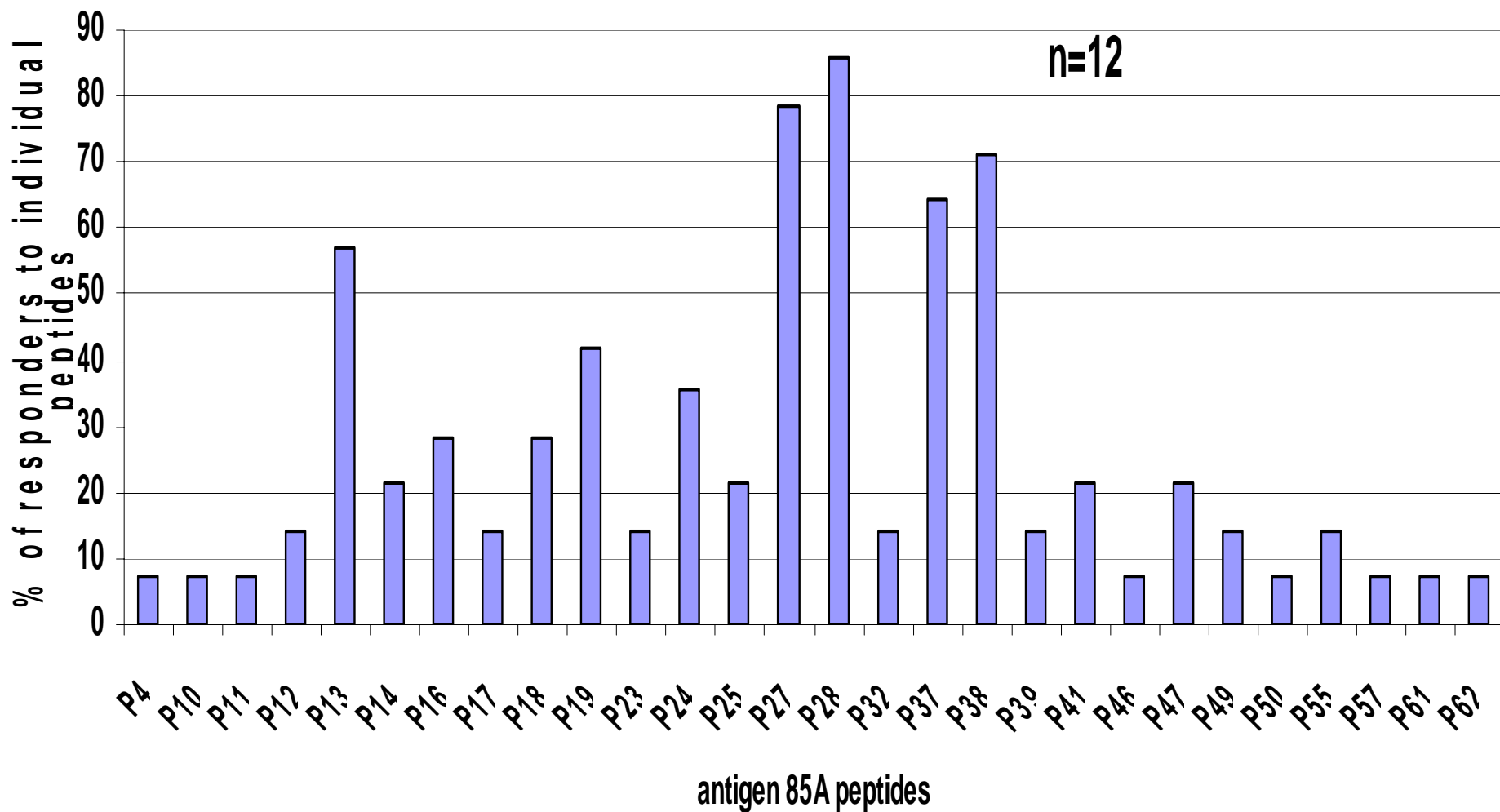
Safety data

- No serious or severe vaccine related adverse events in any clinical trials to date
- Well tolerated
- Mild local reactions common (>90%)
- Mild systemic side effects in up to 30%
- No signs of immunopathology

