Exploring S. Typhi-Specific HLA-E Restricted Immune Responses in Pediatric and Adult Ty21a Recipients

Mark Rudolph
PhD Candidate- University of Maryland Graduate Program in Life Sciences
Institute for Global Health
Center for Vaccine Development
Pediatric volunteers receive Ty21a vaccine for medically indicated reasons (travel to endemic regions). Recruitment is ongoing.
Pediatric Immune Responses

• Cell mediated immune responses (CMI) have been shown to change throughout childhood and into adulthood. He et al., J Virol. 80: 11756-66, 2006

• Thresholds of antigen exposure for inducing immunity also shift through increasing age. Watson, B., J. Infect Disease. Suppl 2: S143-6, 2008

• Our lab has shown that children may have less multifunctional responses than adults in response to stimulation with superantigen. Booth et al., Front Immunol. 5: 249, 2014

• We don’t know how these differences may impact the pediatric response to Ty21a vaccination, or how could this affect Ty21a protection against the development of typhoid disease in different age groups.
**Ty21a Efficacy in Children - Field Studies**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Placebo</th>
<th>Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-9 yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td># of children</td>
<td>7193</td>
<td>7034</td>
</tr>
<tr>
<td># of cases</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td>-</td>
<td><strong>59% (16-80%)</strong></td>
</tr>
<tr>
<td>10-14 yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td># of children</td>
<td>9710</td>
<td>9992</td>
</tr>
<tr>
<td># of cases</td>
<td>32</td>
<td>11</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td>-</td>
<td><strong>67% (35-83%)</strong></td>
</tr>
<tr>
<td>≥ 15 yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td># of children</td>
<td>5001</td>
<td>5142</td>
</tr>
<tr>
<td># of cases</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td>-</td>
<td><strong>85% (42-96%)</strong></td>
</tr>
</tbody>
</table>

Ty21a efficacy was previously observed to be lower at a younger age; however, (1) these data showed large overlapping confidence intervals, and (2) responsiveness does not necessarily correlate with efficacy.

*Adapted from: Levine et al., The Lancet 329: 1049-1052, 1987*
Experimental Design

**Target Cells**
721.221.AEH

- **S. Typhi Infection**
- **γ-irradiation**

PBMC

- **14-18 hr incubation**
- **Mass Cytometry**
  (38 parameters)
  - Memory subsets
  - Cytotoxic T cells
  - Helper T cells

**Experimental Design**

- Infected AEH Co-culture
- Uninfected AEH Co-Culture (Control)

Thanks to Dr. McArthur for this slide
HLA-E Restricted Antigen Presentation

- Non-classical MHC class Ib
- Present a more conserved set of peptides:
  - HLA-A2 leader peptide (inhibitory)
  - *Bacterial chaperonins* (stimulatory)
  - *Heat-shock proteins* (stimulatory)
- We have shown in adult volunteers HLA-E restricted CD8\(^+\) T cell responses for up to 2 years following Ty21a vaccination.

Adapted from: Rodgers et al. Nat Rev Immunol 5: 459-71, 2005

CD8 Activation (CD69+)
HLA-E restricted S. Typhi responses

Expression of the activation marker CD69 on CD8+ T effector memory (CD62L−/CD45RA−) cells provides preliminary data that HLA-E-restricted S. Typhi responses are observed in a higher proportion of adults than children.

Unpaired t-test
Median (interquartile range)
Baseline HLA-E restricted S. Typhi responses

Gated on CD8\(^+\) T effector memory (CD62L\(^-\)/CD45RA\(^-\)) Cells

Both children and adults exhibited baseline HLA-E-restricted S. Typhi CD8\(^+\) effector memory responses

Unpaired t-test
Median (interquartile range)
Ty21a vaccination elicits increases in HLA-E restricted S. Typhi responses

Gated on CD8+ T effector memory (CD62L-/CD45RA-) Cells

No differences in increases above baseline HLA-E-restricted S. Typhi-responsive CD8+ T_{em} effectors were observed between children and adults

Unpaired t-test
Median (interquartile range)
* \( p = 0.05 \)
Ty21a vaccination elicits increases in HLA-E restricted multifunctional S. Typhi-responses

Gated on CD8$^+$ T effector memory (CD62L$^-$/CD45RA$^-$) Cells

<table>
<thead>
<tr>
<th>Effector Molecule</th>
<th>Pediatric (14-15) $n = 5$</th>
<th>Pediatric (16-17) $n = 9$</th>
<th>Adult (total) $n = 9$</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF$\alpha$</td>
<td>$+$</td>
<td>$+$</td>
<td>$+$</td>
</tr>
<tr>
<td>IFN$\gamma$</td>
<td>$-$</td>
<td>$+$</td>
<td>$-$</td>
</tr>
<tr>
<td>IL-2</td>
<td>$-$</td>
<td>$-$</td>
<td>$+$</td>
</tr>
</tbody>
</table>

Unpaired t-test
Median (interquartile range)
* $p = 0.05$
** $p = 0.01$

Preliminary analyses showed some differences in increases above baseline HLA-E restricted S. Typhi-responsive MF CD8$^+$ T$_{em}$ effectors between children and adults.
Conclusions

• Expression of the activation marker CD69 on CD8+ $T_{EM}$ cells provides preliminary data that HLA-E-restricted S. Typhi responses are observed in a higher proportion of adults than children.

• Children exhibited baseline HLA-E-restricted CD8$^+$ effector memory responses to S. Typhi antigens, suggesting previous exposure to HLA-E-restricted antigens.

• It appears that for some functions the proportion of responders following vaccination in adults are higher than in children (analyses ongoing).

• Preliminary analyses showed some differences in increases above baseline HLA-E-restricted S. Typhi-responsive MF CD8+ $T_{EM}$ effectors between children and adults. These differences, however, appear to be less than those observed following SEB stimulation.
Future Directions

• Expand our HLA-E restriction experiments to include our youngest volunteers (6-14 years, n=8)

• Continue our analysis of soluble antigen (GroEL, OmpC, FliC) responses in pediatric and adult helper T cells

• Use Epstein-Barr Virus transformed autologous B-lymphoblastoid cell lines (already generated) to measure responses to classical HLA-restricted (HLA-A,B,C) S. Typhi antigen presentation in pediatric and adult T cells

• Assess Ty21a vaccination induced correlations between S. Typhi immune responsiveness and functional characteristics of the gut microbiota (in cooperation with the Institute for Genome Sciences)
Acknowledgements

Center Vaccine Development, UMB

Immunology Group
Marcelo B. Sztein
Monica McArthur
Stephanie Fresnay
Rosangela Mezghanni
Franklin Toapanta
Jay Booth
Rekha Rapaka
Rezwan Wahid
Paula Bernal
Cathy Storrer
Regina Harley
Haiyan Chen

Thesis Committee
Marcelo Sztein (advisor)
Monica McArthur
Larry Magder
Claire Fraser
Eileen Barry
George Lewis

Supported by grants U19 AI082655 (UM-CCHI) & R01 AI-36525 from the NIH