Otago Spotlight Series

Infectious Disease Research

Deciphering the protective immune response to TB

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Microbiology & Immunology

Tuberculosis (TB)

- Kills more people globally than any other bacterial pathogen
- Emergence of MDR and XDR Tb strains makes treatment difficult

TB and New Zealand

- Ongoing TB transmission occurs in NZ, primarily driven by migration (>300 notifications annually)

TB and New Zealand

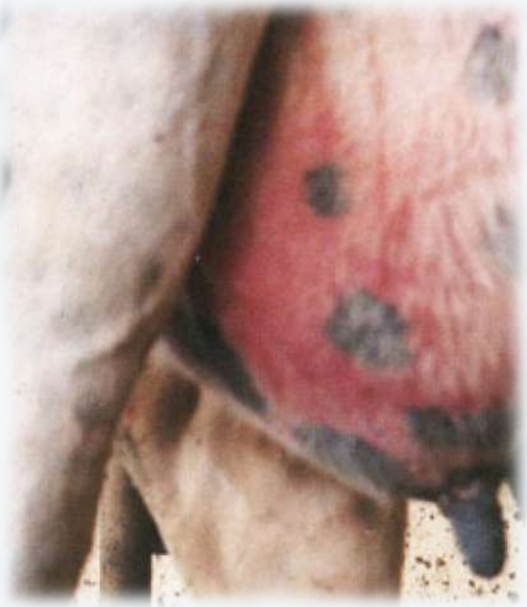
- Ongoing TB transmission occurs in NZ, primarily driven by migration (>300 notifications annually)
- **>60% of TB cases occur in SE Asia and the Western Pacific – regions close to NZ**

“Only a highly efficacious TB vaccine will ensure elimination of TB worldwide.”

Dr Mario Raviglione – WHO Stop TB Department

The current vaccine: BCG

- Live, attenuated *Mycobacterium bovis*
- One of the most widely administered vaccines in the world
- Developed a century ago!



Where are we now?

BCG is the only vaccine licensed for human use

- most effective in neonates and children
- effectiveness wanes over time
- overall efficacy of ~50%

What is wrong with BCG?

1. Unreliable efficacy (0-80% protection)
2. Diversity (3 genetically distinct lineages)
3. Safety concerns using a live vaccine in HIV-infected or immunodeficient infants

We don't understand how BCG works when it works and why BCG fails when it fails

How might BCG work when it is effective? Through T cells?

