



UNIVERSITY OF
OXFORD

Aerosol Vaccination for TB

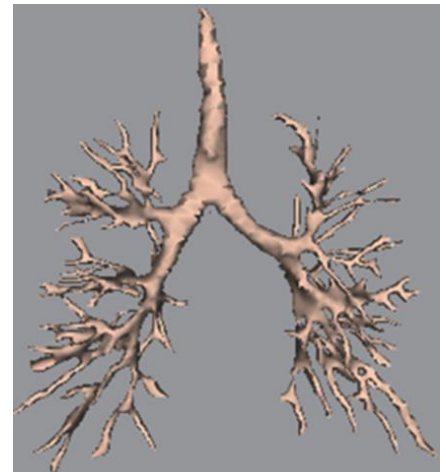
Helen McShane
The Jenner Institute
University of Oxford





An inhaled TB vaccine

- Route of immunisation = route of infection
- BCG does not reliably protect against pulmonary TB
- Mucosal immunisation can generate potent durable immune responses
- Specialised lymphoid tissue
- Inhalation is a common route of drug delivery
- Feasible
- Needle free
- Pain free
- Not a new idea!





MVA85A

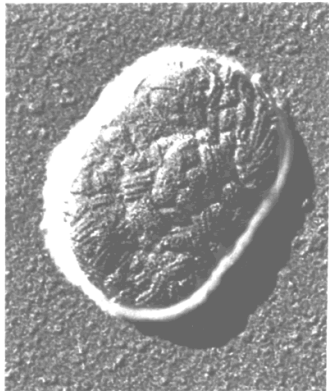
Modified vaccinia Ankara (MVA)

