Promise of Novel Vaccines for TB

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University of Washington

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Disclaimer

• No Financial Conflicts of Interest

• Funding

NIH

BILL & MELINDA GATES foundation

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DORIS DUKE CHARITABLE FOUNDATION
Talk Outline

• A brief history of TB vaccines
• Recent updates from the field
• Future prospects
The Goal of TB Elimination

![Graph](b)
Active TB
The Tip of the Iceberg

Active TB
9 million

Latent TB
2300 million
A Brief History of BCG (Bacillus Calmette Guerin)

- Attenuated strain of *Mycobacterium bovis*.
- Shown to be effective in cattle
- Shown to be effective in infants (1921) – prevents disseminated disease and death
- Still the standard of care worldwide – over 1 billion doses administered.
Efficacy of BCG

Disseminated TB in infants

Pulmonary TB in Adults

Babies don’t spread TB, so BCG will not stop the epidemic!


Slide courtesy of Tom Scriba
What’s wrong with BCG?

- Serial passage of bacteria over 90 years may have resulted in loss of virulence and efficacy.
- Different strains of BCG may vary in their ability to induce protective immunity.
- Exposure to environmental mycobacteria may blunt the immune response induced by BCG.
- The protective immune response wanes over time.
- We may be giving it by the wrong route.
Making a Better TB Vaccine

Kaufmann and McMichael Nature Medicine 2005
The Case for T cells

- *M. tuberculosis* is an intracellular pathogen, so antibodies may not be as important as T cells.

- T cells are essential for protection against *M. tuberculosis* in animal models (mice and non-human primates)

- HIV co-infection increases risk of developing active TB (as a result of T cell depletion?)
Heterologous prime boost strategy to evaluate candidate vaccines.

- **Prime**
  - Birth
  - BCG (Whole Bacteria)

- **Boost**
  - 6, 10, 14 weeks
  - Specific antigens, delivered in viral vectors, or with adjuvants

- **Boost**
  - Adolescence
Safety and efficacy of MVA85A, a new tuberculosis vaccine, in infants previously vaccinated with BCG: a randomised, placebo-controlled phase 2b trial

Michele D Tameris*, Mark Hatherill*, Bernard S Landry, Thomas J Scriba, Margaret Ann Snowden, Stephen Lockhart, Jacqueline E Shea, J Bruce McClain, Gregory D Hussey, Willem A Hanekom, Hassan Mahomed†, Helen McShane†, and the MVA85A 020 Trial Study Team

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo (n=1395)</th>
<th>MVA85A (n=1399)</th>
<th>Vaccine efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endpoint 1 (primary efficacy endpoint)</td>
<td>39 (3%)</td>
<td>32 (2%)</td>
<td>17.3% (−31.9 to 48.2)</td>
</tr>
<tr>
<td>Endpoint 2 (exploratory efficacy endpoint)</td>
<td>52 (4%)</td>
<td>55 (4%)</td>
<td>−6.9% (−56.1 to 26.9)</td>
</tr>
</tbody>
</table>
The TB Vaccine Pipeline

**Phase 1**
- Ad5 Ag85A
  - McMaster, CanSino
- ChAdOx185A/MVA85A (ID/IM/Aerosol)
  - U. Oxford

**Phase 2a**
- RUTI
  - Archivel Farma, S.L
- H4: IC31
  - Sanofi Pasteur, SSI, Aeras
- MTBVAC
  - Biofabri, TBVI, Zaragoza, Aeras
- ID93 + GLA-SE
  - IDRI, Wellcome Trust
- TB/FLU-04L
  - RIBSP
- BCG Revaccination

**Phase 2b**
- DAR-901
  - Dartmouth, GHIT
- M72 + AS01E
  - GSK, Aeras
- H56: IC31
  - SSI, Valneva, Aeras

**Phase 3**
- Vacciap™
  - Anhui Zhifei Longcom
- VPM 1002
  - SII, Max Planck, VPM, TBVI (Phase 2/3)
- MIP
  - Cadila, ICMR

**Types of Vaccines**
- Live attenuated: 3
- Inactivated: 4
- Recombinant (subunit): 7
Thinking Outside the Box

Antigens

- Protective immunity
- Antibodies

- T cells

Antigen stability
- 1 day
- 1 year
- 10 years
- No change

Successful vaccines
- H. influenzae B
- HBV
- Pneumococcus
- Polio (IPV)
- Meningococcus
- Measles
- MMR
- Tetanus
- Papillomavirus
- HAV

