Lymphocyte Migration to/from the Gut

Tissue-specific markers of enteric vaccines' immunogenicity

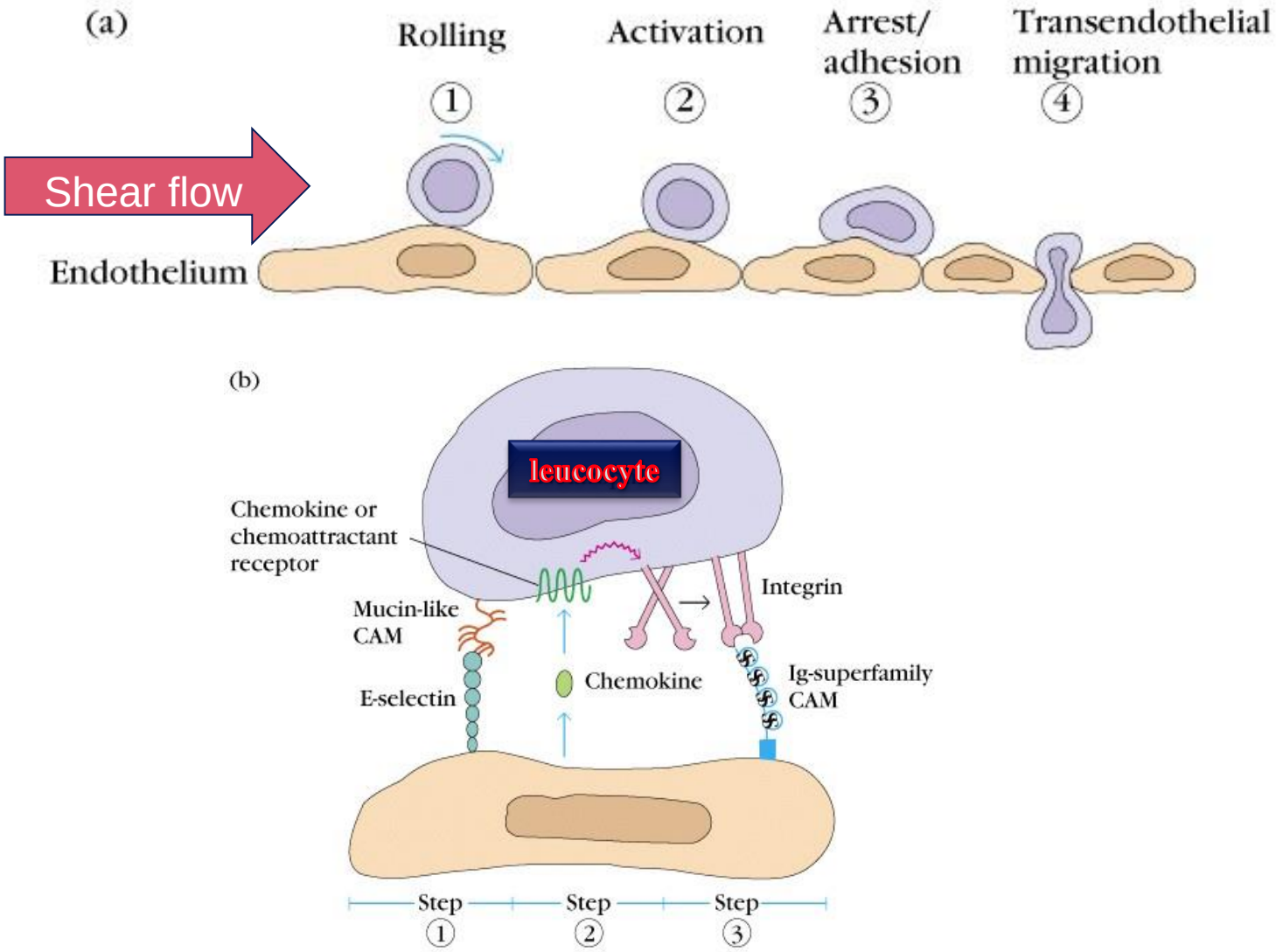
Quantitative aspects of lymphocyte migration

