Lung mucosal immunity & mucosal TB vaccination for human application

Zhou Xing

McMaster Immunology Research Centre,
Department of Pathology & Molecular Medicine
McMaster University, Canada
Infectious diseases for which there are no effective vaccines

<table>
<thead>
<tr>
<th></th>
<th>Global deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV/AIDS</td>
<td>1,100,000</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>1,800,000</td>
</tr>
<tr>
<td>Malaria</td>
<td>429,000</td>
</tr>
</tbody>
</table>

WHO 2016
French scientists Albert Calmette and Alphonse Guerin, introduced BCG, used first in France as TB vaccine (1921)

American scientist Selman Waksman discovered Streptomycin, the first anti-TB drug (1943); Nobel prize laureate (1952)
TB FACTS TODAY

5-10% develop the disease upon exposure
1/3 world population latently infected
5-10% develop the disease
10.4 million new cases/year
1.8 million deaths/year

Lengthy chemotherapy
Increasing multi-drug resistant \textit{M.\text{\text{t}}b}
Collision with HIV/AIDS
BCG vaccination will continue

WHO Report 2016
Need for developing effective boosting vaccination strategies to enhance protective immunity in the lung following parenteral BCG priming
Understanding why the “natural immunity” is ineffective in control of primary pulmonary *M.tb* infection
Anti-TB “natural immunity”
Suppressed innate immune activation in the lung
(naïve animals)

$L_{s}$pg/mL Lung

Days Post-challenge

0 20 40 60 80 100 1200 1400

Naive Day 5 Day 10 Day 14 Day 21

IL-10 pg/mL Lung

Days Post-challenge

0 200 400 600 800 1000

Naive Day 7 Day 14 Day 21

Anti-TB “natural immunity”
Delayed Th1 immunity and protection in the lung (naïve animals)

**Total CD4+ IFNγ+ T cell /Lung** (x10³)

- Media
- Stimulated

Log₁₀ CFU/lung

Day 5 Day 10 Day 14 Day 21

Days Post-challenge

Anti-TB “natural immunity”

Granuloma—a symbiotic immune-suppressed environment (naïve animals)

- CD11b+
- CD11C+
- CD11b+CD11C+

Antigen-presenting cells (APCs)

Airway lumen

Granuloma

CD4+ IFNγ+

Purified T cells

Purified CD11b+ APCs

IL-10 production (pg/mL)

Shaler et al, Am J Pathol 2011
**Anti-TB “near-natural immunity”**

Th1 immunity remains markedly delayed in the lung (s.c BCG-vaccinated animals)

<table>
<thead>
<tr>
<th>Day 5</th>
<th>Day 10</th>
<th>Day 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.7</td>
<td>10.8</td>
<td>36.3</td>
</tr>
</tbody>
</table>

**CD4+IFN-γ+ T cells**

**Log_{10} CFU/lung**

- **Day 14 post-M.tb**
  - Naïve: 3.8
  - BCG: 3.6

---

*Horvath et al, Mucosal Immunol, 2012*
New vaccination strategies to induce sufficiently “un-natural immunity” in the lung against *M.tb*
A human serotype 5 replication-defective adenovirus-based vector expressing *M.tb* Ag85A

**AdHu5Ag85A**

- **ΔE1**
- **E2**
- **ΔE3**
- **E4**

**AdHu5 backbone**

**CMV**

**Ag85A**

**Poly A**
Vaccine-induced anti-TB “un-natural immunity”
Respiratory mucosal vaccination improves lung protection

Wang et al, J Immunol 2004
Vaccine-induced anti-TB “un-natural immunity”
Respiratory mucosal vaccine-induced long-lasting Tissue Resident Memory T cells (Trm) in the lung

Jeyanathan et al, Am J Respir Crit Care Med 2010
Before M.tb infection

Lung interstitium

Airway lumen

Vasculature

Day 14 after M.tb infection

Property of Immunity

Natural Immunity
- Suppressed innate immune responses in the lung/dLN
- Delayed T cell immunity in the lung (18-21 days)
- Mainly CD4 T cells

Near-natural Immunity
- Suppressed innate immune responses in the lung
- Delayed T cell immunity in the lung (7-14 days)
- CD8 & CD4 T cells

Un-natural Immunity
- Vaccine-Trained Innate Immunity in the lung
- T cell immunity available in the lung right away
- Tissue resident memory CD8 & CD4 T cells (Trm)
Validation of the concept of viral-based (AdHu5) respiratory mucosal vaccination in large-size animal models & human studies
AdHu5Ag85A – preclinical & clinical evaluation

- **human phase 1**
  - i.m (Canada)

- **primate studies (W. Univ)**
  - i.m/i.t/aerosol (China)

- **bovine studies (VLA)**
  - i.d/e.d (UK)

- **goat studies (CReSA)**
  - i.m (Spain)

