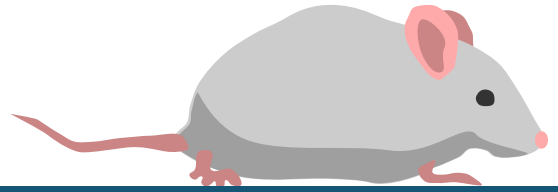
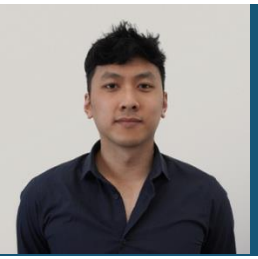


Development of a Novel Self-Adjuvanting Vaccine Platform for Tuberculosis (TB)



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7th Global Forum on TB Vaccines, 2024

VALIDATE
VAccine deveLopment for complex Intracellular negIecteD pAThogEns

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Protein Subunit Vaccines

✓ Highly reproducible and customisable

✓ Easier to store

✓ No live organisms

X Requires the use of adjuvants

X Limited access to existing adjuvants

X Long duration from DNA to cell line to purified protein

X Formulation and validation of multiple components

X Licensing challenges for existing adjuvants

X Cost of development and production


PCF
Platform CTB-Fc

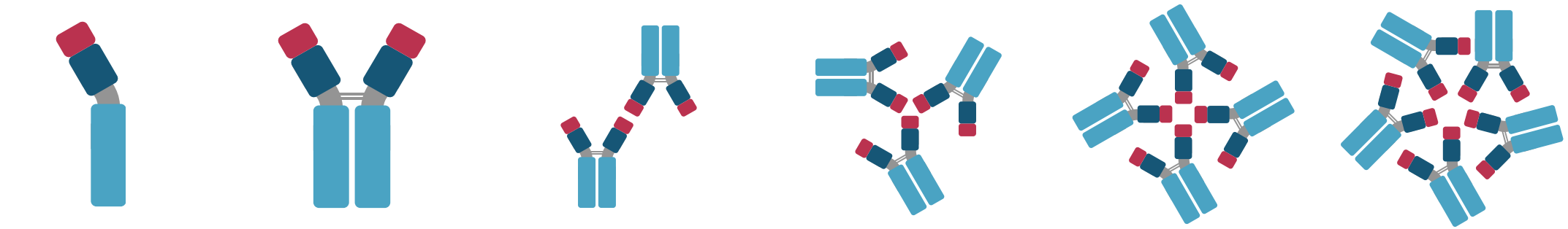
PCF (Platform CTB-Fc)

A novel self-adjuvanting single-polypeptide vaccine platform (Patent in application)

Dengue

SARS-CoV2

TB



Single-chain Monomer Polymerisation

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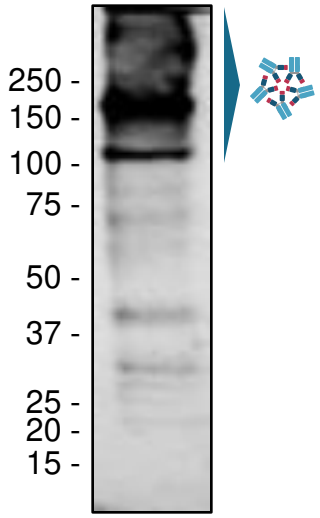
Plant Expression System

- Mammalian cell production of recombinant proteins requires sterile conditions and expensive reagents
- Transient expression system using *N. benthamiana* allows for rapid production of large quantities of recombinant protein
- Customisable post-translational modifications (glycosylation profiles) similar to that of mammalian cell systems

In vitro Characterisation of TB-PCF

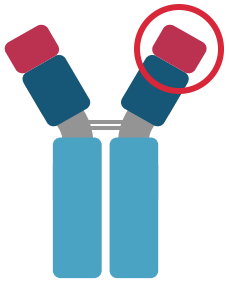
SDS-PAGE

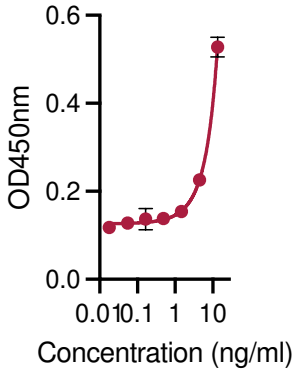
TB-PCF
(NR)