Poxvirus

No replication in mammalian tissues

Good T cell boosting vector

Excellent safety record



M.tb antigen 85A

Mycolyl transferase

Major target antigen

Protective in small animals

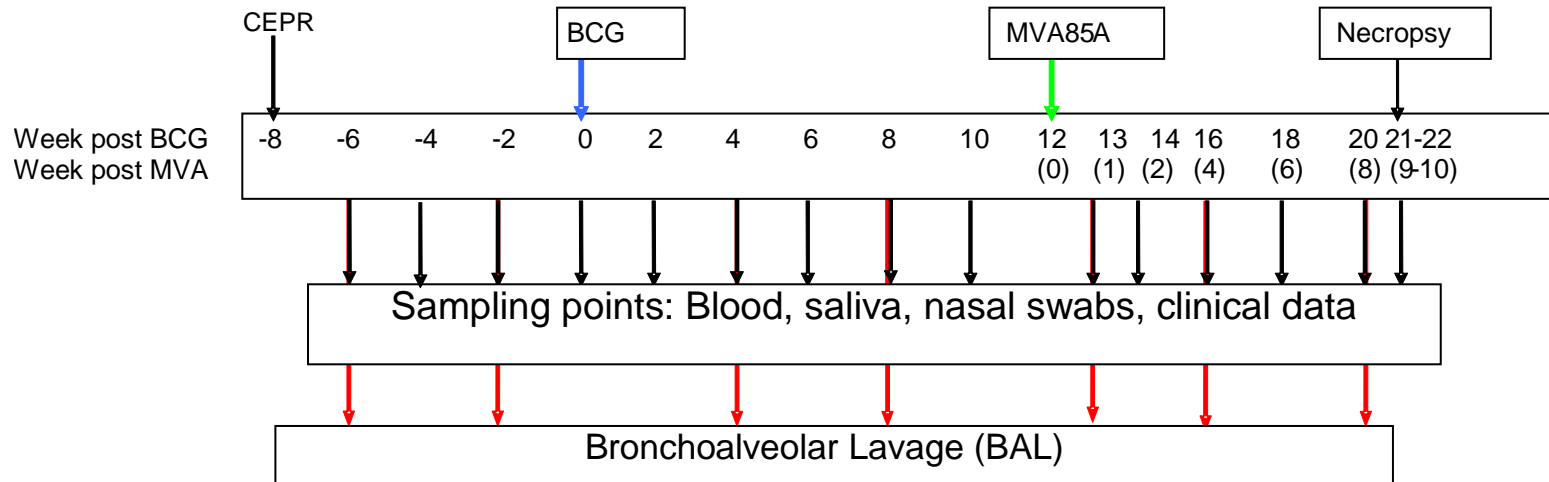
In all environmental
mycobacteria

Doesn't interfere with new
diagnostic tests

BCG - MVA85A regimen

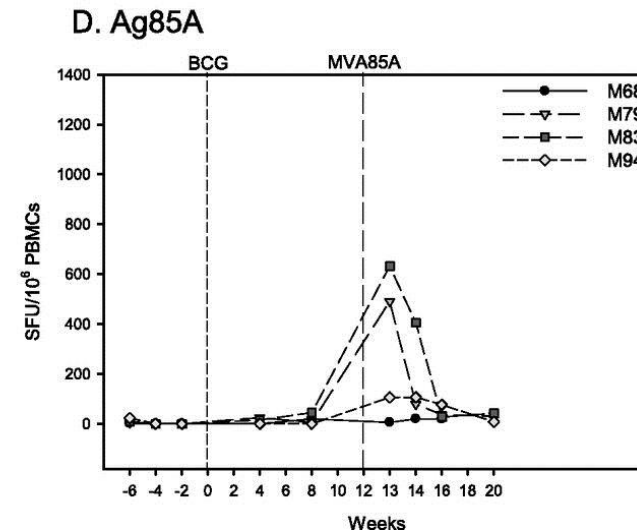
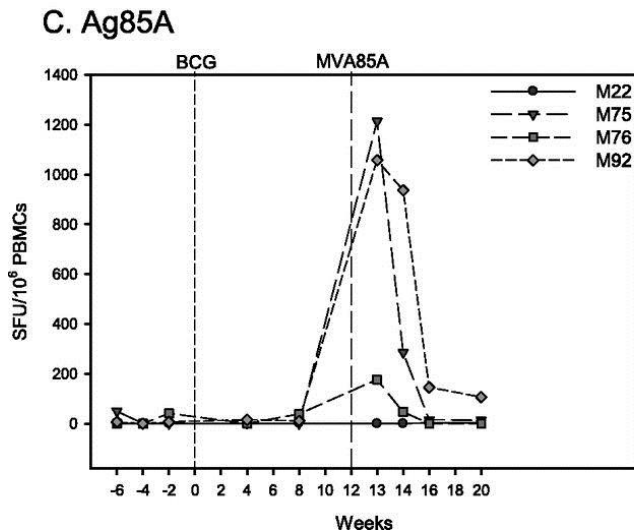
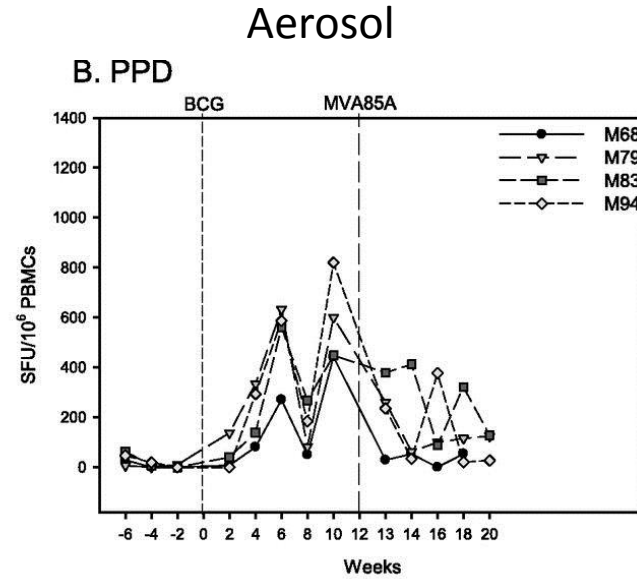
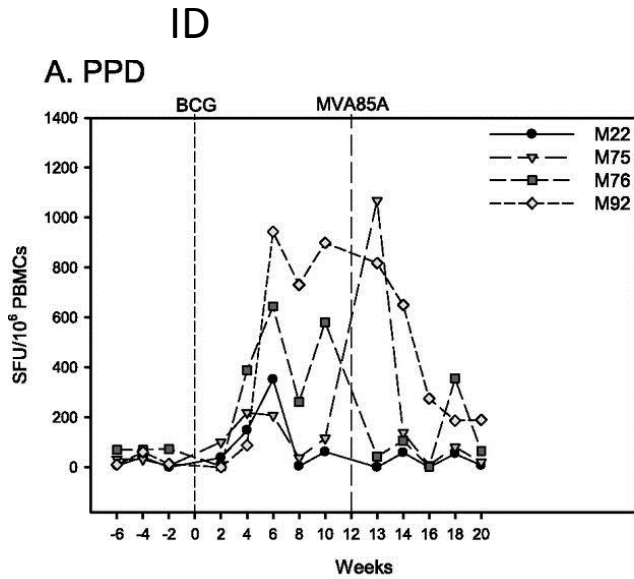


