Respiratory mucosal immunity & novel vaccination strategies against pulmonary TB

TBVI Symposium 2016

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Need for developing effective boosting vaccination strategies to enhance protective immunity in the lung following parenteral BCG priming

A novel strategy is to target the immune check-points where natural host defense fails in response to \textit{M.\textit{tb}}
The immune check-points where natural host defense fails in response to *M.tb*
Innate immune suppression in the lung following pulmonary *M. tb* infection (naïve animals)

**TNF-α pg/mL Lung**

<table>
<thead>
<tr>
<th>Days Post-challenge</th>
<th>Naive</th>
<th>Day 5</th>
<th>Day 10</th>
<th>Day 14</th>
<th>Day 21</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**IL-10 pg/mL Lung**

<table>
<thead>
<tr>
<th>Days Post-challenge</th>
<th>Naïve</th>
<th>Day 7</th>
<th>Day 14</th>
<th>Day 21</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>400</td>
<td>1000</td>
<td>1200</td>
</tr>
</tbody>
</table>

Type I Interferon Suppresses Type II Interferon–Triggered Human Anti-Mycobacterial Responses

Rosane M. B. Teles, Thomas G. Graeber, Stephan R. Krutzik, Dennis Montoya, Mirjam Schenk

Host-directed therapy of tuberculosis based on interleukin-1 and type I interferon crosstalk

Katrin D. Mayer-Barber, Bruno B. Andrade, Sandra D. Oland, Eduardo P. Amaral, Daniel L. Barber, Jacqueline Gonzalez
Delayed onset of protective T cell immunity in the lung following pulmonary *M. tb* infection (naïve animals)

### Total CD4+ IFN-γ+ T cell /Lung (x10³)

- **Media**
- **Stimulated**

### Log₁₀ CFU/lung

- **Day 5**
- **Day 10**
- **Day 14**
- **Day 21**

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T cell immunity continues to be subject to mycobacterium-imposed immune suppression in granuloma

CD11b+ APCs

Purified CD11b+ APCs

Purified T cells

Airway lumen

Granuloma

CD4+ IFNγ+

IL-10 production (pg/mL)

media  m.tb CF  BCG

Shaler et al, Am J Pathol 2011
Delayed onset of protective T cell immunity in the lung following pulmonary *M. tb* infection (s.c BCG-vaccinated animals)

Horvath et al, Mucosal Immunol, 2012
Delayed lung protection due to suppressed innate immunity and late-arrived CD4 T cell immunity

Lung

M. tb

CD4 T cells migrate via pulmonary vasculature to lung interstitium and airway lumen

18-21 days (BCG host: 7-14 days)

Alveolar Space

DC

AM

infected DC migrate to LN

10-14 days

Ag-specific CD4 T cell priming

Draining Lymph Node

**Immune check-points**

- **Innate immunity in the lung**
- **Th1-suppressing Type 1 IFNs**
- **Timing of T cell immunity in the lung**
- **Type of effector T cell subsets**

**Mtb**

- **TNF, APC ↓**
- **IFNα/β ↑**
- **Delayed**
- **CD4 T cells**
Novel vaccination strategies to target the immune check-points where natural host defense fails in response to *M. tb*
Immune check-points

Innate immunity in the lung

Th1-suppressing Type 1 IFNs

Timing of T cell immunity in the lung

Type of effector T cell subsets

TNF, APC ↓

IFN$\alpha/\beta$ ↑

Delayed

CD4 T cells

Choice of vaccine vectors vaccine routes
A human serotype 5 replication-defective adenovirus-based vector expressing *M. tb* Ag85A

**AdHu5Ag85A**

- **AdHu5 backbone**
  - ΔE1
  - E2
  - ΔE3
  - E4

- **CMV**
- **Ag85A**
- **Poly A**
Differential protection in the lung by intramuscular and intranasal AdHu5Ag85A vaccination in mice

Wang et al, J Immunol 2004

Log10 *M. tb* cfu/lung

- PBS
- AdAg85A i.m.
- AdAg85A i.n.
- BCG s.c.
Mechanisms of parenteral vs respiratory mucosal AdHu5Ag85A vaccination
(differential distribution of CD8 T cells)

Parenteral vaccine-activated T cells, when recruited into the airway, provide enhanced protection.

Mtb CF or Ag85 proteins (x2 or x6)

s.c BCG- or i.m AdHu5Ag85A-vaccinated

Interim Conclusion:

Viral vector-based respiratory mucosal vaccination offers superior lung protection due to lasting airway luminal CD8 T\textsubscript{RM} cells, but NOT the lung interstitial T cells.
Airway luminal T cells: A newcomer on the stage of TB vaccination strategies

Table 1. Relationship between TB vaccine-activated T cell distribution and pulmonary protection.