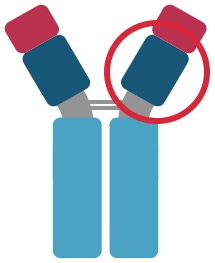
Anti-ESAT-6

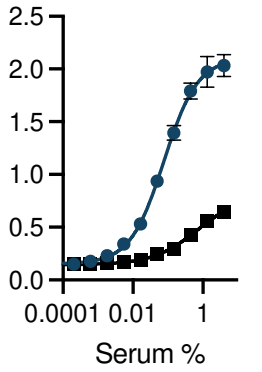
CTB



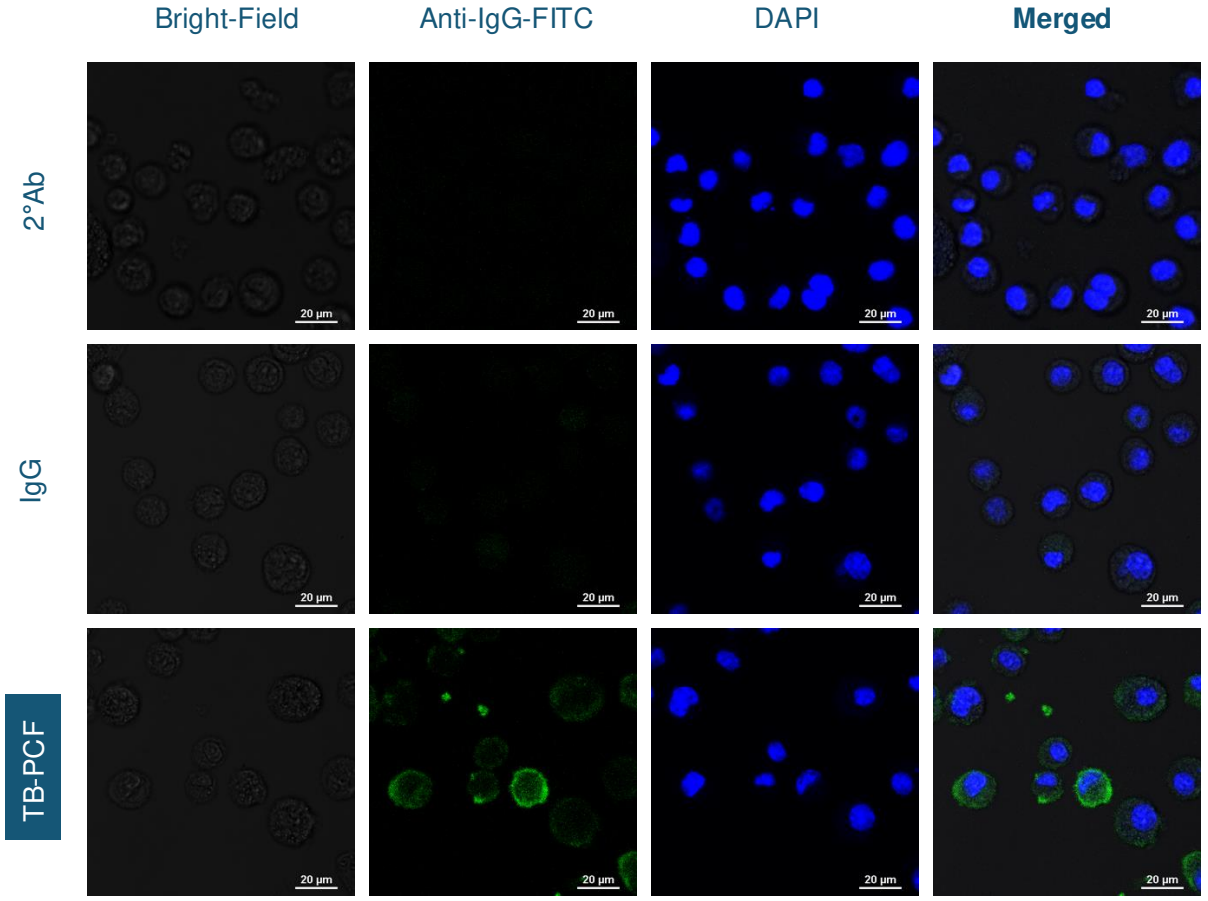


Antigen





Myeloid Cell Binding and Internalisation



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Aerosolisation

- Safer and more practical than needle-based vaccine delivery
- Can induce mucosal immune response