NHP Aerosol immunogenicity study





Immunogenicity of BCG-prime MVA85A boost by aerosol or ID vaccination in NHPs

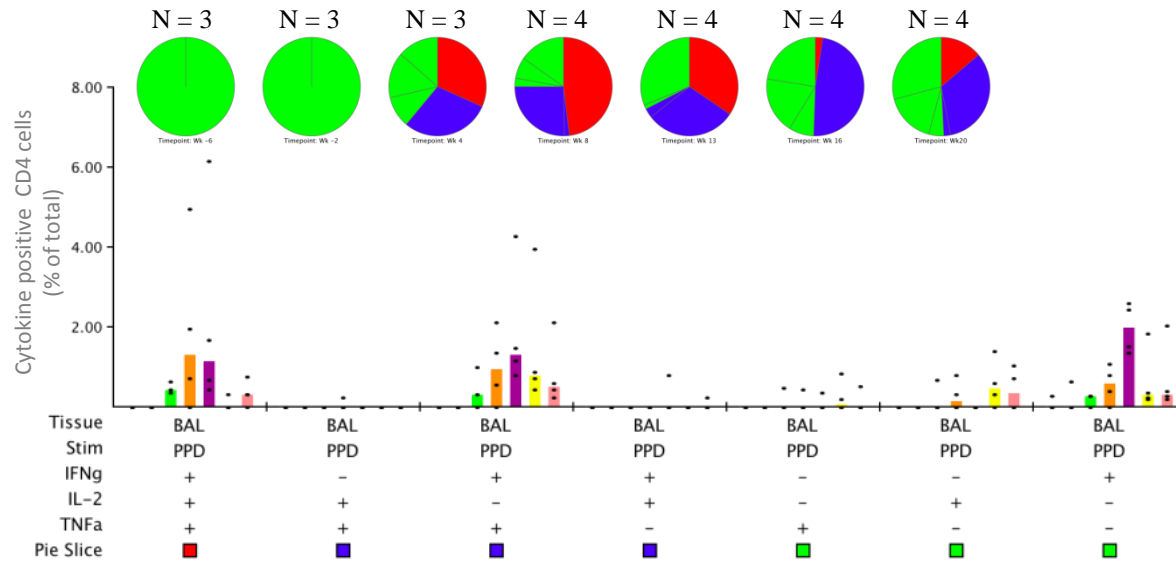




Group median PPD-specific BAL CD4+ T-cell responses

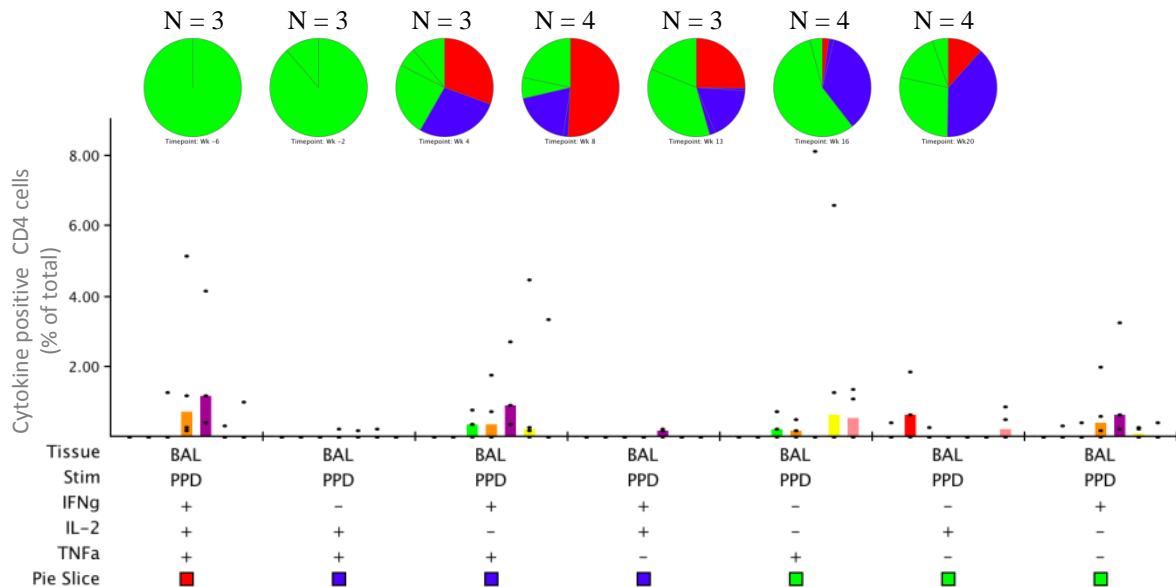
Bar Chart Legend

- Timepoint: Wk -6
- Timepoint: Wk -2
- Timepoint: Wk 4
- Timepoint: Wk 8
- Timepoint: Wk 13
- Timepoint: Wk 16
- Timepoint: Wk20



Bar Chart Legend

- Timepoint: Wk -6
- Timepoint: Wk -2
- Timepoint: Wk 4
- Timepoint: Wk 8
- Timepoint: Wk 13
- Timepoint: Wk 16
- Timepoint: Wk20