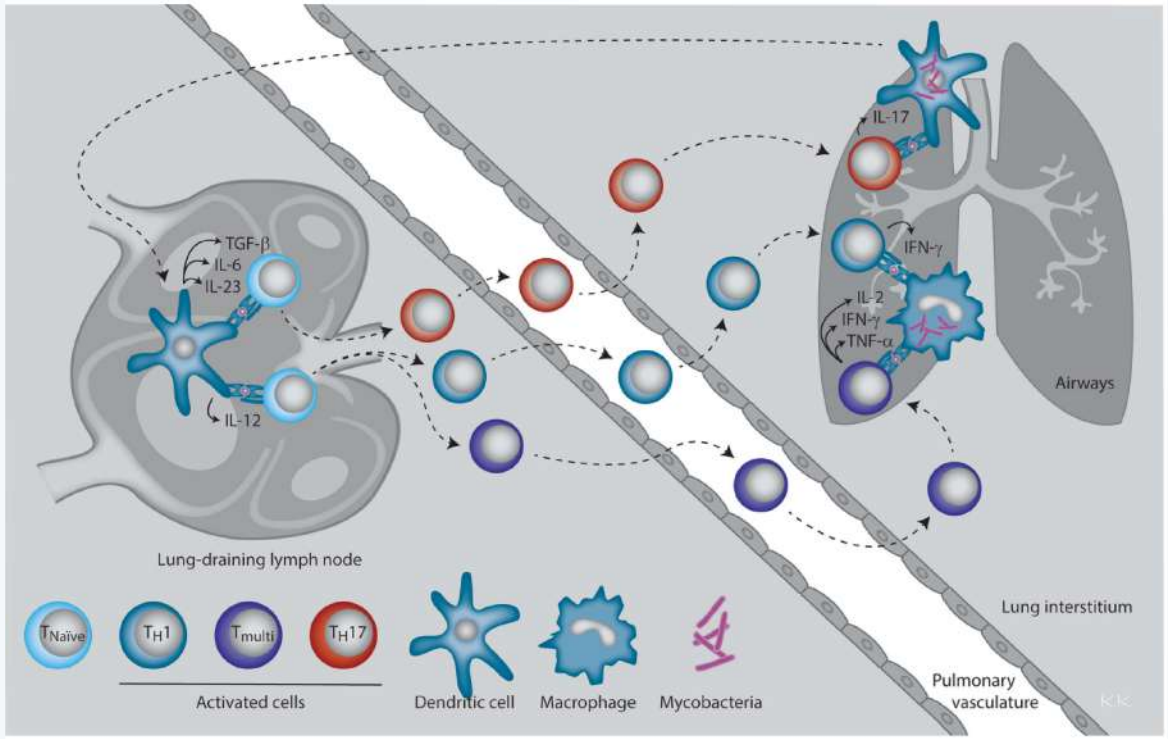


Figure from: Kirman *et al* Microbiol Spectr. 2016 Dec;4(6).

T cells are essential for the immune system to fight a primary TB infection

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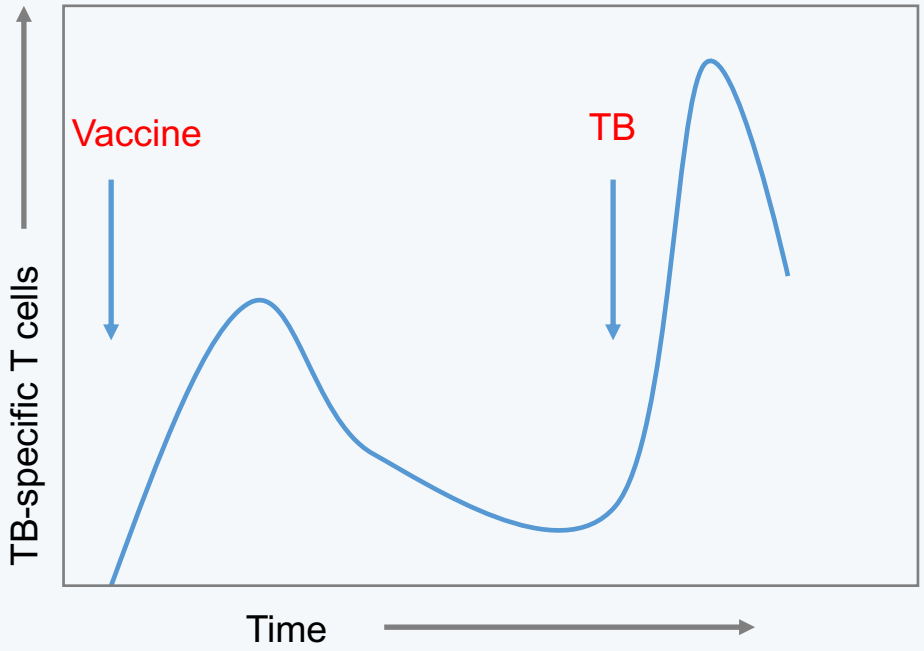
BCG activates TB-specific T cells

BUT

Does BCG protect through T cells?

Does BCG work through T cell memory?