- Low-cost and widely available devices such as the Omron Micro Air U22

- Aerosolisation process may degrade proteins and affect their function

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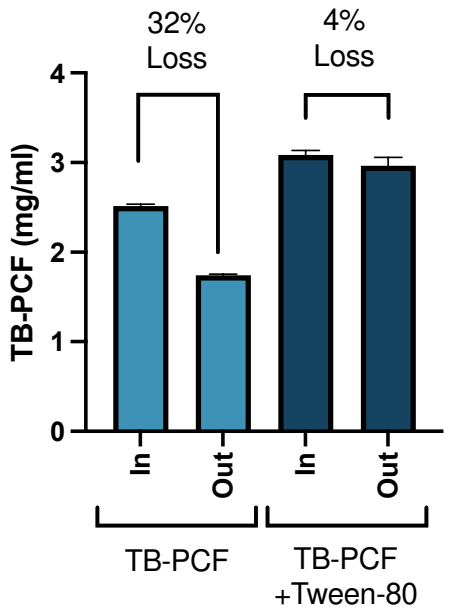
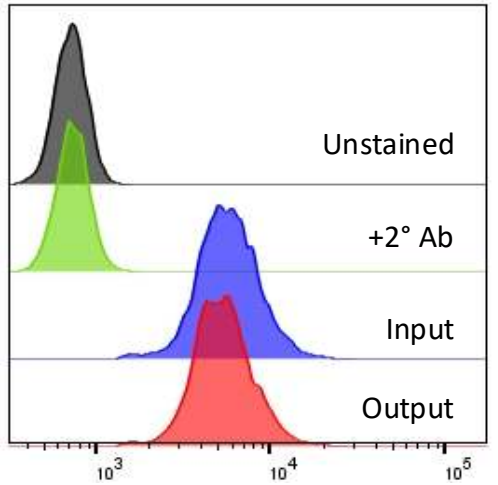
Protein Recovery by ELISA



Binding to Macrophage Cell Line



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In vivo Experiment

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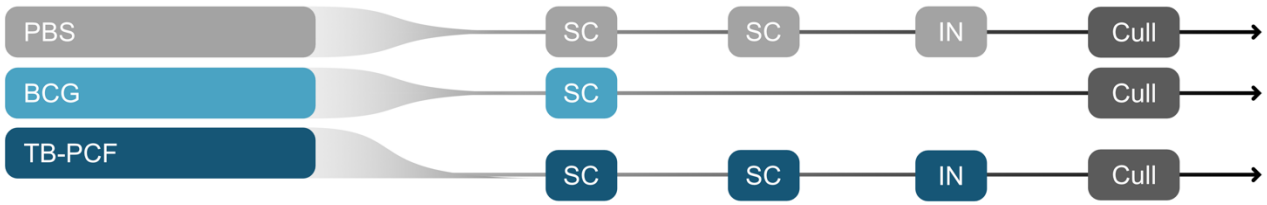
Immunogenicity

