



UNIVERSITY OF
OXFORD

Insights from a TB (BCG) controlled human infection model

Helen McShane
The Jenner Institute
University of Oxford

Why do we need a human mycobacterial challenge model?

- To provide a biological signal of efficacy with new vaccines
- To identify potential immune correlates of protection
- As a model of the immunobiology of disease



Developing a mycobacterial controlled human infection model

- Challenge agent

- BCG
- Attenuated *M.tb*

- Challenge route

- Skin
- Lung

- Endpoints

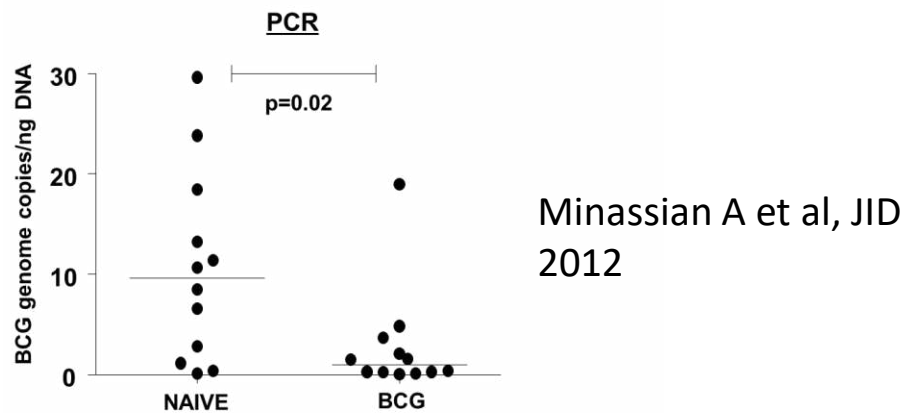
- Mycobacterial quantification
 - CFU/PCR
- Safety
- Immunogenicity



Using a CHIM to provide a biological signal of efficacy with candidate vaccines

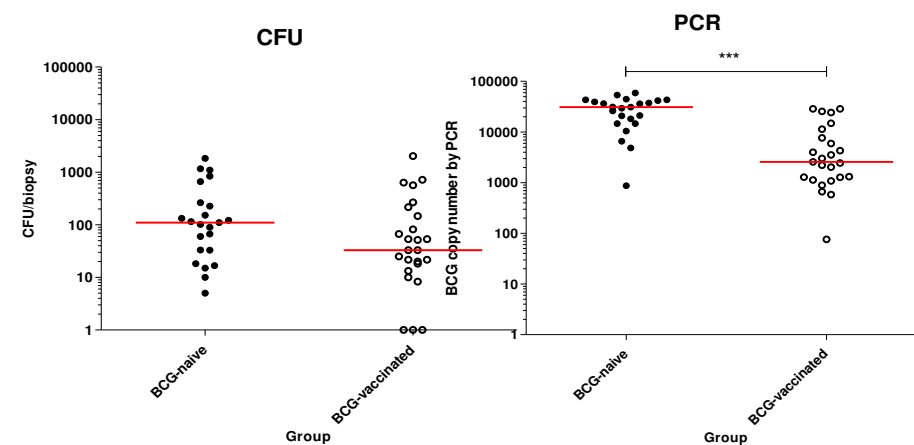
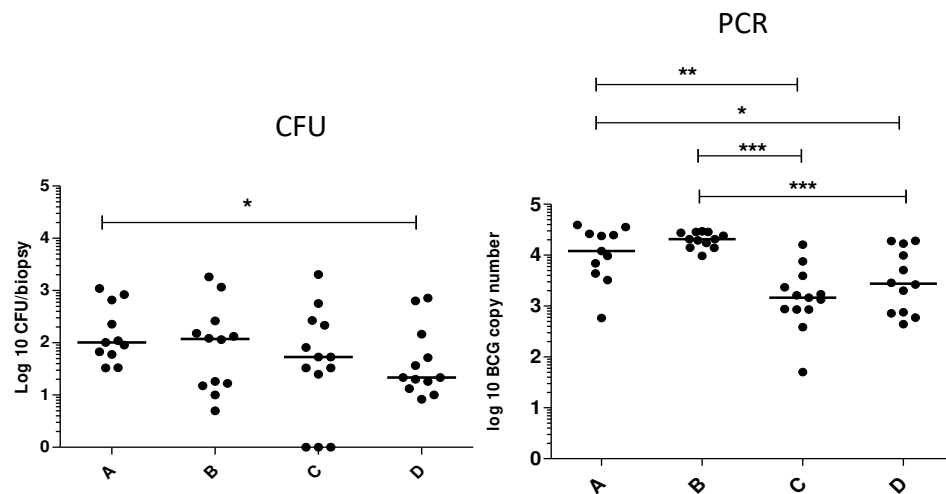
- Key to use of a CHIM by vaccine developers is confidence that the model is measuring something that is biologically meaningful = *validation*
 - A CHIM can de-risk vaccine development
- Ultimate ‘validation’ of a CHIM is comparison of candidate vaccine ‘efficacy’ in a CHIM vs efficacy in a field efficacy study
- In the absence of field efficacy data, we can ‘validate’ a CHIM model against a known vaccine effect