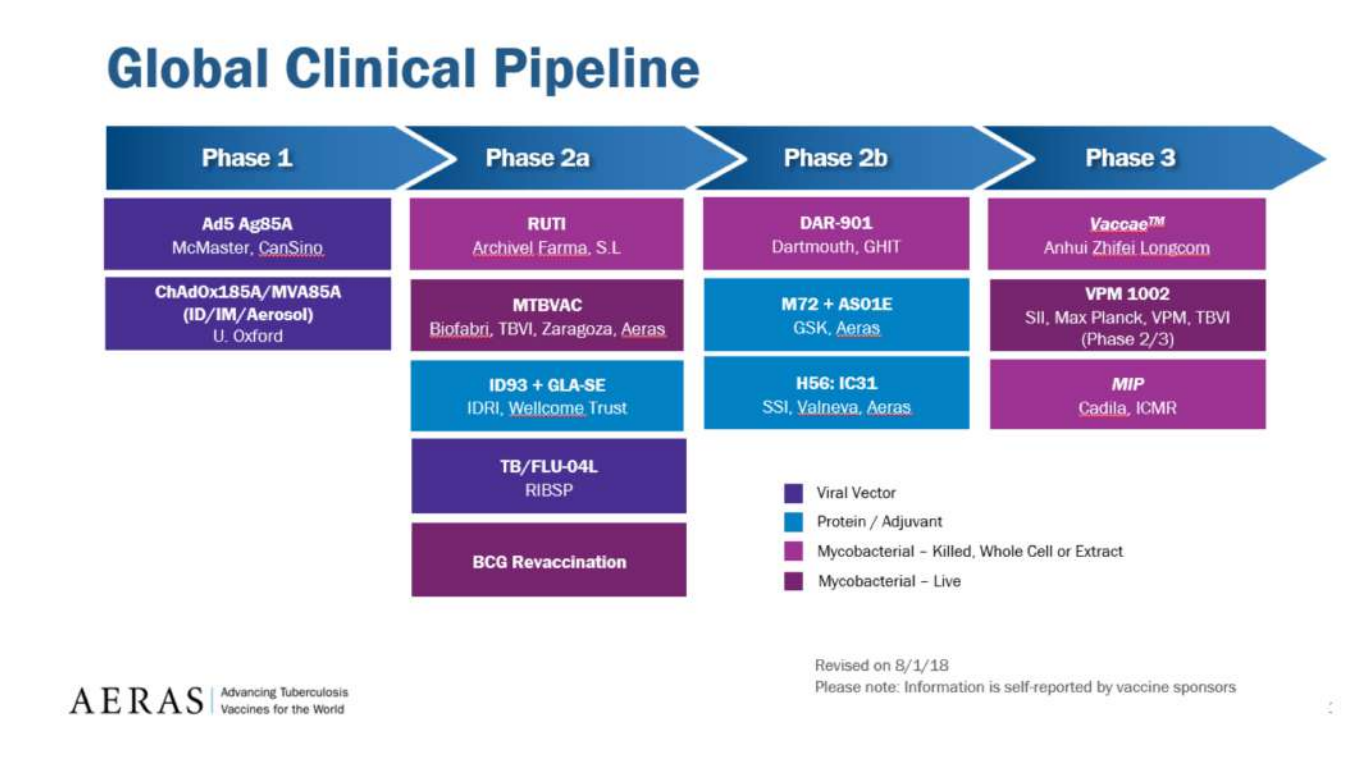


Memory T cells are thought to:

1. Be present in high numbers
2. Act faster
3. Produce appropriate effector molecules

A memory T cell response is considered to be a "souped-up" primary T cell response

Many preventative TB vaccines in the clinical testing pipeline aim to induce T cell memory



There is no correlation between the ability of a TB vaccine to induce a strong T cell response and the ability of the vaccine to protect

REVIEW

Half-truths and selective memory: Interferon gamma, $CD4^+$ T cells and protective memory against tuberculosis

Lisa Goldsack, Joanna R. Kirman*

Tuberculosis (Edin) 2007

Many preventative TB vaccines in the clinical testing pipeline aim to induce T cell memory

What is the mechanism of vaccine-induced protection against TB?

We don't understand how BCG works when it works and why BCG fails when it fails

This knowledge could assist us to develop an improved BCG or alternative vaccine

Renewed hope for a successful TB vaccine

New or revitalised ideas

Vaccines that induce:

- *Central or 'resting' memory T cells*
- *Unconventional lymphocytes*
- *'Trained' innate immunity*
- *Mucosal antibody*