n=3
C57BL6/J



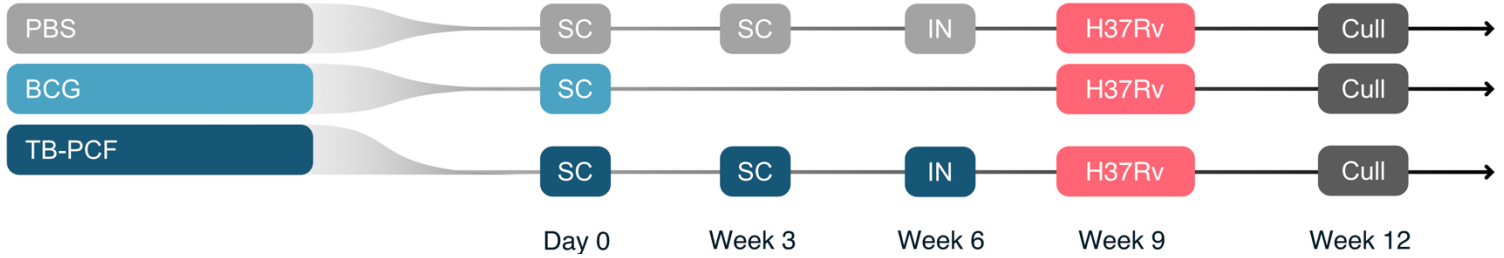
CD4, CD8
Antigen Recall

Antibody
Responses

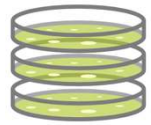
Modified
MGIA

Efficacy

n=6
PBS, BCG n=7
C57BL6/J