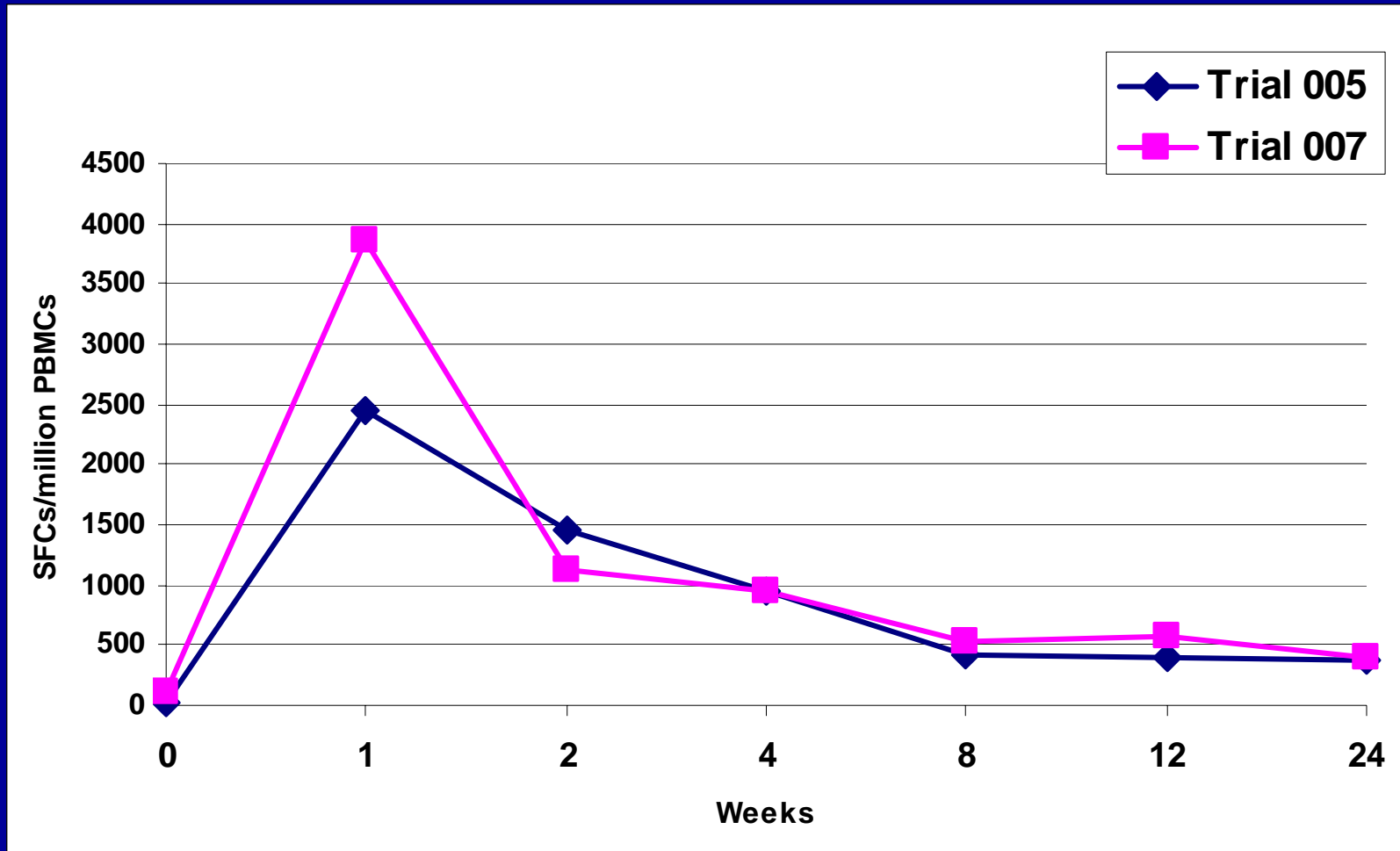
Median Elispot summed peptide pool responses: BCG v MVA85A v BCG-MVA85A (n = 17)



Broad range of CD4+ T cell epitopes across the whole antigen recognised after vaccination with MVA85A in BCG vaccinated individuals



Comparison of priming with BCG (T005) and priming with *M.tb* (T007): Median Elispot responses to peptide pools