Targeting central memory T cells

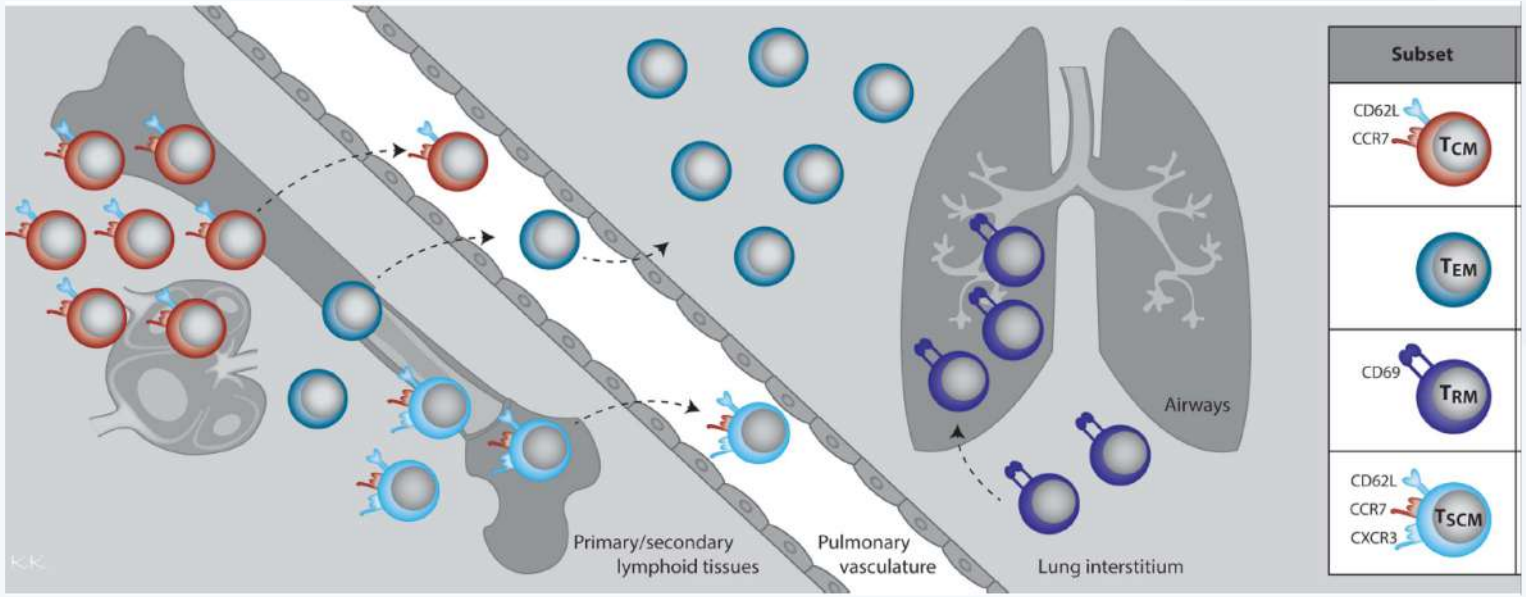
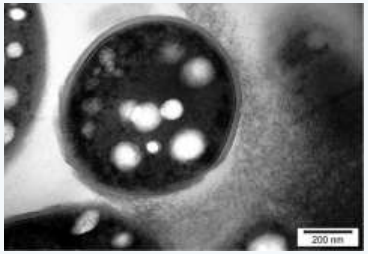


Figure from: Kirman *et al* Microbiol Spectr. 2016 Dec;4(6).