Lung Histology



Lung/Spleen
CFU

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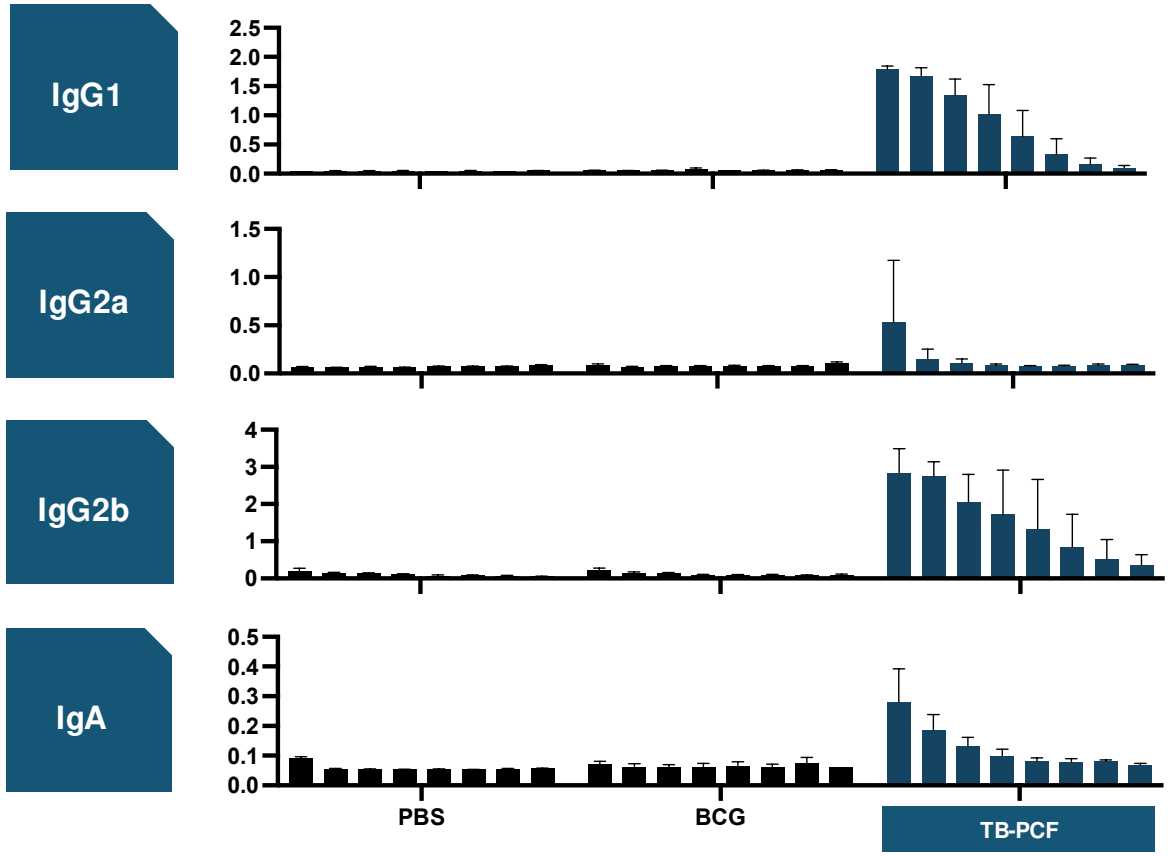
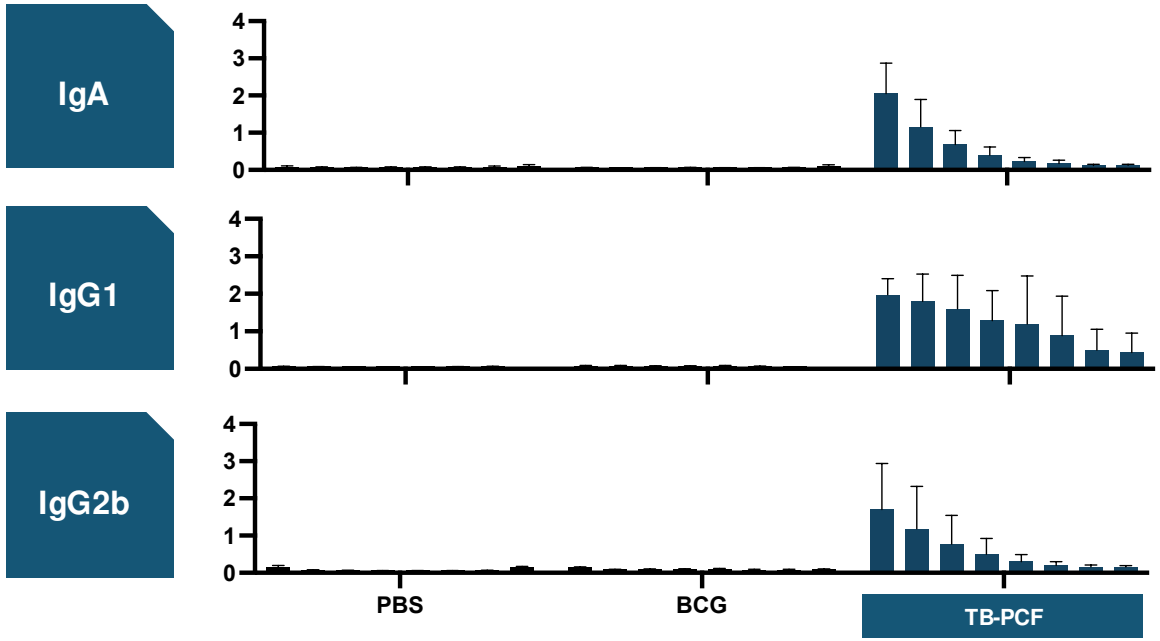
Antibody Responses

