The non-specific immunological impact of human oral vaccination with live-attenuated *Salmonella* Typhi

Shaun Pennington

11th international conference on typhoid and other invasive salmonellosis
Live attenuated *Salmonella* and trained immunity
Live attenuated *Salmonella* and trained immunity
Study outline

Vaccine
- Day 0
  - Oral Dose 1
- Day 2
  - Oral Dose 2
- Day 4
  - Oral Dose 3

Day 0
Peripheral Blood

Day 14
Peripheral Blood

Month 3
Peripheral Blood

Month 6
Peripheral Blood

Control

Pennington et al., Science Advances (2019)
Changes to monocytes

Monocytes with an enhanced capacity to detect, destroy and display pathogens

The nature and longevity of changes consistent with the generation of innate immune memory

Pennington et al., Science Advances (2019)
Monocyte phenotype

**TLR-4**

*LPS recognition*

MFI

Control

Vaccinated

NS

P = .041

NS

P = .003

Pennington et al., Science Advances (2019)
Monocyte phenotype

TLR-4
LPS recognition

TLR-5
Flagella recognition

CD303
Antigen capture

CD16 and CD64 (FcR):
Antibody binding

CD11b and CD11c
Complement binding

Pennington et al., Science Advances (2019)
Monocyte phenotype

**HLA-DR**
Antigen presentation

**CD206**
Glycan recognition

**CD18**
Cell signalling

**CD14**
LPS coreceptor

**CD123**
Differentiation
Impact on immunity to other pathogens

Changes in output across multiple cell types in response to stimulation array of different pathogens

Changes indicative of reduced susceptibility to infections caused by unrelated pathogens

Pennington et al., Science Advances (2019)
Impact on immunity to other pathogens

- 5 stimuli
- 5 cytokines
- 6 cell types

- More than 21,000 lines of data
- Analysed using linear DAPC
  - Model 1: 92.4%
  - Model 2: 92.4%
DAPC: largest contributing variables

<table>
<thead>
<tr>
<th>CELL TYPE</th>
<th>CYTOKINE</th>
<th>SIMULUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monocytes</td>
<td>IFN-γ</td>
<td>C. albicans</td>
</tr>
<tr>
<td>B cells</td>
<td>IL-4</td>
<td>C. albicans</td>
</tr>
<tr>
<td>B cells</td>
<td>TGF-β</td>
<td>Influenza</td>
</tr>
<tr>
<td>CD4⁺ T cells</td>
<td>IFN-γ</td>
<td>Ty21a</td>
</tr>
<tr>
<td>(\gamma\delta) T cells</td>
<td>IL-17</td>
<td>C. albicans</td>
</tr>
<tr>
<td>B cells</td>
<td>IL-17</td>
<td>Tetanus Toxoid</td>
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Pennington et al., Science Advances (2019)
DAPC: largest contributing variables

- IL-4 is essential for the development of protective $T_H1$ (IFN-γ) responses against *C. albicans*
Implications

Naïve adaptive immune cells → Clonal expansion → Adaptive immune memory → Effective adaptive defences against typhoid

Live-attenuated typhoid vaccine → Progenitor reprogramming → Innate immune memory → Enhanced innate defences against other pathogens

Potential to save more lives
Acknowledgements

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