BCG vaccination protects against intradermal BCG challenge in humans



And MVA85A does not protect against a BCG skin challenge...

- A - Naïve
- B - MVA85A
- C - BCG
- D - BCG-MVA85A



Harris et al, JID 2014

Aerosol BCG CHIM studies

BCG naïve volunteers

- TB041
 - Dose escalation 10^4 – 10^7 cfu aerosol BCG
 - Bronchoscopy @ D14
 - Blood taken at multiple time points
 - ID BCG control group
 - Satti et al, Lancet Infectious Diseases 2024

- TB043
 - 10^7 cfu inhaled BCG, inhaled saline control group
 - Bronchoscopy @ D2,7,14,28,56
 - Blood taken at multiple time points
 - Marshall, Satti et al, submitted

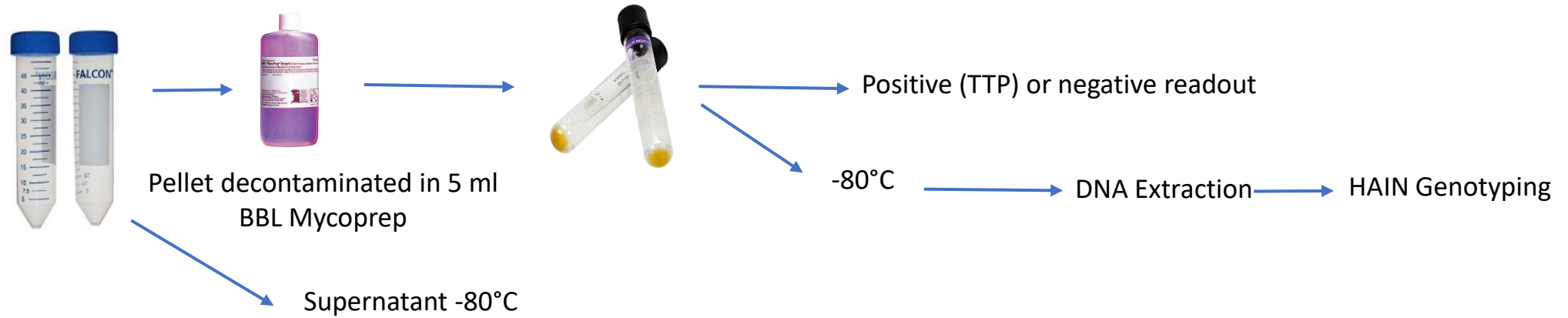
BCG vaccinated volunteers

- TB044
 - Dose escalation 10^4 – 10^7 cfu aerosol BCG
 - Bronchoscopy @ D14
 - Blood taken at multiple time points
 - Fredsgaard-Jones, Harris et al, submitted

