Lymphocyte Migration to/from the Gut

Tissue-specific markers of enteric vaccines’ immunogenicity
Quantitative aspects of lymphocyte migration

~2% (1 x 10^{10}) of lymphoid cells are in the blood at any one time
Lymphocytes stay in the blood for ~30 minutes

~ 90% of lymphocytes leave the blood to enter organs such as the liver, lung, gut lamina propria, spleen and bone marrow. Traffic is 5 times faster than traffic through lymphoid tissue
Extravasation of leukocytes

(a) 
- Rolling (1)
- Activation (2)
- Arrest/adhesion (3)
- Transendothelial migration (4)

Shear flow

(b) 
- Chemokine or chemoattractant receptor
- Mucin-like CAM
- E-selectin
- Integrin
- Ig superfamily CAM
- Chemokine

Step 1  Step 2  Step 3
Initial contacts of activated (effector) T cells

Mucosal-homing effector T cell and plasmablasts

Intestinal lamina propria endothelium

Skin-homing effector T cell

Skin dermal venule endothelium

Tertiary extralymphoid tissue

α4β7
Migration and diapedesis

Firm adhesion causes the leukocyte to flatten and migrate between endothelial cells.

Leukocyte migrates towards the site of infection/vaccination by sensing and following a gradient of chemokines produced by epithelial cells that have encountered the vaccine/microorganisms.

Arrest is reversible if diapeisis does not occur.

~10 Minutes
### Differential Co-expression of Tissue-Specific Integrins and Chemokine Receptors Directs B and T Cell Localization to the Small and Large Intestines

<table>
<thead>
<tr>
<th></th>
<th>SMALL INTESTINE</th>
<th>LARGE INTESTINE</th>
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<tbody>
<tr>
<td>IgA Plasmablasts</td>
<td>α4β7</td>
<td>α4β7</td>
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<tr>
<td></td>
<td>CCR9 + CCR10</td>
<td>CCR10</td>
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<tr>
<td>Effector T Cells (CD4 TH1, TH2, FTH)</td>
<td>CCR9 + CCR5 + <strong>CXCR4</strong></td>
<td><strong>GPR15</strong> + CCR6 + <strong>CXCR4</strong></td>
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<tr>
<td>Tregs (CD25+, FOXP3+)</td>
<td>CCR9 + CCR5 + CCR7</td>
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<tr>
<td>TH17 Cells</td>
<td>CCR9 + <strong>CCR6</strong></td>
<td><strong>CCR6</strong> + GPR15</td>
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<tr>
<td>Intra-epithelial T Cells</td>
<td><strong>CCR9</strong></td>
<td></td>
</tr>
<tr>
<td>• CD8αβ and CD4αβ</td>
<td>CCR9 + GPR18</td>
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<tr>
<td>• CD8αα</td>
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#### Peyers's Patches

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<table>
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<tbody>
<tr>
<td>CD22</td>
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<tr>
<td>Naive B Cells</td>
<td><em>St6gal1</em></td>
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<tr>
<td>Memory B Cells</td>
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</table>
Anatomic segmentation of the intestinal immune response in non-human primates

Different distribution of antibody-secreting cells (ASC) after oral and rectal immunizations with cholera toxin (CT)

Eriksson K et al. 1994

IgA anti-CT ASC / million MNC
Practical implications:

• How/where to administer?
  → formulation issues (delivery systems, protective vehicles, mucoadhesives, surfactants)

• Where and how to measure mucosal immune responses?
No qualified/validated assay accepted by regulators → no mucosal correlates/surrogates of protection → Extensive clinical development (efficacy)
TRACKING MUCOSAL ANTIBODY RESPONSES IN BLOOD!

NASAL

GENITAL

SUBLINGUAL

ORAL (PER OS)

RECTAL

INTRAMUSCULAR

SUBCUTANEOUS

BLOOD

Spleen, Nodes, marrow

skin

lung

Small intestine

Large intestine

genital tract
Poliovirus infection: non-mechanistic CoPs in blood after OPV and IPV

Antibody Secreting Cells (ELISPOT)
OPV & IPV immunised children

Serum IgA (ELISA)
Adults, naturally immune & IPV immunised

Dey et al. PLoS ONE 2016

Buisman et al. J Infect Dis 2008
Challenges

• Validation of tissue-specific blood ASCs in human challenge studies (rota, cholera, ETEC, Shigella, typhoid vaccines);

• Phenotypic definition and homing properties of mucosal ”memory” B cells;

• Mucosal effector T cells (CTLs, NKTs, Tregs) ?

• Mucosal Innate Immune markers
Tuesday 22 March 2016
Session 1
Workshop: NOVEL APPROACHES TO CORRELATE MUCOSAL IMMUNE RESPONSES WITH PROTECTION IN HUMANS

• 08:30 - 08:45  Introduction to the workshop: intestinal B and T cells “homing”
  Cecil Czerkinsky
08:45 - 09:00  Discussion

• 09:00 - 09:20  Mucosally derived antibody-secreting B cells
  Anu Kantele
09:20 - 09:35  Discussion

• 09:35 - 09:55  Th1, Th17 and T follicular helper cell responses to oral vaccination
  Anna Lundgren
09:55 - 10:10  Discussion

  10:10 - 10:30  Coffee break

• 10:30 - 10:50  Heterotypic B cell immunity to rotavirus- new insights
  Harry Greenberg
10:50 - 11:05  Discussion