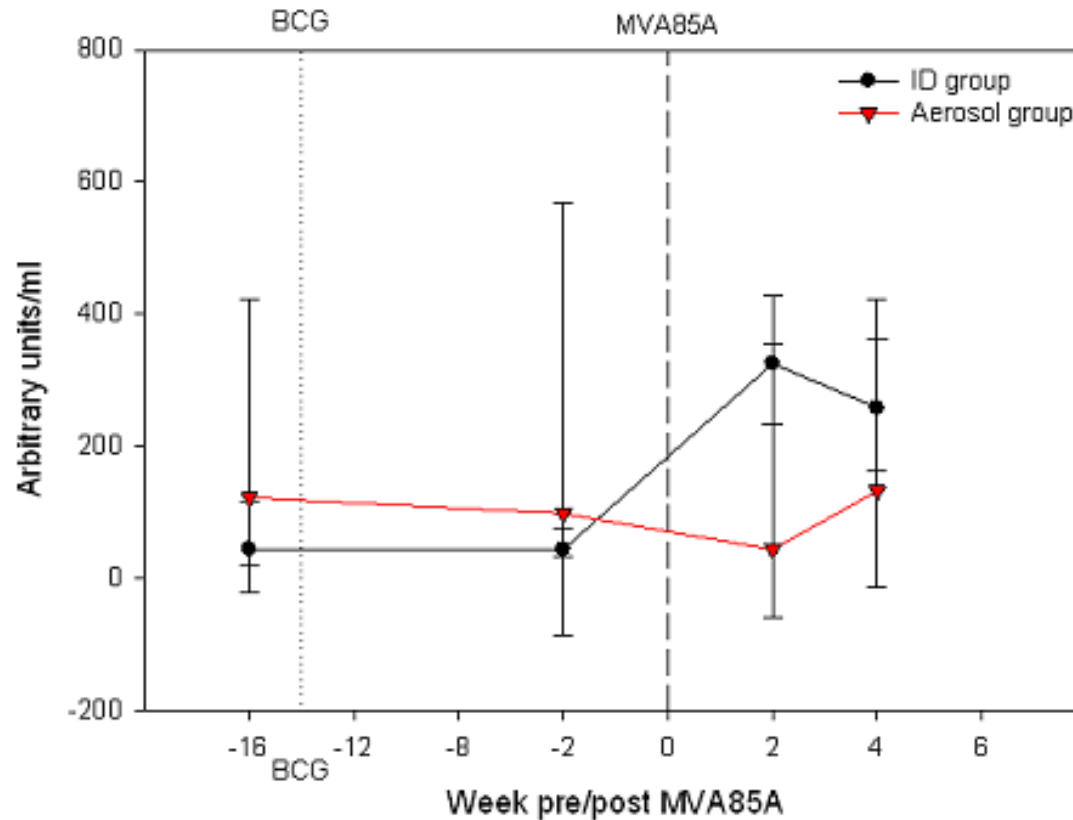


White A and Sharpe S,
CVI 2013



Anti-MVA Antibodies in NHP

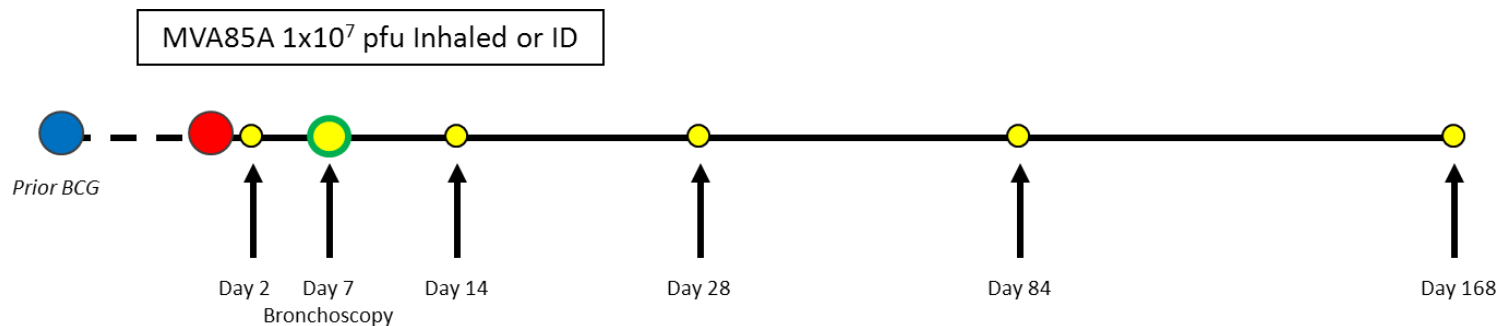
Anti-vaccinia Ig-G levels (arbitrary U/ml) measured in serum samples
Vaccination group median (\pm SD)