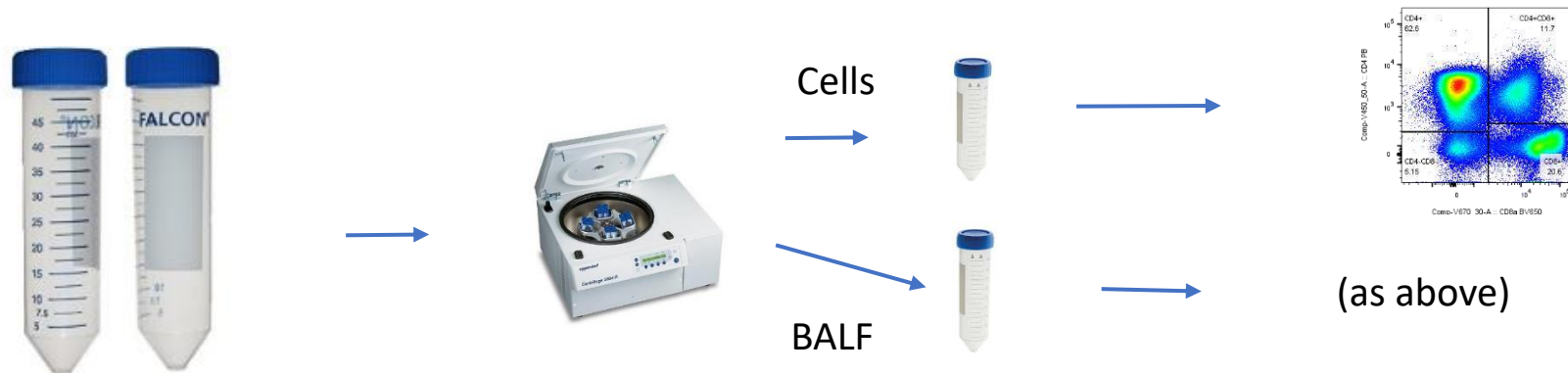
- TB045
 - Evaluation of prior BCG and IDRI93/GLA-SE vaccination
 - Aerosol BCG challenge and bronchoscopy @ 2 weeks
 - Immune correlate evaluation

Detection of BCG in the BAL

- Using whole BAL sample for BCG detection



- Splitting BAL sample for BCG detection and flow cytometry



BCG recovery from BAL 2 weeks post aerosol BCG

BCG naïve subjects	Dose of inhaled BCG (CFU)	Number of volunteers	Number of BCG+ BAL samples
	1×10^4	3	2
	1×10^5	3	3
	1×10^6	3	3
	$1 \times 10^7^*$	12	5

* For the 1×10^7 dose, only BAL supernatant was put into the MGIT system

BCG vaccinated subjects	Dose of inhaled BCG (CFU)	Number of volunteers	Number of BCG+ BAL samples
	1×10^4	3	0
	1×10^5	3	0
	1×10^6	3	0
	1×10^7	3	0

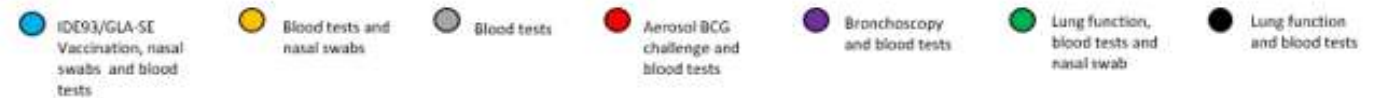
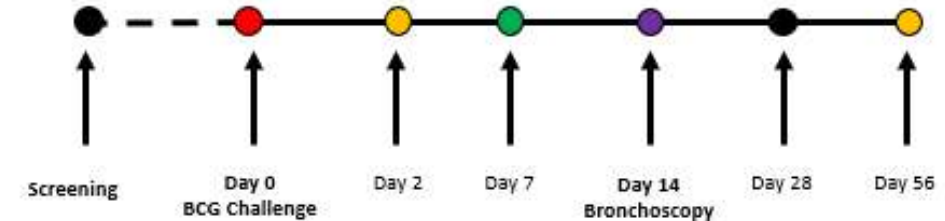
TB045: Evaluating BCG and IDRI93/GLA-SE in an aerosol BCG CHIM

Group	Number of Volunteers	Historic BCG Vaccination Status	ID93/GLA SE dose and Schedule
A	12	BCG-Vaccinated	2 µg ID93 + 5 µg GLA-SE at Day 0 and Day 56
B	12	BCG-Vaccinated	None
C	12	BCG-Naïve	2 µg ID93 + 5 µg GLA-SE at Day 0 and Day 56
D	12	BCG-Naïve	None