~2% (1×10^{10}) of lymphoid cells are in the blood at any one time

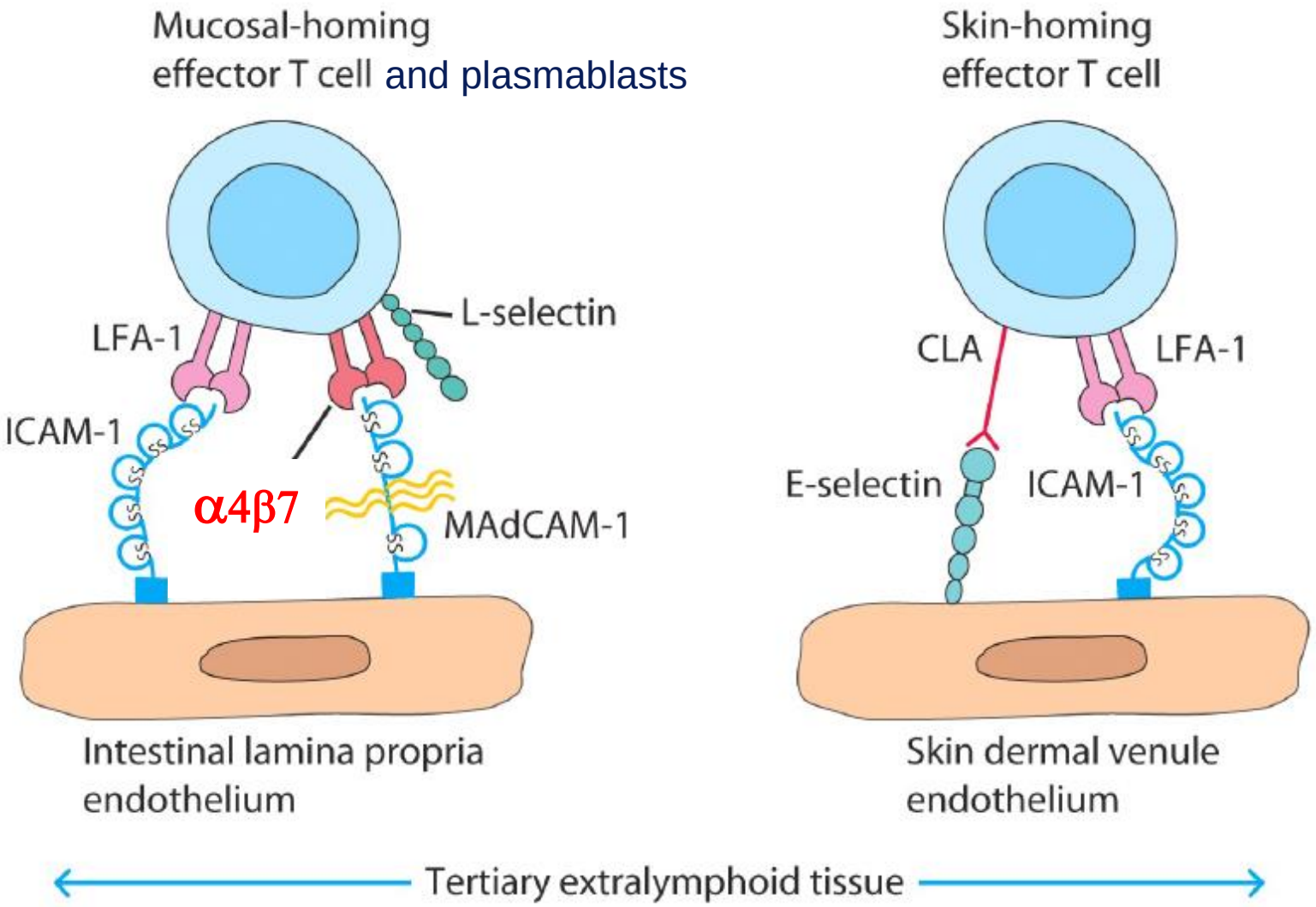
Lymphocytes stay in the blood for ~30 minutes

