Deciphering the protective immune response to TB

Joanna Kirman, PhD
Microbiology & Immunology

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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...
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

Mucosal vaccine delivery

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

Design of bacterial inclusion bodies as antigen carrier systems

S Chen, S Sandford, J Kirman, and B Rehm
Advanced Biosystems, in press

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 unconventional 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

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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

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