DONOR UNRESTRICTED T-CELLS (DURTS)

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Global Forum on TB Vaccines
New Delhi, India
Immunity to TB
Detection of Intracellular Infection

- Where is Mtb located in the human host?
  - The granuloma?
  - Myeloid cells?
  - Epithelial cells?
  - The lung?
- How do T cells detect intracellular infection?
- How do T cells control mycobacterial growth?
How do T cells contribute to antimicrobial immunity?
Donor Restricted T Cells: Sampling the Peptidome

- Distinguishing self from non-self
  - Diverse TCR repertoire
  - Diverse MHC
- Implications for Vaccine Design
  - Immune-evasion
  - Immuno-dominance
- Not all epitopes elicited by a vaccine are necessarily presented by the Mtb-infected cell
  - Bennekov et al., Eur J Immunol 2006
  - Nyendak et al., Scientific Reports 2016

Lewinsohn et al., NPJ Vaccines 2017
Donor Unrestricted T Cells: A Shared Human T Cell Response

The Journal of Immunology, 2015
Can DURTS Facilitate Control of Mtb
What do DURTs Recognize

**CD1**
- Lipids
- Glycolipids
- Sulfoglycolipids
- LAM

**HLA-E**
- Peptides
- Glycopeptides

**γδ**
- isopentenyl pyrophosphate [IPP]
- (E)-4-hydroxy-3-methyl-but-2-enylpyrophosphate [HMBPP]

**MR1**
- Riboflavin metabolites
- Photolumazines
- Novel Mycobacterial Ligands
MR1 Loaded During Intracellular Infection

*M. smegmatis*

Molecular Networking

PL1: Synthesis and Tetramer Production

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Curtis McMurtrey
William Hildebrand
Oklahoma University Health Sciences Center
Can DURTS Facilitate Control of Mtb: Lung Enrichment

**MAITs in TB BAL**

Wong et al., In Revision

**MAITs in NHP Lung**

Greene et al., Mucosal Immunology 2017

**TBor not TB Network: CD1-dependent Growth Inhibition in BAL**

Busch et al., AJRCCM 2016
MAIT cells localize to the mucosal surface in the human airway

Meermeir and Worley Unpublished
Can DURTS Facilitate Control of Mtb?

Polycytotoxicity

LAM Responsive PBMC

Vγ9Vδ2 T Cells

Busch et al., AJRCCM 2016

Spencer et al., PLoS Pathog. 2013

HLA-E

upregulated in blood MAITs
upregulated in all MAITs
upregulated in lung MAITs

Meermeier, Unpublished

Meller et al., Nature Immunology 2015

IL-26 production by MAIT T cell clones

Courtesy David Weiss, Modlin Lab
Evidence That DURTS Can be Protective: Knock Out Studies

Qa-1 (HLA-E)

A. Percent survival

- Qa-1\(^{+/+}\)
- Qa-1\(^{+/-}\)

\(p = 0.03\)

Days post-infection

B. CFU/organ (Log10)

<table>
<thead>
<tr>
<th>Organ</th>
<th>Time (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spleen</td>
<td>2, 3, 4</td>
</tr>
<tr>
<td>Lung</td>
<td>2, 3, 4</td>
</tr>
</tbody>
</table>

Sakala et al., 2015 JI

MR1

Day 10

***

\((P = 0.0006)\)

CFU/mouse

WT

MR1\(^{-/-}\)

Bian et al., PlosPathogens 2018
Evidence That DURTS Can be Protective: Adoptive Transfer

CD1b: Mycolic Acid Specific Effector T Cells

γδ: Zoledronate/IL-2 Stimulation

Zhao et al., eLife 2015

Qaqish et al., JI 2017
What about DURT Based Vaccination?

Gérald Larrouy-Maumus et al., Vaccine 2017
What about DURT Based Therapeutic Vaccination?

Chen et al., PLoS Pathogens, 2012
Does BCG Elicit DURTs
South African cohorts: Delayed BCG study

Healthy infants

G1, n = 25

G2, n = 25

G3, n = 25

G4, n = 25

One vial of PBMC is available from each infant
Do DURTS have Memory?

Anele Gela, Unpublished

10 QFT+ Adolescents

CD1
Chetan Shesadri, UW
Branch Moody, Harvard
Ildiko Van Rhijn, Harvard

MR1
Dave Lewinsohn, OHSU

HLA-E
Tom Ottenhoff, Leiden
Simone Joosten, Leiden

γδ
Dan Hoft, SLU

PI: Tom Scriba, SATVI
Expansion of MAITs with Age

n=10
Anela Gela, Unpublished
Memory

Peter C. Doherty
Rolf M. Zinkernagel

Figure 4. Immunologically naive (primary) CBA/J (H-2k) mice, or mice that had been infected with the PR8 (H1N1) influenza A virus 32 days previously (secondary), were challenged with the HKx31 (H3N2) influenza A virus (68). Splenic cells were assayed (1000:1) at the intervals shown on H-2-compatible targets infected with a range of influenza A viruses, or with an influenza B virus (triangles). Both the enhanced kinetics and potency of the recall response are very apparent. Later experiments with HKx31 infection of C57Bl/6J (H-2b) mice have shown very little CTL activity in lymphoid tissue following primary exposure (68).
DURT Cells: Innate or Adaptive?
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