Assessing the inhaled route in a human clinical trial

- Phase I trial
 - 22 BCG vaccinated adults randomised to 1×10^7 pfu MVA85A **inhaled or ID**
 - Randomised single blinded paired placebo design
 - Bronchoscopy day 7 BAL



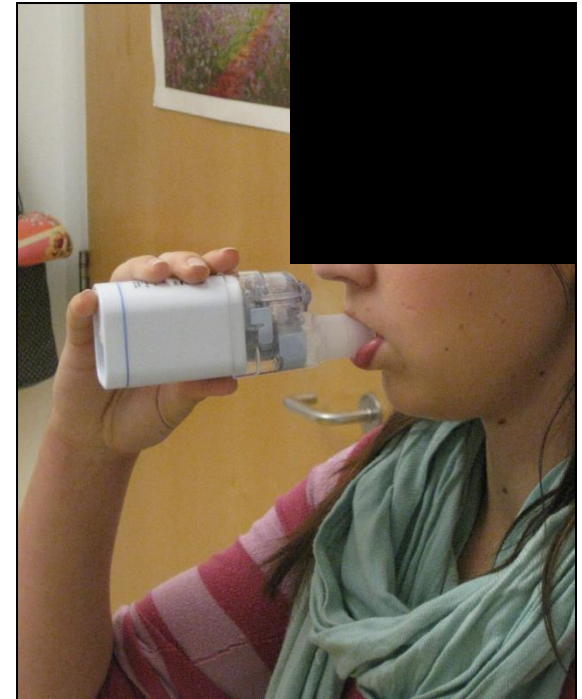
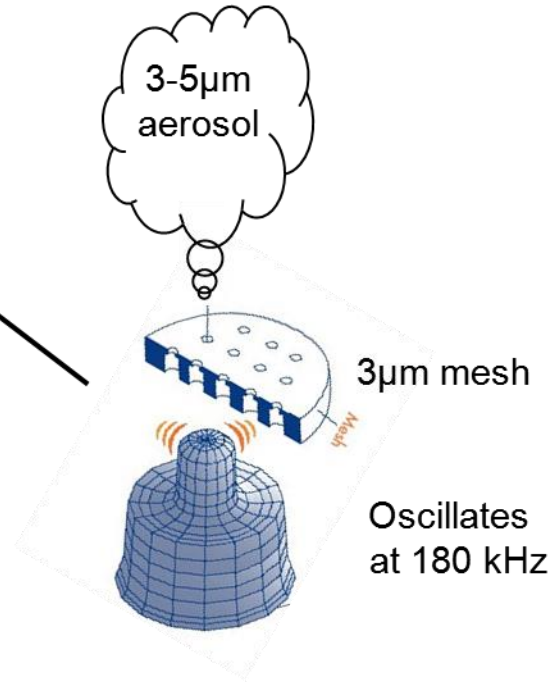
- Primary and secondary outcome
 - Safety: local & systemic AEs, S_aO_2 , spirometry, bronchoscopy
 - Systemic and mucosal cellular immunogenicity: blood and BAL



