Lessons in Protection from the Human Model

Chetan Seshadri, M.D.
University of Washington School of Medicine

WGNV/NIAID Virtual Workshop
June 14th, 2023
The Spectrum of Human TB (Not Animal TB)

<table>
<thead>
<tr>
<th></th>
<th>Infection eliminated</th>
<th>Latent TB infection</th>
<th>Subclinical TB disease</th>
<th>Active TB disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>With innate immune response*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With acquired immune response</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Mycobacterium tuberculosis**

**Granuloma**

- **Lung**
- **Heart**

<table>
<thead>
<tr>
<th>Test</th>
<th>Negative</th>
<th>Positive</th>
<th>Positive</th>
<th>Positive</th>
<th>Usually positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGRA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Culture</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sputum smear</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infectious</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Sporadically</td>
<td>Yes</td>
</tr>
<tr>
<td>Symptoms</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Mild or none</td>
<td>Mild to severe</td>
</tr>
<tr>
<td>Preferred treatment</td>
<td>None</td>
<td>None</td>
<td>Preventive therapy</td>
<td>Multidrug therapy</td>
<td>Multidrug therapy</td>
</tr>
</tbody>
</table>

**No animal model**

Pai M. *Nature Microbiology* 2017
‘Resistance’ to M.tb infection

- “Resisters” (RSTRs)
  - Exposure (high risk score)
  - Diagnostic Testing (TST x 6 and IGRA x 3)
  - Durability (median 9 years)

- Adaptive immune responses to ESAT-6 and CFP-10 in RSTRs
  - IFN-γ independent T cells
  - Class-switched Abs (IgG and IgA)

Harriet Mayanja-Kizza
Henry Boom
Cathy Stein
Tom Hawn
Lenette Lu
Galit Alter

Stein et al. Clinical Infectious Diseases 2018; Lu et al. Nature Medicine 2019
T cells also recognize non-peptide antigens

Donor-unrestricted T cells (DURTs) mediate ‘universal’ responses independent of genetic background

Van Rhijn & Moody, J Immunology 2015
TCR-α clonotypes are associated with RSTR status

- Significantly more clonotypes associated with RSTR than would be expected by chance alone (p<0.0001)

Cross et al. bioRxiv 2022
Association between MR1Ts and RSTR Status

MR1T cells

\[ p = 0.028 \]

Frequency of CD3+ MR1T cells

TCR-Seq of sorted MR1Ts

TRA V 1-2 TRAJ33-1 CAVDDSNYQLIW

TRA V 1-2 TRAJ20-1 CAVIGDDYKLFS

Cross et al. bioRxiv 2022
MR1Ts display ligand discrimination

Most ligands are undiscovered and/or undefined!

Harriff et al. Science Immunol 2018
DURTs as Helpers (Not Effectors)

- iNKT cells (not Tfh cells) constitute ~70% of IL-4 producing cells during early viral infection and is correlated with anti-Zika neutralizing Abs in macaques.
- γδ T cells are required for priming a protective CD8 T cell in response to IV PfSPZ and malaria challenge in mice.
- Tfh-like MAIT cells mediate B cell help to generate mucosal IgA responses to *V. cholerae* in mice.

Jensen et al. *Sci Immunol* 2022
Gaya et al. *Cell* 2018
Zaidi et al. *J. Immunol* 2017
How to validate and prioritize for pre-clinical and clinical development?

Huang et al. PNAS 2019
Huang et al. Nature Biotech 2020
Controlled Human Infection with Mycobacteria (CHIM)

Grade 1

Grade 3

scRNA-Seq + TCR-Seq

Analysis of *in-situ* T cell clonotypic expansions

Jim Kublin
Chetan Seshadri
Chandler Church
David Sherman
Sean Murphy

UW Medicine
SCHOOL OF MEDICINE

Fred Hutch
Cancer Center
Summary

• ‘Resistance’ to M.tb infection is an important clinical phenotype for which there is no good animal model
• MR1Ts are expanded in RSTRs compared to LTBI controls, including at least two MAIT cell clonotypes
• Significantly more TCR-α clone sharing among RSTRs compared to LTBI suggests a role for DURT in mediating ‘resistance’ to M.tb infection
• The dearth of known non-peptide T cell antigens (and assays) limits progress
• DURT can be helpers as well as effectors
• Peptide antigen discovery in RSTRs is ongoing (GLIPH2)
• CHIM provides a mechanism to characterize the true antigenic breadth of in situ T cell responses to mycobacteria in humans.
Questions?

Post-doctoral applications welcome!