Antibody responses against ESAT-6/CFP-10 fusion protein following TB-PCF vaccination in C57BL6/J mice by ELISA

Serum
n=3, 1:50 → 3-fold



Bronchoalveolar Lavage (BAL) Fluid
n=3, IgA = 1:1 → 2-fold. IgG1, IgG2b = 1:2 → 2-fold



Mean of 3 biological replicates, error bars = SEM
y = absorbance 450nm

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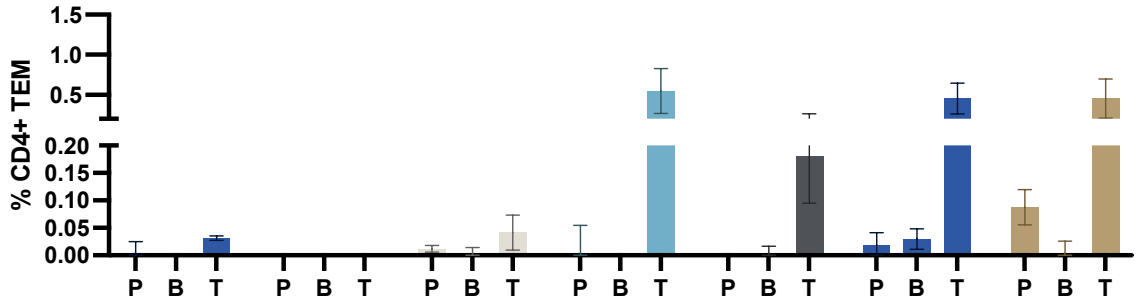
Antigen Recall