Aerosol vaccination using the Omron MicroAIR device

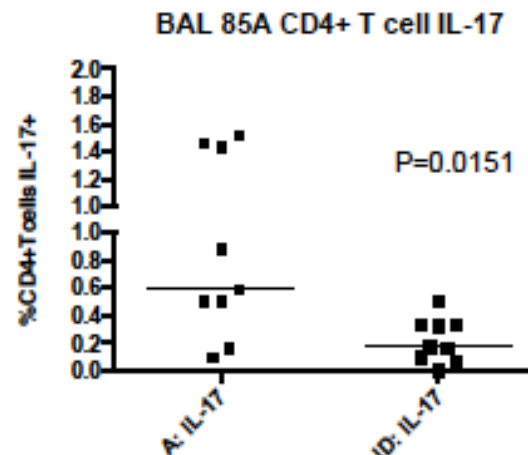
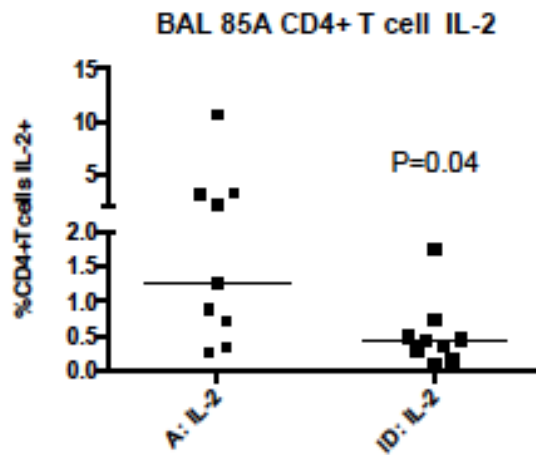
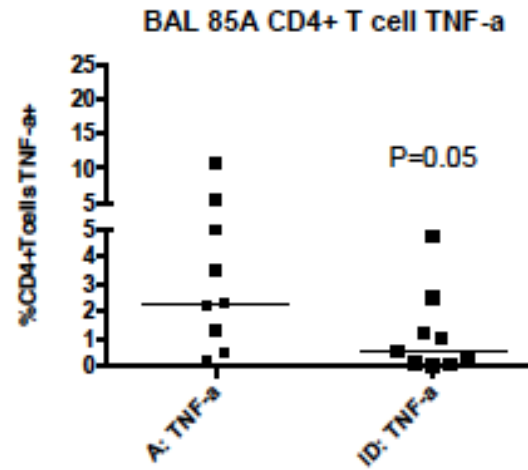
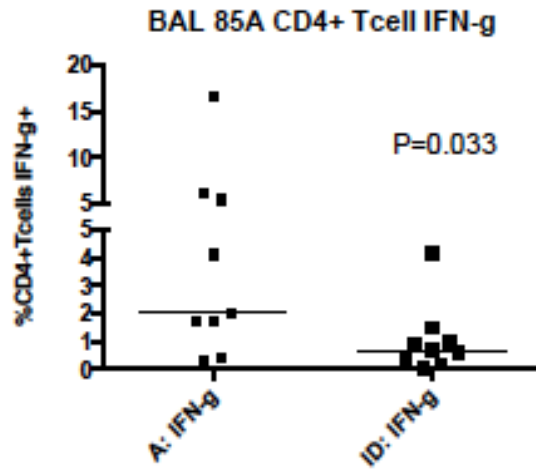


Omron MicroAIR
Hand held nebuliser





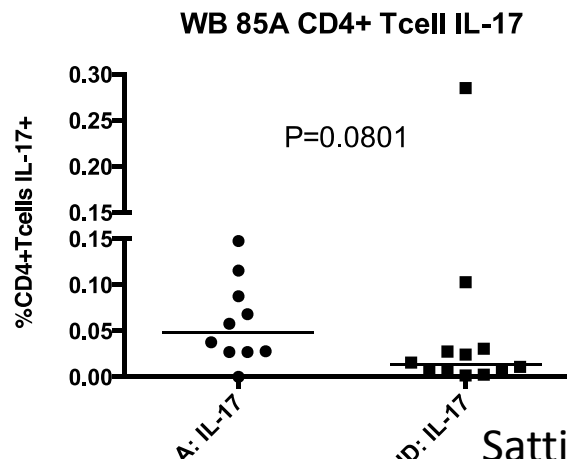
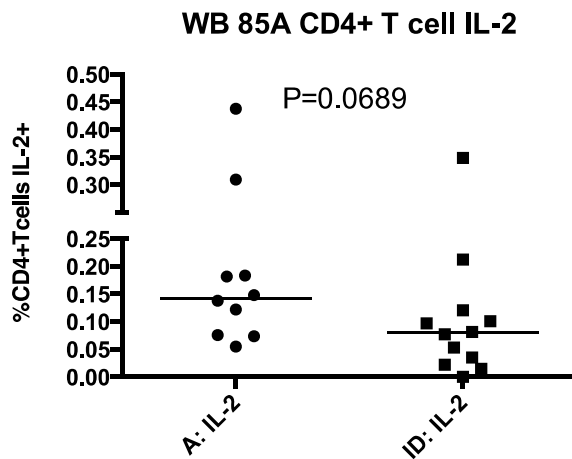
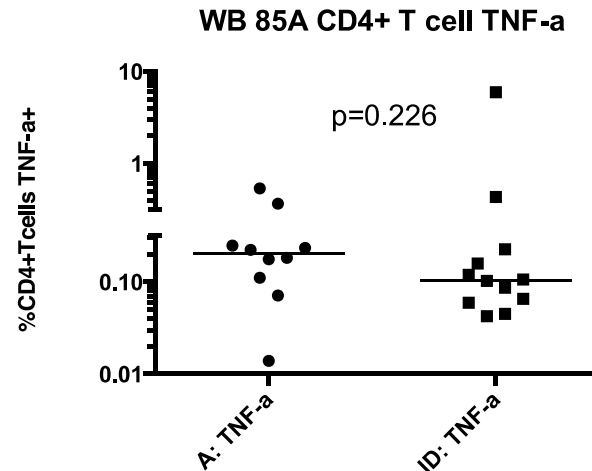
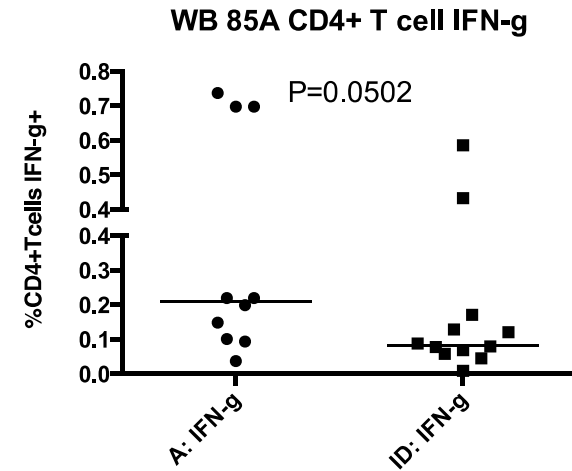
BAL Ag85A specific CD4+ T cell responses stronger after aerosol than i.d administration