<table>
<thead>
<tr>
<th>Route of immunization</th>
<th>T cell distribution</th>
<th>Protection in Lung (log reduction)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Airway lumen (BAL)</td>
<td>Lung interstitium</td>
</tr>
<tr>
<td>Ad (i.m)</td>
<td>±</td>
<td>++++</td>
</tr>
<tr>
<td>Ad (i.n)</td>
<td>+++</td>
<td>++++</td>
</tr>
<tr>
<td>Ad (i.m) + proteins (i.n)</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>DNA (i.m)</td>
<td>±</td>
<td>+</td>
</tr>
<tr>
<td>DNA (i.m) + proteins (i.n)</td>
<td>+++</td>
<td>++++</td>
</tr>
<tr>
<td>DC (i.m)</td>
<td>±</td>
<td>++++</td>
</tr>
<tr>
<td>DC (i.n)</td>
<td>+++</td>
<td>++++</td>
</tr>
<tr>
<td>BCG (s.c)</td>
<td>±</td>
<td>++</td>
</tr>
<tr>
<td>BCG (i.n)</td>
<td>?</td>
<td>++</td>
</tr>
<tr>
<td>BCG (s.c)+Ad (i.m)</td>
<td>±</td>
<td>++++</td>
</tr>
<tr>
<td>BCG (s.c)+Ad (i.n)</td>
<td>+++</td>
<td>++++</td>
</tr>
<tr>
<td>BCG (s.c)+fusion protein (i.n)</td>
<td>?</td>
<td>++++</td>
</tr>
</tbody>
</table>
Lung vascular perfusion only removes <5% memory T cells (Anderson KJ, *J Immunol* 2012)

Questioning the authenticity of previously believed “lung interstitial T cells”
Intravascular staining for discrimination of vascular and tissue leukocytes

Kristin G Anderson¹, Katrin Mayer-Barber², Heungsup Sung¹, Lalit Beura¹, Britnie R James³, Justin J Taylor¹, Lindor Qunaj¹, Thomas S Griffith³, Vaiva Vezys¹, Daniel L Barber⁴ & David Masopust¹

D 0
AdHu5Ag85A i.m vaccination

D 30
i.v anti-CD45.2-Percp-cy5.5

in 3 minutes
harvesting the lung

CD45.2 Percp+CD8+tet+  →  intra-pulmonary vascular T cells

CD45.2 Percp -CD8+tet+  →  lung interstitial T cells
Not only the airway lumen but also the lung interstitium are restricted T cell entry sites.
Innate immunity in the lung

Th1-suppressing Type 1 IFNs

Timing of T cell immunity in the lung

Type of effector T cell subsets

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Immune check-points

Viral-based respiratory mucosal vaccination

**TNF, APC**

**IFNα/β**

**Delayed**

**CD4 T cells**

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**APC**

**IFNα/β**

**Immediatley available**

**CD8 & CD4 T cells**

(BCG-primed hosts)
Validation of the concept of viral-based (AdHu5) respiratory mucosal vaccination in large-size animal models & clinical studies
Intranasal Mucosal Boosting with an Adenovirus-Vectored Vaccine Markedly Enhances the Protection of BCG-Primed Guinea Pigs against Pulmonary Tuberculosis

Zhou Xing, Christine T. McFarland, Jean-Michel Sallenave, Angelo Izzo, Jun Wang, David N. McMurray

- BCG/i.d (1,000 cfu)
- AdAg85A i.m or AdAg85A i.n
- M.tb challenge
- BCG/AdAg85A i.m
- BCG/AdAg85A i.n
- saline

Percent survival vs. weeks
Protection Induced by Simultaneous Subcutaneous and Endobronchial Vaccination with BCG/BCG and BCG/Adenovirus Expressing Antigen 85A against *Mycobacterium bovis* in Cattle

Gillian S. Dean, Derek Clifford, Adam O. Whelan, Elma Z. Tchilian, Peter C. L. Beverley, Francisco J. Salguero, Zhou Xing, Hans M. Vordermeier, Bernardo Villarreal-Ramos
AdHu5Ag85A Respiratory Mucosal Boost Immunization Enhances Protection against Pulmonary Tuberculosis in BCG-Primed Non-Human Primates

Mangalakumari Jeyanathan, Zhongqi Shao, Xuefeng Yu, Robin Harkness, Rong Jiang, Junqiang Li, Zhou Xing, Tao Zhu

% survival by 18 wks post-\textit{M. tb} Erdman

<table>
<thead>
<tr>
<th></th>
<th>BCG</th>
<th>BCG/Ad i.m</th>
<th>BCG/Ad i.t</th>
<th>BCG/Ad aerosol</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>2/5</td>
<td>4/5</td>
<td>6/6</td>
<td>7/7</td>
</tr>
</tbody>
</table>

BCG i.d
BCG/AdHu5 i.t
BCG/AdHu5 aerosol
BCG/AdHu5 i.m
TUBERCULOSIS

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 Thanthriye-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,*
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

Iman Satti*, Joel Meyer*, Stephanie A Harris, Zita-Rose Manjaly Thomas, Kristin Griffiths, Richard D Antrobus, Rosalind Rowland, Raquel Lopez Ramon, Mary Smith, Sharon Sheehan, Henry Bettinon, Helen McShane

<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>
Novel chimpanzee adenovirus-vectored respiratory mucosal tuberculosis vaccine: overcoming local anti-human adenovirus immunity for potent TB protection

M Jeyanathan\textsuperscript{1,3}, N Thanthrige-Don\textsuperscript{1,3}, S Afkhami\textsuperscript{1,3}, R Lai\textsuperscript{1}, D Damjanovic\textsuperscript{1}, A Zganiacz\textsuperscript{1}, X Feng\textsuperscript{1}, X-D Yao\textsuperscript{1}, KL Rosenthal\textsuperscript{1}, M Fe Medina\textsuperscript{1}, J Gauldie\textsuperscript{1}, HC Ertl\textsuperscript{2} and Z Xing\textsuperscript{1}
Final Conclusion

Respiratory mucosal vaccination with an appropriate viral vector offers most effective lung protection by targeting the immune check-points where natural host defense fails or does not fare well.
Acknowledgments

-Past and present Xing Lab members
-McMaster Vector Core members
-McMaster clinical TB Vaccine Trial Team
-Natl & Intl partners and collaborators