 Diseases
- Malaria
- HIV
- TB
"Conventional" T cells

<table>
<thead>
<tr>
<th></th>
<th>CD8</th>
<th>CD4</th>
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</thead>
<tbody>
<tr>
<td>Antigen</td>
<td>Peptide</td>
<td>Peptide</td>
</tr>
<tr>
<td>Source</td>
<td>Cytosolic</td>
<td>Intravesicular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Extracellular</td>
</tr>
<tr>
<td>Pathogen</td>
<td>Virus</td>
<td>Bacteria</td>
</tr>
<tr>
<td>Function</td>
<td>Cytolytic</td>
<td>Helper</td>
</tr>
</tbody>
</table>
“Unconventional” T cells

- Peptide-specific T-cell
  - CD8?
  - HLA-E
  - TB

- Metabolite-specific T-cell
  - CD8
  - MR1
  - TB

- γδ T-cell
  - BTN3A1
  - TB

- Lipid-specific T-cell
  - CD4?
  - CD8?
  - CD1
  - DN

Van Rhijn & Moody, J Immunology 2015
CMV-based vaccine for HIV

Vaccine efficacy due to unconventional CD8 T cells
- HLA-E
- MHC-II (not MHC-I)
CMV-based vaccine for TB

- Attenuated rhesus-CMV (strain 68-1) packaged with *M. tuberculosis* antigens (n=9)
- Vaccine efficacy 41% (14 of 34 rhesus macaques protected)

Immune correlates of protection?
- T-cells
- Blood transcriptional signature

Hansen et al. *Nature Medicine* 2018
Does Route of BCG Administration Matter?

- Intravenous *P. falciparum* sporozoite vaccine protects against controlled human malaria infection
- Protection associated with $\gamma\delta$ T cell frequency

<table>
<thead>
<tr>
<th>Vaccination Dose</th>
<th># Inj</th>
<th>CHMI Parasite*</th>
<th># of Subjects</th>
<th>Parasite Free</th>
<th>Vaccine Efficacy</th>
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<tbody>
<tr>
<td>None</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>$1.35 \times 10^5$</td>
<td>4</td>
<td>3D7</td>
<td>6</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>$1.35 \times 10^5$</td>
<td>5</td>
<td>3D7</td>
<td>6</td>
<td>6</td>
<td>60%</td>
</tr>
<tr>
<td>$1.35 \times 10^5$</td>
<td>5</td>
<td>3D7</td>
<td>6</td>
<td>6</td>
<td>100%</td>
</tr>
</tbody>
</table>

- IV BCG protects against challenge with virulent M.tb in rhesus macaques (1971)
- Replication study in progress
- Role for unconventional T cells?
Vaccine to Prevent Initial Infection

- RCT to evaluate prevention of infection as defined by IGRA conversion in South African adolescents

<table>
<thead>
<tr>
<th>Month</th>
<th>1-6</th>
<th>7-12</th>
<th>13-18</th>
<th>19-24</th>
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<tbody>
<tr>
<td>IGRA</td>
<td><img src="image1.png" alt="Image" /></td>
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<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
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<tr>
<td>Vaccine</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>BCG</td>
<td>X</td>
<td>--</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H4:IC31</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>H4:IC31</th>
<th>BCG</th>
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<tbody>
<tr>
<td></td>
<td>30.5% (p=0.08)</td>
<td>45.4% (p=0.013)</td>
</tr>
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</table>

Nemes et al NEJM 2018
"Now, this is not the end.  
It is not even the beginning of the end.  
But it is, perhaps, the end of the beginning."

- Winston Churchill
Acknowledgements

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Adriaan Minnaard

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Questions?

seshadri@uw.edu
Inactivated Mycobacterial Vaccine: *M. obuense* (DAR-901)

- RCT in HIV-infected Tanzanian adults (CD4 > 200/mm$^3$)

  - Endpoints
    - $1^\circ$: disseminated TB. HR = 0.52 (95%CI 0.21-1.34)
    - $2^\circ$: culture pos TB. HR = 0.61 (95%CI 0.39-0.96)

- Current Phase IIb prevention of infection trial (IGRA conversion) among adolescents in Tanzania ends Dec. 2018