A: Aerosol
ID: Intradermal



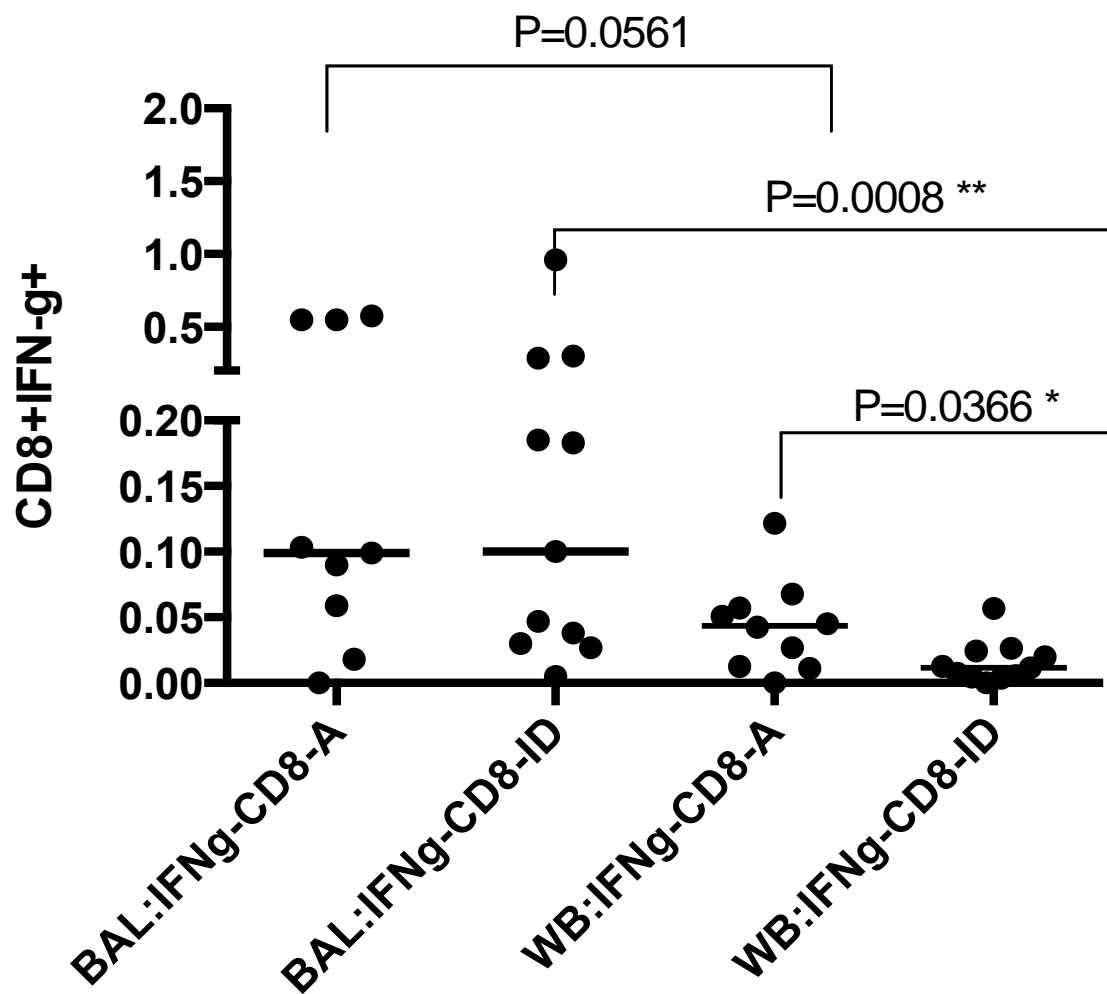
Whole blood Ag85A CD4+ T cell responses at least as strong after aerosol than i.d administration