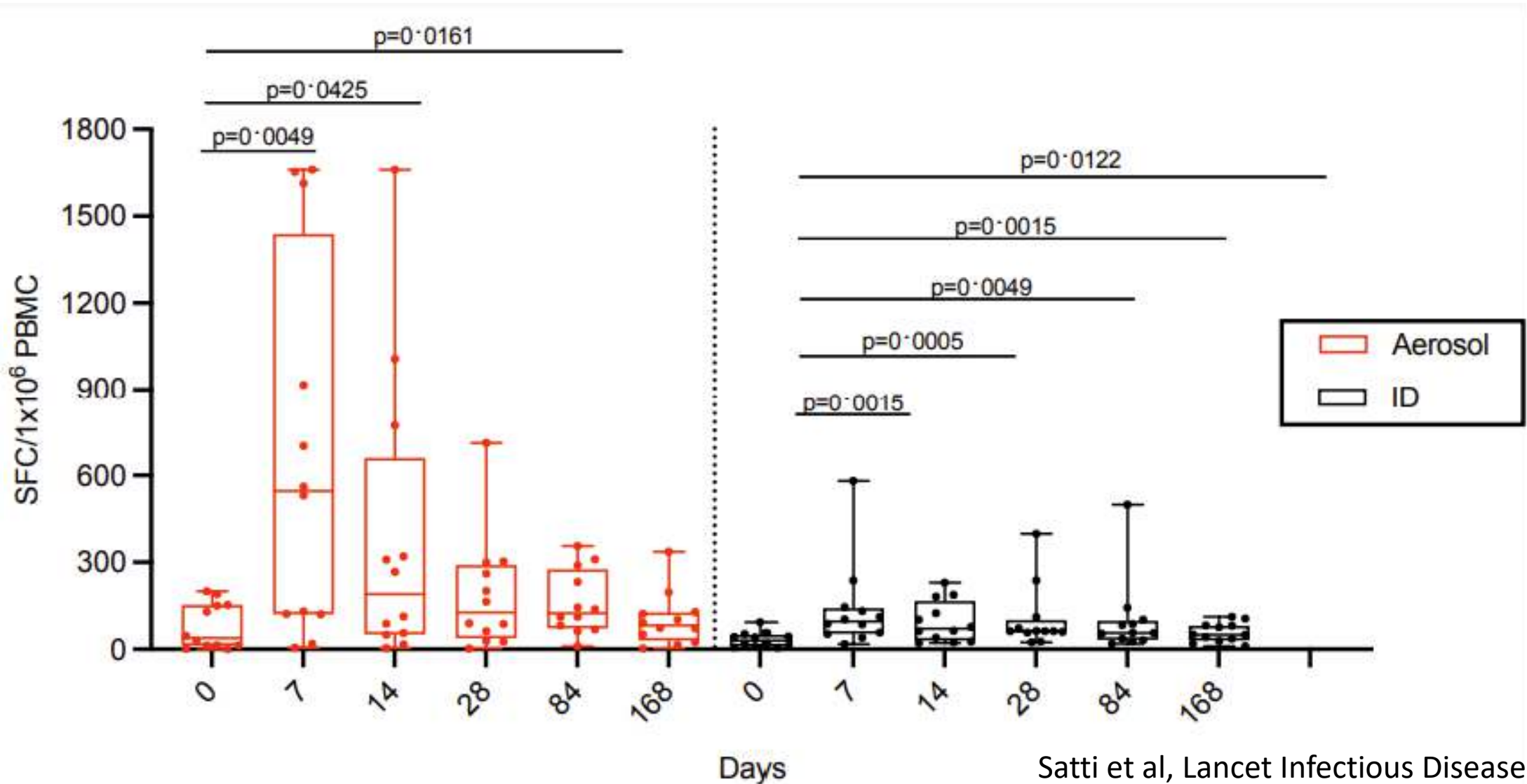
Group A and C: Volunteers will receive two doses of ID93/GLA-SE 2 months apart, and then 2 months later receive a “challenge” of aerosol BCG and 14 days later undergo a bronchoscopy