New antigen-delivery strategies

Bioparticle-based vaccines

- Targets antigen-presenting cells
- Elicits T and B cell responses

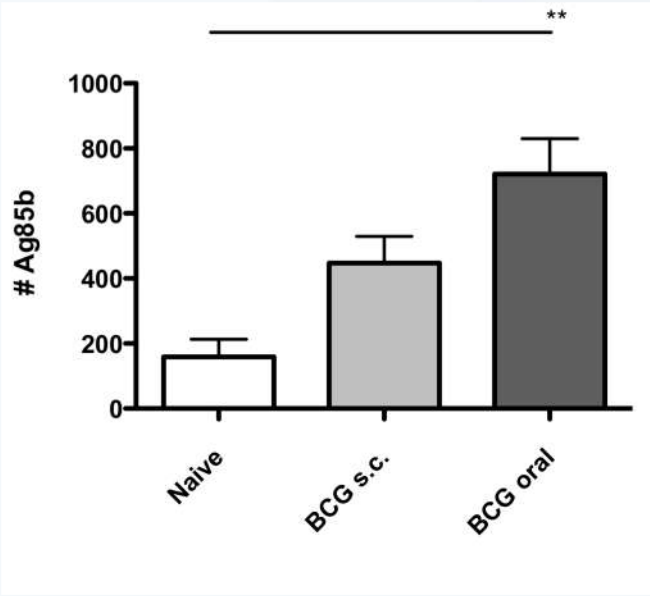


Design of bacterial inclusion bodies as antigen carrier systems

S Chen, S Sandford, J Kirman, and B Rehm

Advanced Biosystems, *in press*

Mucosal vaccine delivery



Ancelet *et al* PLoS One 2012: 7(9)e45888

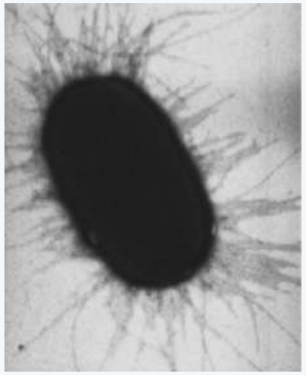
Figure from: Mifune *et al* Appl Environ Microbiol 2009 75: 4668

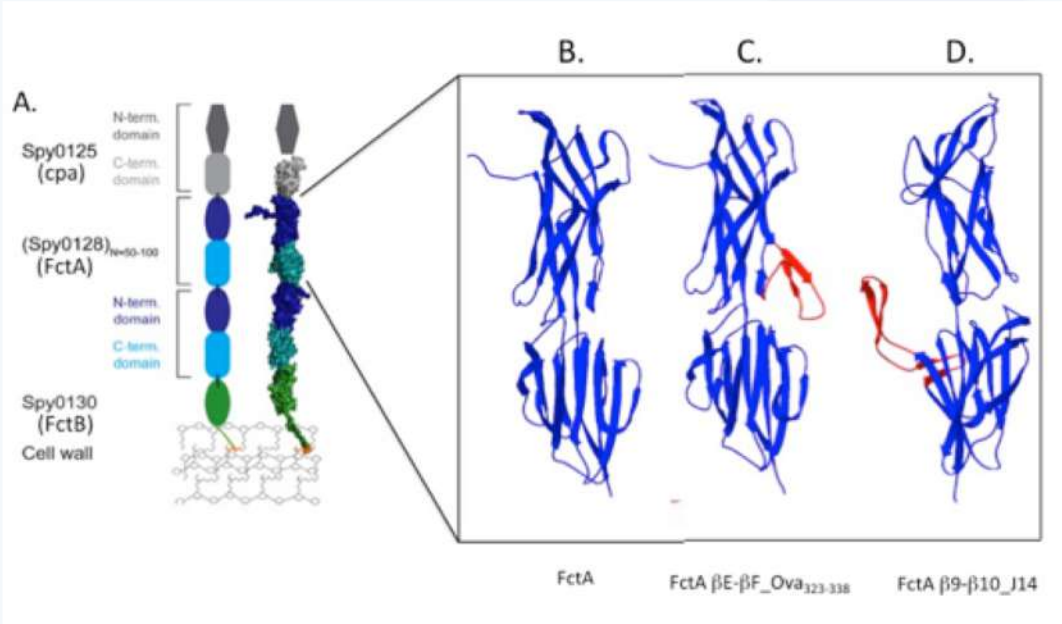
Reviving old ideas: Antibody

- Lower risk of progression to TB disease in BCG vaccinated infants correlated with higher serum Ag85A IgG[1]
- Potential role for mucosal antibody: IgA
  - may direct *Mycobacterium* to the most potent phagocytes
- May need to couple this approach with other immune targets