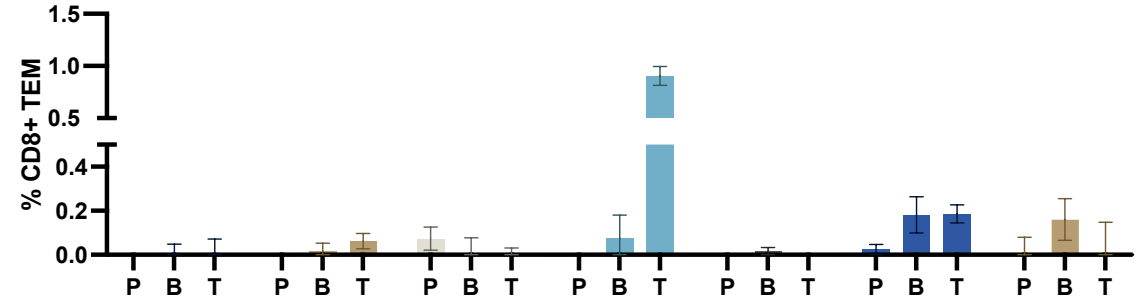
96 hour *ex vivo* antigen recall responses against ESAT-6/CFP-10 fusion protein

Spleen Th1 Responses (IFN-ɣ, IL-2, TNF-α), n=3

CD4 TEM



CD8 TEM

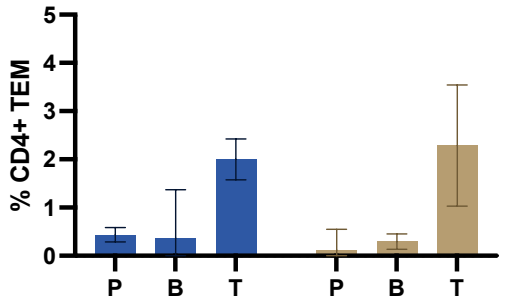


IFN-ɣ	+	+	+	+	-	-	-
IL-2	+	+	-	-	+	+	-
TNF-α	+	-	+	-	+	-	+

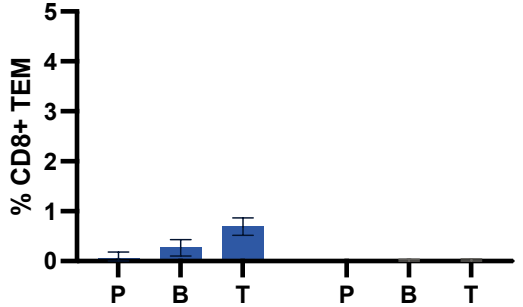
P = PBS, **B** = BCG, **T** = TB-PCF

Spleen Th17 Responses (IL-2, IL-17), n=3

CD4 TEM



CD8 TEM



IL-2	+	-
IL-17	+	+

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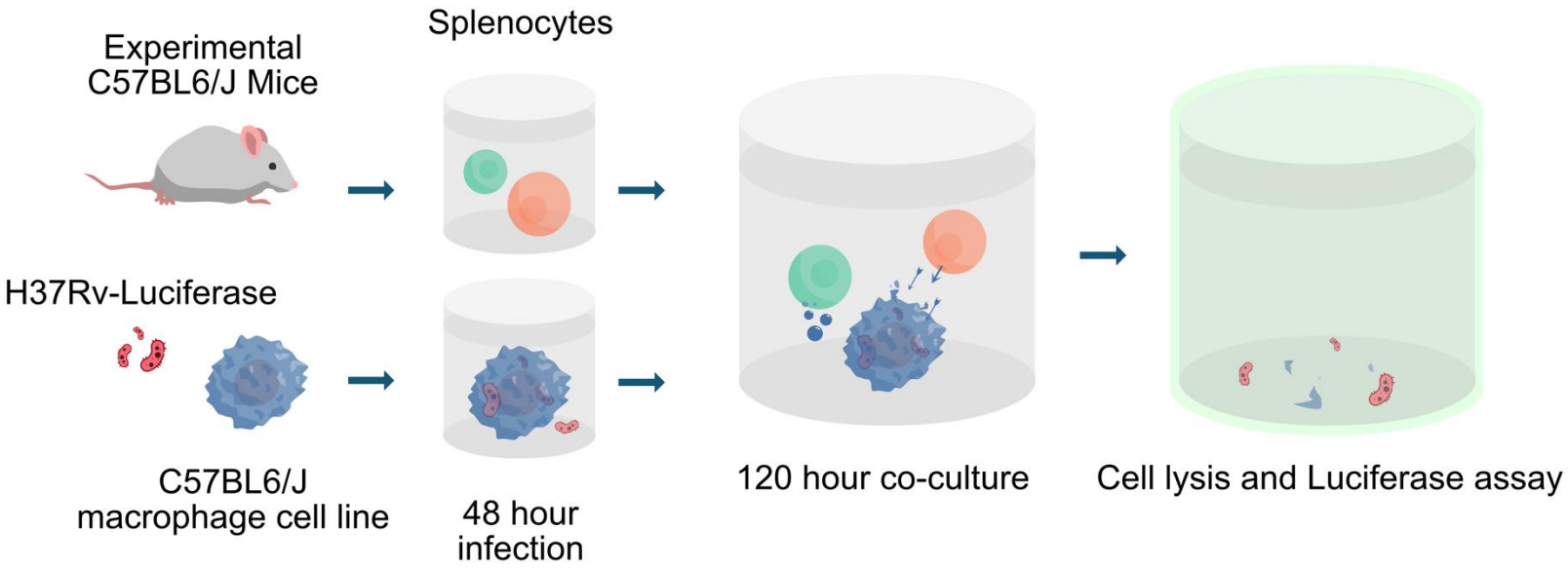
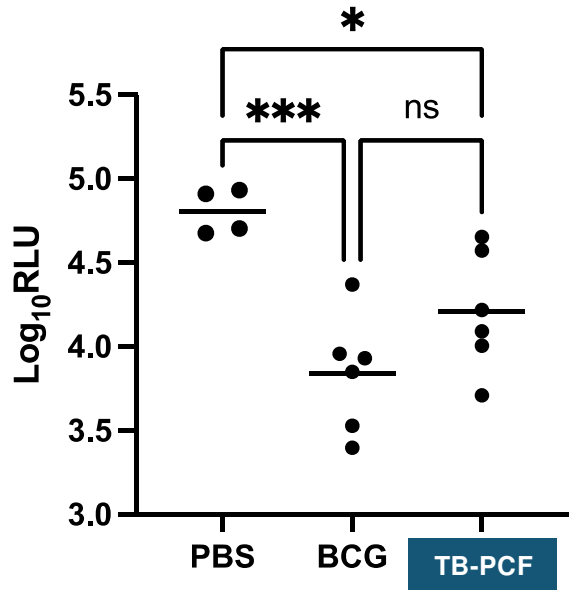
TB-PCF Efficacy (Modified MGIA)