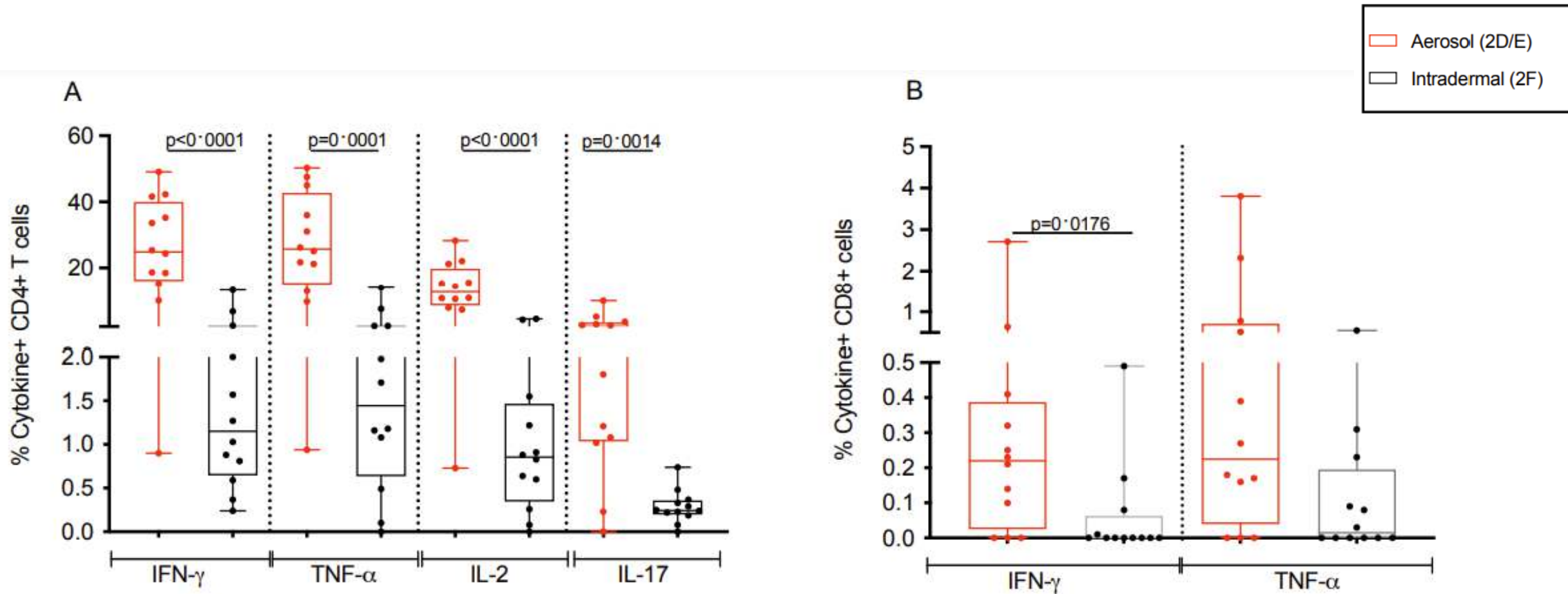
Group B and D: Volunteers will not be vaccinated but will receive a “challenge” of aerosol BCG and 14 days later undergo a bronchoscopy



PPD-specific ELISPOT responses after aerosol or ID BCG



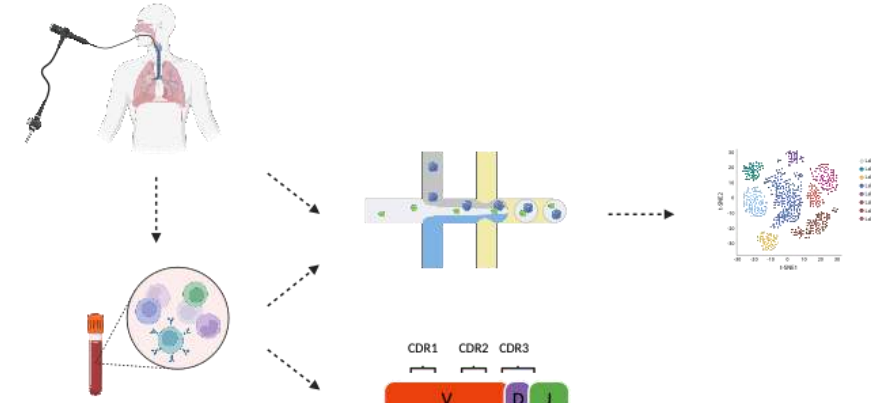
PPD-specific CD4+ and CD8+ T cells in the BAL 2 weeks post-aerosol BCG