[1]Fletcher *et al* Nat Comm 2016 7:11290

Lactococcus lactis-based vaccines

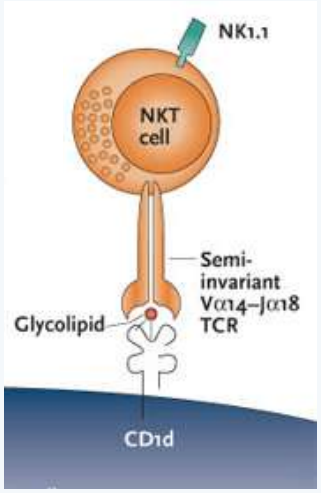


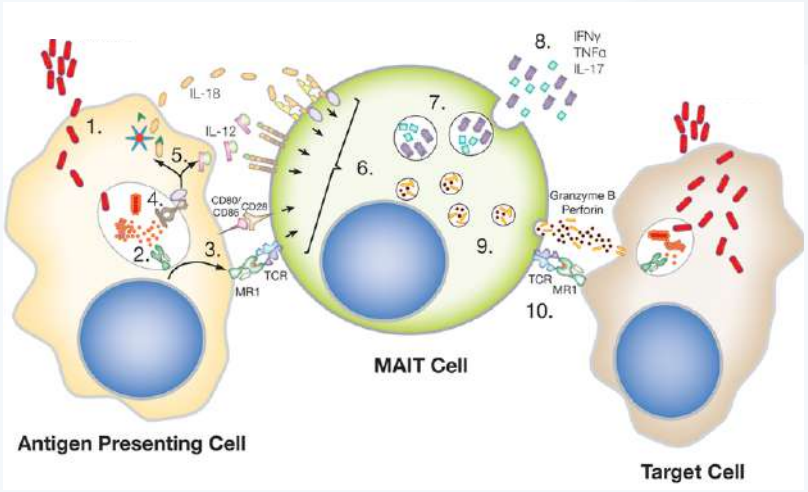


Collaborators: Sam Blanchett and Assoc Prof Thomas Proft (University of Auckland)

Targeting uncoventional lymphocytes

- Use of glycolipid antigens to target NK T cells
- Potential to target innate-like lymphocytes eg MAIT cells, ILCs



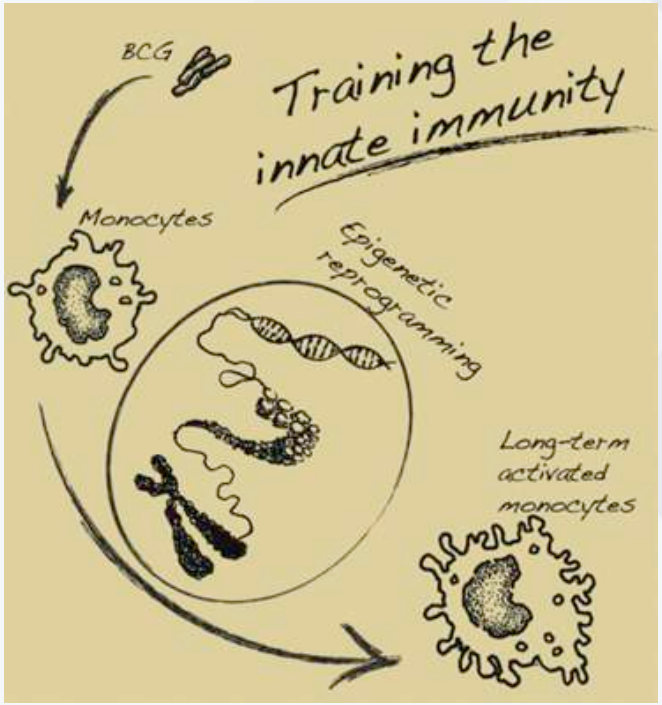


"BCG vaccination drives accumulation and effector function of innate lymphoid cells in murine lungs" Steigler *et al* ICB 2018 96:379

Targeting ‘trained’ innate immunity

BCG can impart short-term *heterologous* protection against unrelated infectious organisms

- Epigenetic modifications to monocytes in response to BCG leads to acquisition of heightened effector function
- Renewed interested in prevention of infection rather than prevention of disease



An adolescent and adult TB vaccine with 60% efficacy delivered to 20% of adolescents and adults globally could prevent as many as 17 million new TB cases in its first 25 years of use

Aeras