~ 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



Initial contacts of activated (effector) T cells

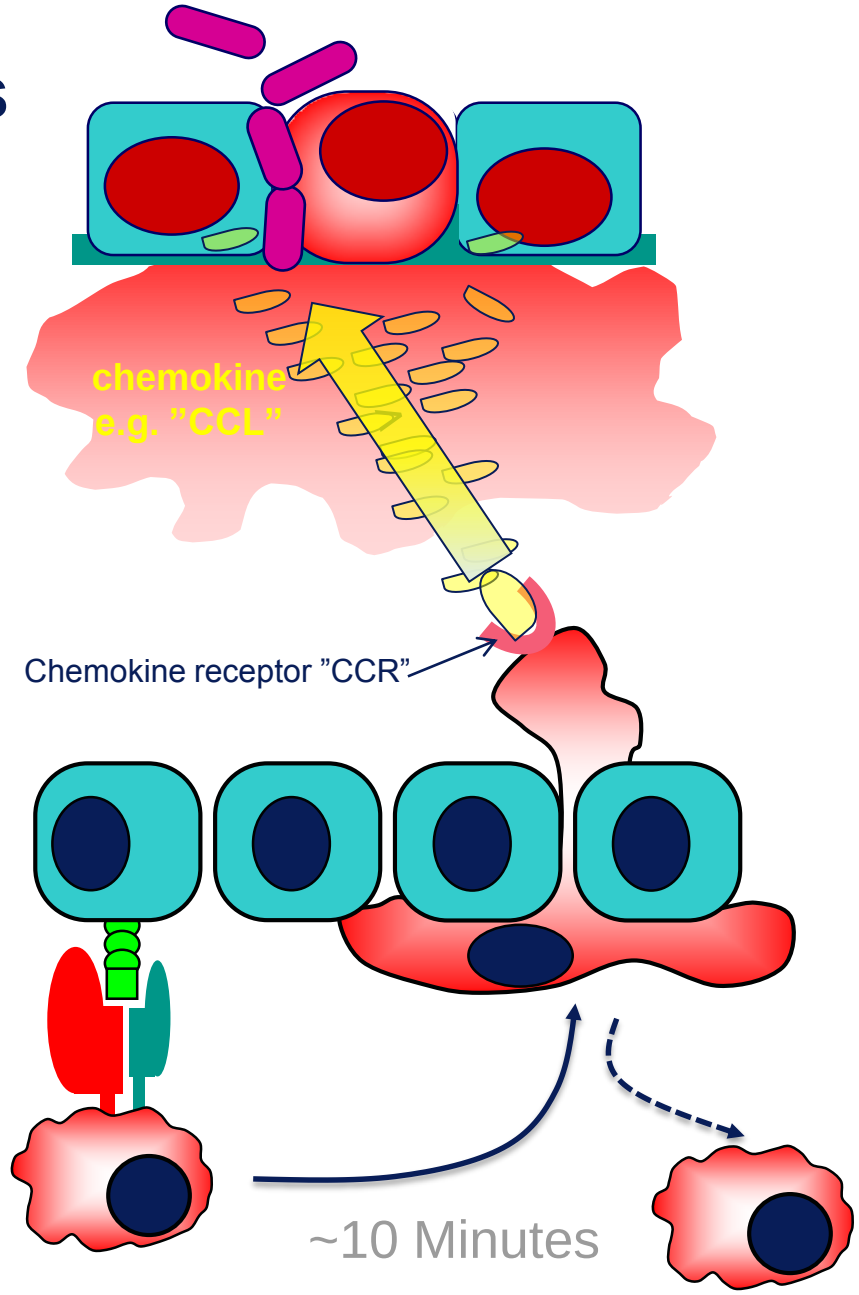


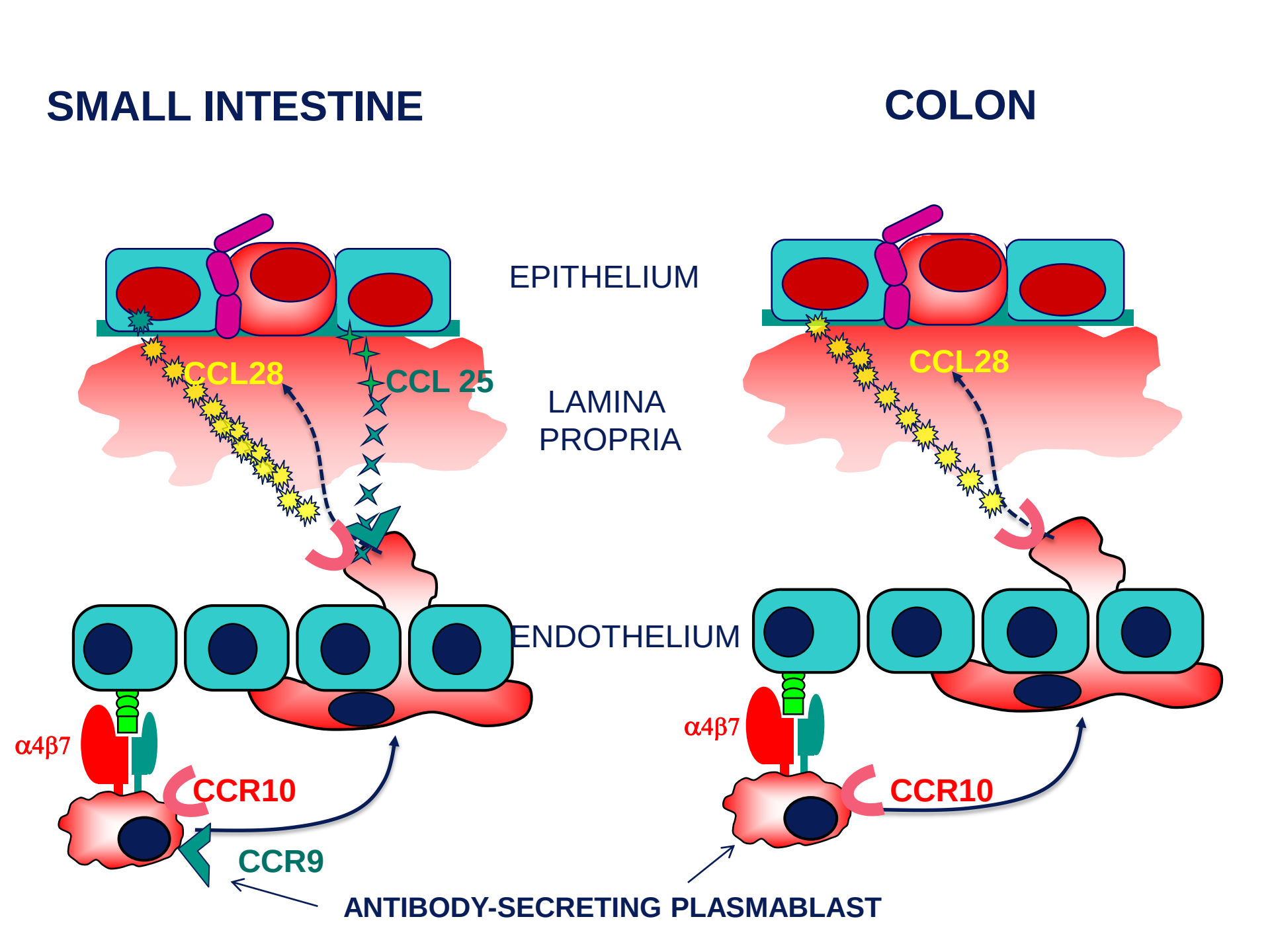
Migration and diapedesis

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



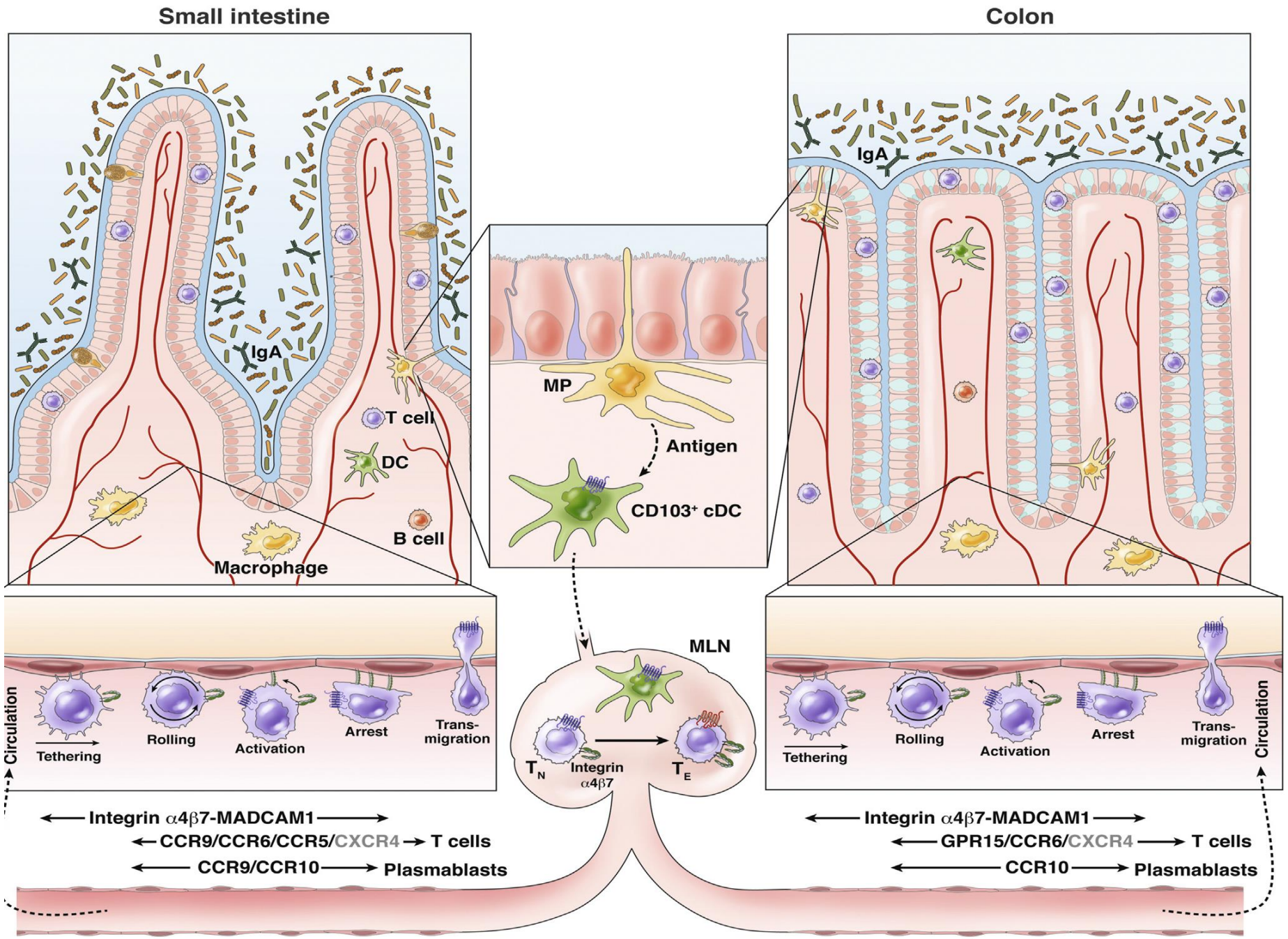

SMALL INTESTINE
COLON
EPITHELIUM
LAMINA PROPRIA
ENDOTHELIUM
CCL28
CCL 25
CCL28
α4β7
CCR10
CCR9
α4β7
CCR10
ANTIBODY-SECRETING PLASMABLAST

DIFFERENTIAL CO-EXPRESSION OF TISSUE-SPECIFIC INTEGRINS AND CHEMOKINE RECEPTORS DIRECTS B AND T CELL LOCALIZATION TO THE SMALL AND LARGE INTESTINES

	SMALL INTESTINE	LARGE INTESTINE
	α4β7	α4β7
IgA PLASMABLASTS	CCR9 + CCR10	CCR10
EFFECTOR T CELLS (CD4 TH1, TH2, FTH)	CCR9 + CCR5 + **CXCR4***	**GPR15** + CCR6 + **CXCR4***
Tregs (CD25$^+$, FOXP3$^+$)	CCR9 + CCR5 + CCR7	
TH17 CELLS	CCR9 + **CCR6***	**CCR6*** + **GPR15**
INTRA-EPITHELIAL T CELLS • **CD8αβ and CD4αβ** • **CD8αα**	CCR9 CCR9 + GPR18	?