A: Aerosol
ID: Intradermal



CD8+ T cell IFN- γ response in BAL and WB



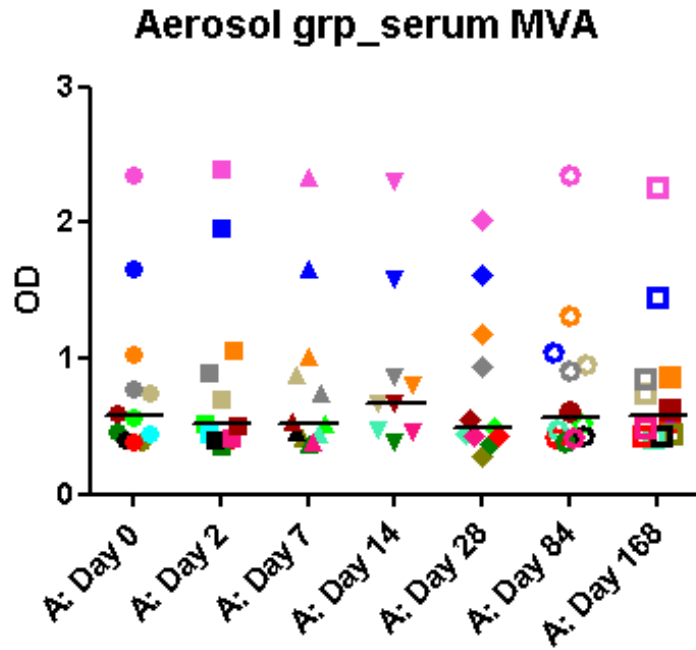


Transcriptomics on TB026 samples

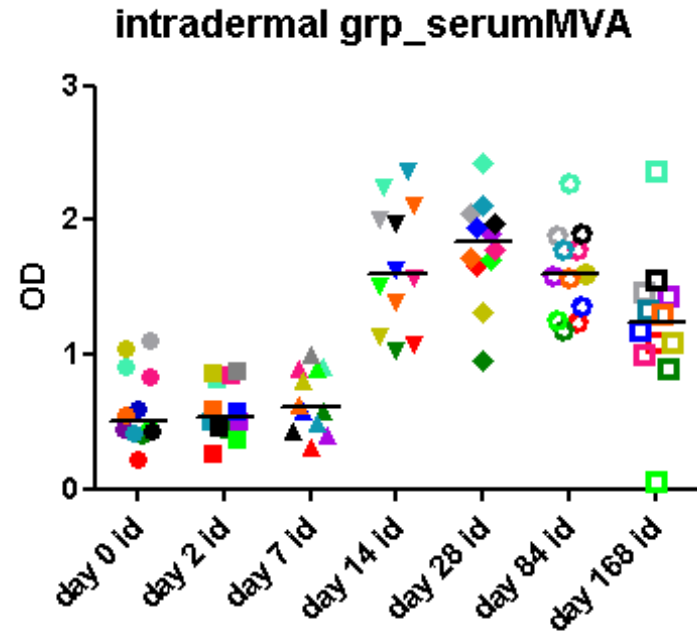
- Day 0, 1, 7: Unstim PBMC: n = 24
- Day 7 Ag85A-stimulated PBMC: n = 24
 - Stimulated 6 hours with 66 peptide pool
- Day 7 BAL cells: n = 13
 - Frozen in lysis buffer on day of collection
 - Unstim



Serum IgG to MVA



Aerosol grp_ALL
A: Day 0
vs
A: Day 14
0.4832



intradermal grp
day 0 id
vs
day 14 id
< 0.0001

Same pattern for IgM and IgA

Satti et al, Lancet Infect Dis 2015



Homologous Boosting by Heterologous Route

Prime

Boost

Group 1



Collecting stimulated BAL sample for transcriptomic analysis

Group 2



Group 3



Manjaly-Thomas et al,
unpublished data



Next steps: TB040

- Safety and immunogenicity of aerosol MVA85A in LTBI

- Status
 - Fully approved
 - Recruitment commenced
 - N = 1 enrolled to date



Acknowledgements



- **Oxford Centre for Respiratory Medicine**
 - **Henry Bettinson**
- **LSHTM**
 - **Helen Fletcher**

Iman Satti
Zita-Rose Manjaly-Thomas
Magali Matsumiya
Stephanie Harris
Ali Hamidi
Matt O'Shea
Joel Meyer
Rachel Tanner
Rachel Kandt
Sharon Sheehan
Ian Poulton
Morven Wilkie
Raquel Ramon-Lopez
Alison Lawrie
Michael Riste
Morven Wilkie
Sam Vermaak
Elena Stylianou
Ilaria Pepponi



Acknowledgements



Public Health
England

Protecting and improving
the nation's health

Sally Sharpe
Andrew White
Mike Dennis
Ann Williams

welcometrust



**European Commission
Study participants**