MGIA = Mycobacterial Growth Inhibition Assay





One way ANOVA, Tukey's Correction
* P ≤ 0.05
*** P ≤ 0.001

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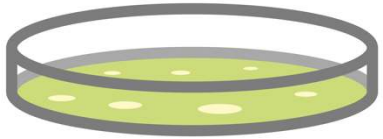
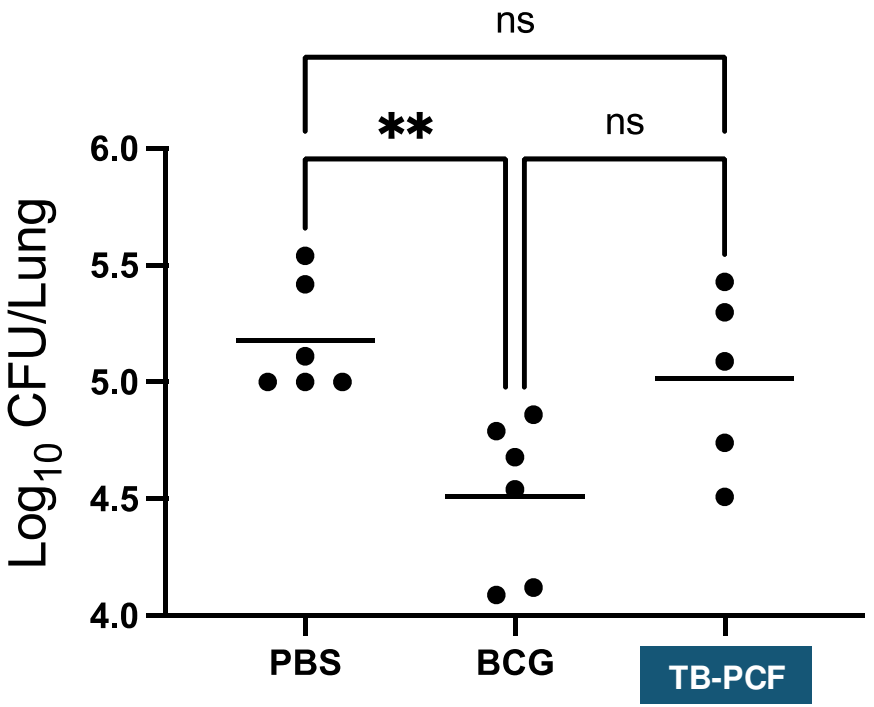
TB-PCF Efficacy (*in vivo* Aerosol Challenge)

Cull 3-weeks post aerosol TB challenge



Enumerate Lung CFU



One way ANOVA, Tukey's Correction. ** P ≤ 0.01

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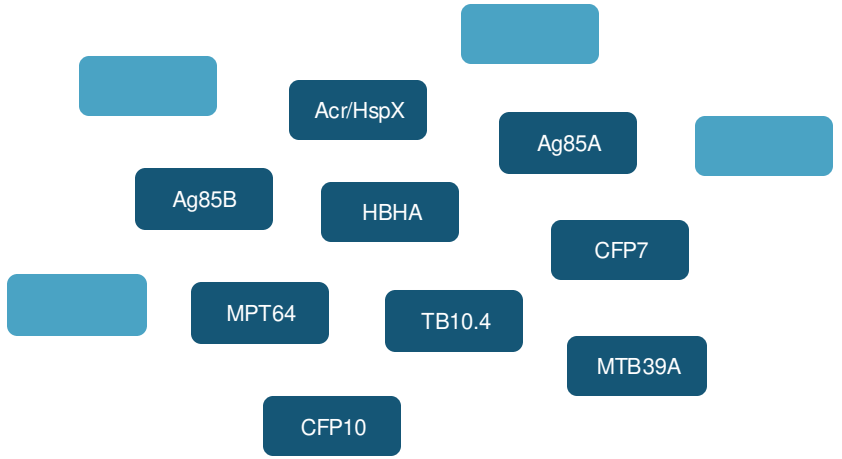
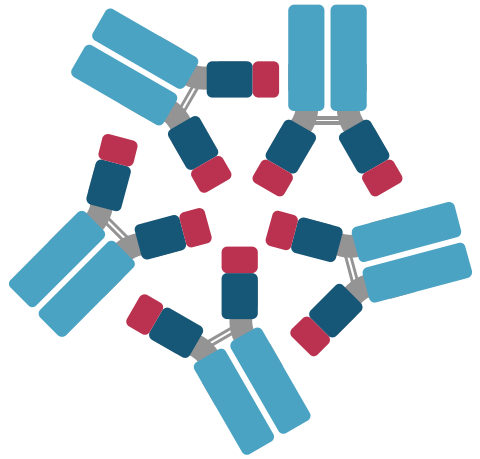
Summary/Future Work

- TB-PCF forms polymers which can be efficiently internalised by APCs
- TB-PCF can be aerosolised with commonly used excipients
- TB-PCF elicits antigen specific antibody responses in both serum and lung mucosa, as well as Th1 and Th17 responses
- MGIA assay reveals a positive effect of TB-PCF vaccination, although no difference in protection was seen in lung CFU post-aerosol H37Rv challenge so far
- Investigation of other TB antigens in PCF platform





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Acknowledgements

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- Lucy Onions
- Marialuisa Crosatti
- University of Leicester PRF

VALIDATE/BMGF
Mice

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VAccine deveLopment for complex Intracellular neglecteD pAThogEns

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