Measuring vaccine induced responses

Novel TB vaccines target cellular immune response > Th cell IFN γ

PBMC IFN γ

1. ELISpot

BCG-MVA85A - Phase I/II Oxford & Cape Town

18 hr

Whole blood ICS - IFN γ & IL-2

2. Multi-parameter flow cytometry

Phase IV BCG (infants) - Cape Town

12-18hr

Whole blood culture supernatant - total IFN γ

3. ELISA

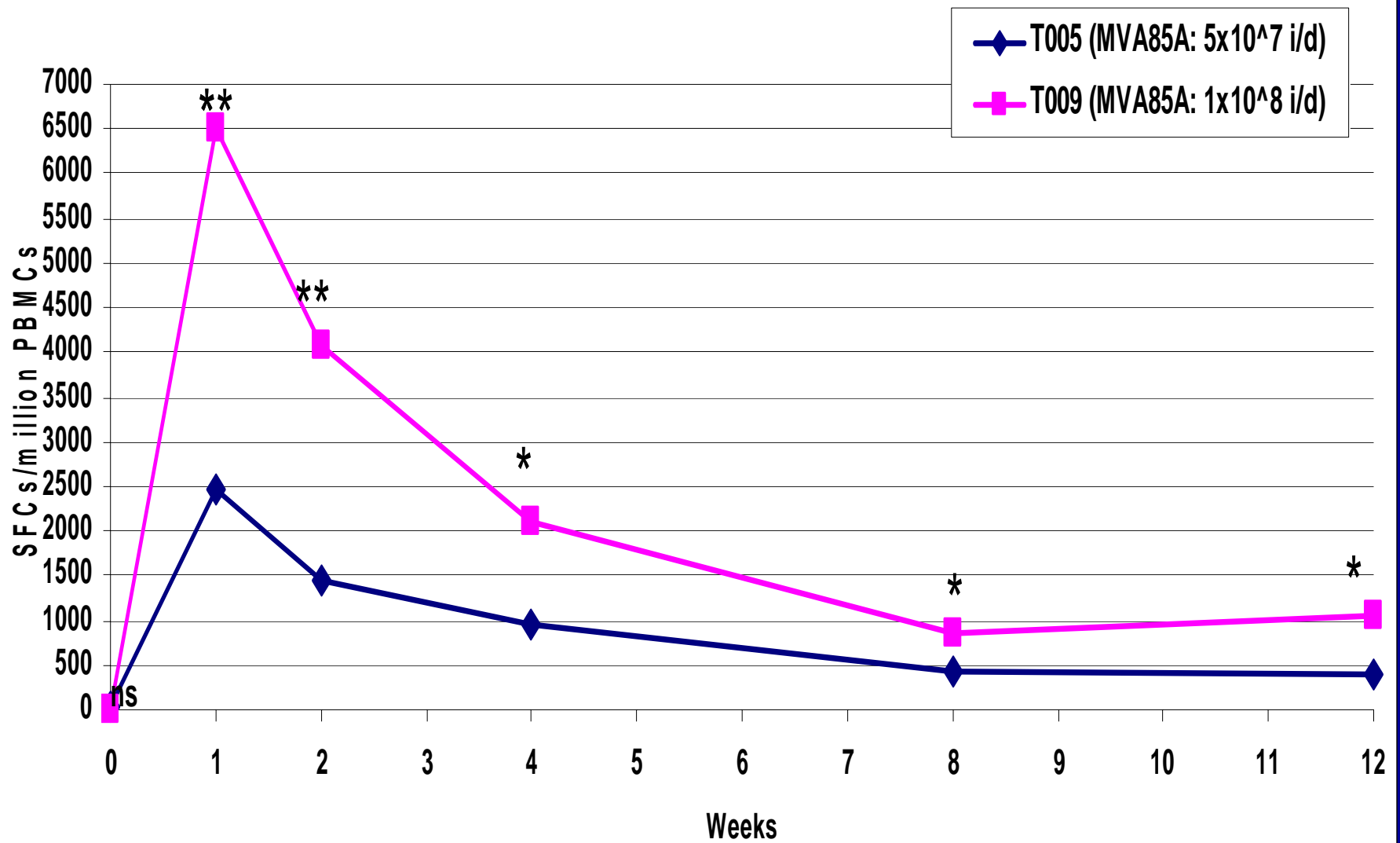
BCG - London & Malawi

6-7 days

High dose trial (10^8 pfu MVA85A)

- 12 BCG primed subjects
 - PBMC IFN γ ELISpot
 - Whole blood 7 day culture supernatant IFN γ ELISA (Dockrell)
 - CFSE proliferation
 - Whole blood ICS (IFN γ & IL-2; $\alpha\beta$ & $\gamma\delta$ T cells) (Hanekom)
- Similar information?
- Measuring comparable populations of responding cells?