- **guinea pig (TAMU)**
  - i.m/i.n (USA)

- **murine studies**
  - i.m/i.n (Canada)
Phase 1 human AdHu5Ag85A Trial Design

-intramuscular route-

12 BCG-naïve
12 BCG+ volunteers

i.m AdAg85A (10^8 pfu) injection

screening  baseline  wk 1  wk 2  wk 4  wk 8  wk 16  wk 24  wk 26

Consent
BCG history
HIV test
QFT test
Chest x-ray

Anti-AdHu5 Abs
Whole blood culture
Fresh PBMC Elispot
Whole blood ICS
A Human Type 5 Adenovirus–Based Tuberculosis Vaccine Induces Robust T Cell Responses in Humans Despite Preexisting Anti-Adenovirus Immunity

Fiona Smaill,1,2 Mangalakumari Jeyanathan,1,3 Marek Smieja,1,2 Maria Fe Medina,1,3
Niroshan Thantrige-Don,1,3 Anna Zganiacz,1,3 Cindy Yin,1,3 Armando Heriazon,1,3
Daniela Damjanovic,1,3 Laura Puri,1 Jemila Hamid,1,4 Feng Xie,4 Ronan Foley,1,3
Jonathan Bramson,1,2,3 Jack Gauldie,1,2,3 Zhou Xing1,2,3

Induction of an Immune-Protective T-Cell Repertoire With Diverse Genetic Coverage by a Novel Viral-Vectored Tuberculosis Vaccine in Humans

Mangalakumari Jeyanathan,1,2,3,4a Daniela Damjanovic,1,2,3,4a Yushi Yao,1,2,3
Jonathan Bramson,1,2,3 Fiona Smaill,2,3,4b and Zhou Xing1,2,3,4b
Health Canada-approved clinical aerosol AdHu5Ag85A vaccine trial

Assembled inhaled aerosol delivery system for clinical TB vaccine studies

Phase 1 inhaled aerosol AdHu5Ag85A trial to be launched…
Safety and immunogenicity of a candidate tuberculosis vaccine **MVA85A** delivered by aerosol in BCG-vaccinated healthy adults: a phase 1, double-blind, randomised controlled trial


<table>
<thead>
<tr>
<th>Intracellular cytokines</th>
<th>MVA85A aerosol</th>
<th>MVA85A i.d</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAL CD4 interferon γ</td>
<td>2.0% (1.1–5.8)</td>
<td>0.7% (0.3–1.2)</td>
</tr>
<tr>
<td>BAL CD4 TNFα</td>
<td>2.3% (0.9–5.2)</td>
<td>0.6% (0.1–1.9)</td>
</tr>
<tr>
<td>BAL CD4 interleukin 17</td>
<td>0.6% (0.3–1.4)</td>
<td>0.2% (0.1–0.3)</td>
</tr>
<tr>
<td>BAL CD8 interferon γ</td>
<td>0.1% (0.1–0.6)</td>
<td>0.1% (0.03–0.3)</td>
</tr>
</tbody>
</table>
A novel virus-vectored respiratory mucosal vaccine enhances anti-tuberculosis immunity in a humanized model system

Yao et al, J Infect Dis 2017 (in press)
Spray dried human and chimpanzee adenoviral-vectored vaccines are thermally stable and immunogenic in vivo

S Afkhami, DA LeClair, S Haddadi, R Lai, S Toniolo, HC. Ertl, ED Cranston, MR Thompson, Z Xing
Conclusion

Respiratory mucosal vaccination with viral-based TB vaccine offers effective lung protection by inducing sufficiently “un-natural” immunity
The Global Clinical Pipeline of TB Vaccine Candidates

Phase 1
- MTBVAC
  - Biofabri, TBVI, Zeragosa
- Ad5 Ag85A
  - McMaster, CanSino
- ChAdOx1.85A / MVA85A
  - Oxford, Birmingham
- MVA85A / MVA85A (ID, Aerosol)
  - Oxford
- TB / FLU-04L
  - RIBSP

Phase 2a
- RUTI
  - Arbovital Farma, S.L.
- H1/H56: IC31
  - SSI, Valneva, Aeras
- H4: IC31
  - Sanofi Pasteur, SSI, Aeras
- ID93 + GLA-SE
  - IDRI, Wellcome Trust, Aeras

Phase 2b
- DAR-901
  - Dartmouth
- VPM 1002
  - SII, Max Planck, VPM, TBVI
- M72 + AS01E
  - GSK, Aeras

Phase 3
- Vaccae™
  - Anhui Zhifei Longcom

Legend:
- Viral Vector
- Protein / Adjuvant
- Mycobacterial – Whole Cell or Extract
Acknowledgments

- Past and present Xing Lab members
- McMaster GMP Vector Core members
- McMaster clinical TB Vaccine Trial Team (Dr. Smaill et al)
- Natl & Intl partners and collaborators