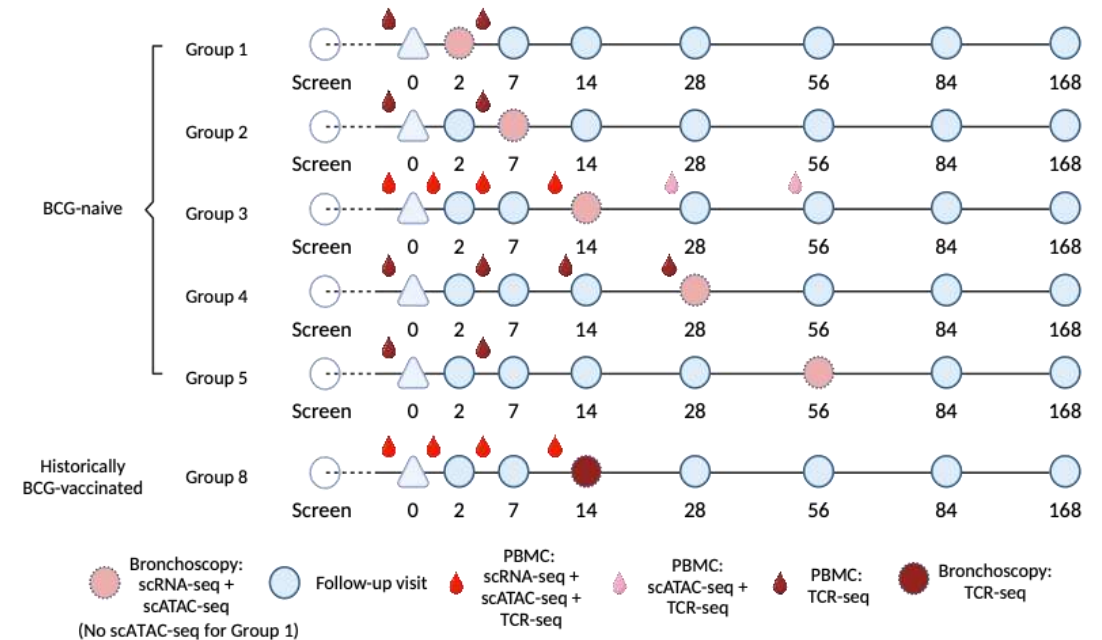
An exploratory study of human immune responses to aerosol BCG challenge

Healthy UK BCG naïve and historically BCG-vaccinated adults
 10^7 CFU BCG Danish by aerosol
 BAL and PBMC analysis:

- Single cell RNA sequencing (scRNA-seq)
- Single cell ATAC sequencing (scATAC-seq)
- Bulk TCR sequencing (TCR-seq)



Group	BCG vaccination	Description	Challenge agent
1	Naive	Bronchoscopy D2	10 BCG and 3 saline per group
2		Bronchoscopy D7	
3		Bronchoscopy D14	
4		Bronchoscopy D28	
5		Bronchoscopy D56	
8	BCG-vaccinated	Bronchoscopy D14	9 BCG



Summary

- A TB CHIM model could facilitate and de-risk early vaccine R&D
- A protective effect of BCG vaccination in a skin and aerosol BCG CHIM has been demonstrated
- Every opportunity should be sought to *validate* a CHIM
 - M72?
- Novel insights into the immunobiology of mycobacterial infection can be identified using an aerosol BCG CHIM

Acknowledgements



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Study participants



PHOENIX / IMPAc-TB TEAM

- Rhea Coler
- Sasha Akins
- Alison Wald