Median IFN-g elispot responses to 85A peptide pools: T009 vs T005



Summary of trials to date

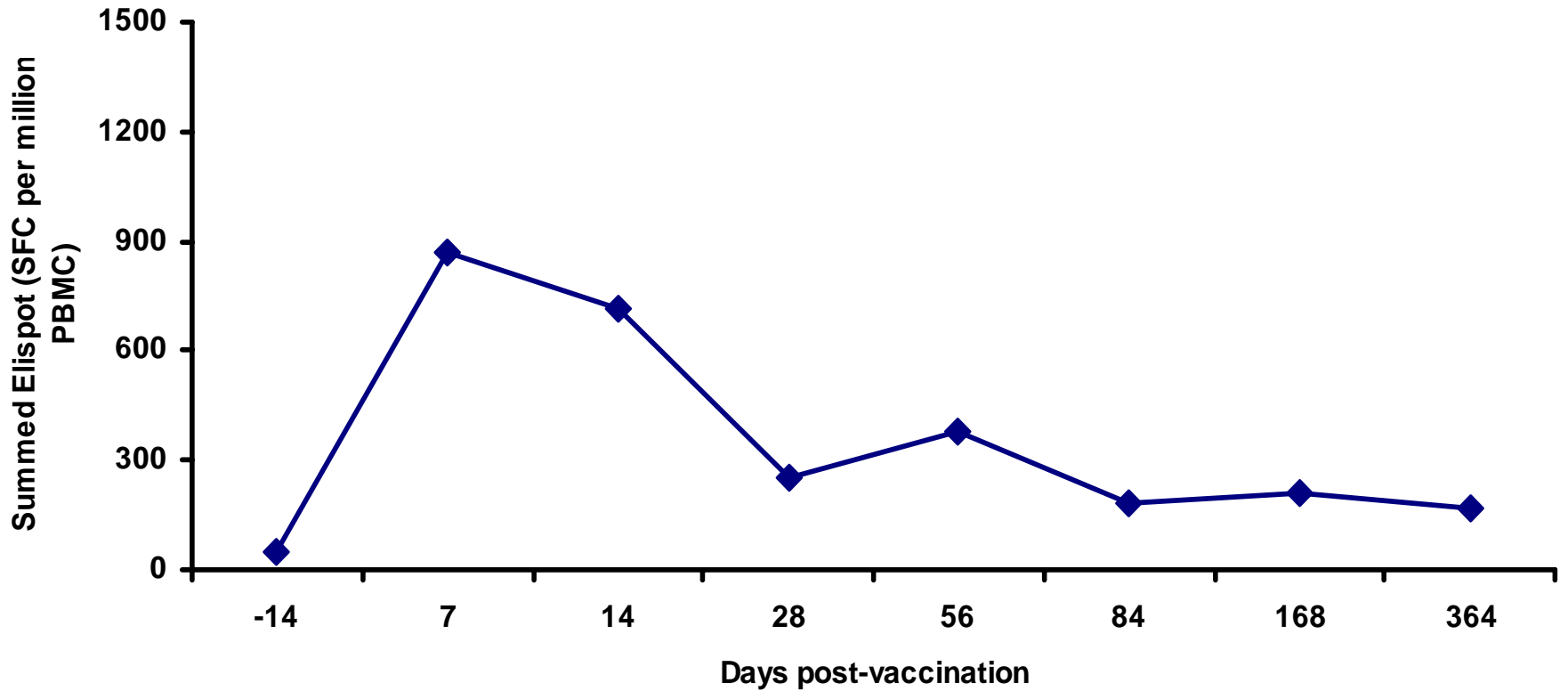
- MVA85A safe in BCG vaccinated and M.tb infected subjects
- MVA85A highly immunogenic in every clinical trial to date
 - High levels of antigen specific IFN- γ secretion
 - Highly polyfunctional cells with high levels of IL2, TNF α and MIP1 β
 - High degree of correlation between different immunological assays
 - PBMC ELISpot v whole blood cultured ELISA ($p = <0.0001$, $n=11$)
 - PBMC ELISpot v frozen PBMC ICS ($p = <0.0005$, $n=6$)
 - Proliferative potential (CFDA-SE dilution) v PBMC ELISpot ($p = <0.05$, $n=4$)

Clinical Development Plan

- UK
 - HIV study underway
- The Gambia
 - Dose finding and non-interference underway
- Cape Town
 - Age de-escalation underway
 - Adult enrolment complete
 - Adolescent arm starting this week
 - Then children and infants
 - High risk groups (HIV infection; TB infection)
 - Awaiting final approval
 - Phase IIb proof-of-concept to start in 2008

Ex-vivo Elispot responses from Cape Town adults

MEDIAN SUMMED AG85A PEPTIDE RESPONSE



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