* during inflammation

	PEYER'S PATCHES
	CD22
NAIVE B CELLS **MEMORY B CELLS**	*St6gal1*

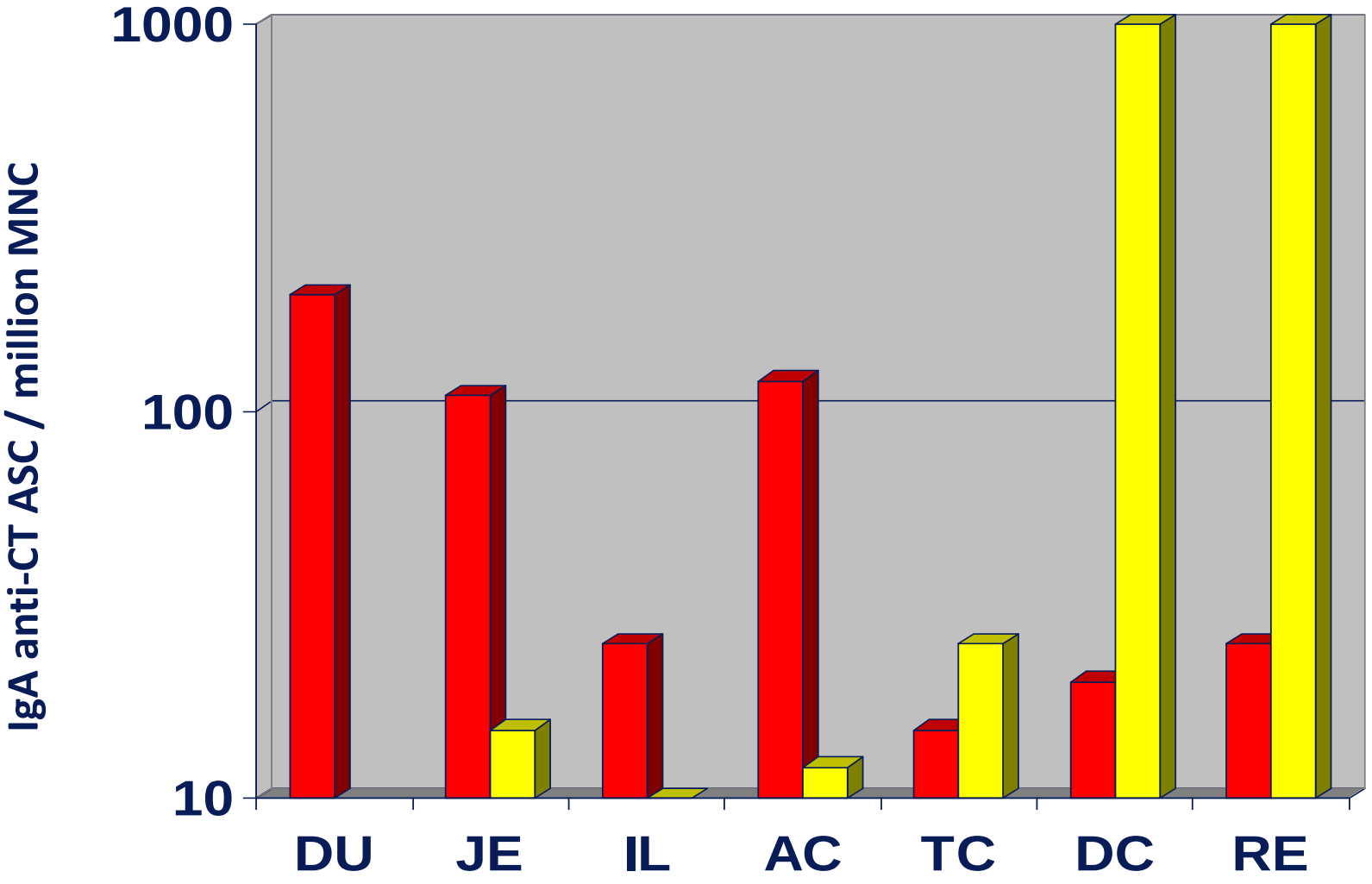


Abtezion et al *Gastroenterology* 2016;150:340–354

Eriksson K et al. 1994

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)



Practical implications:

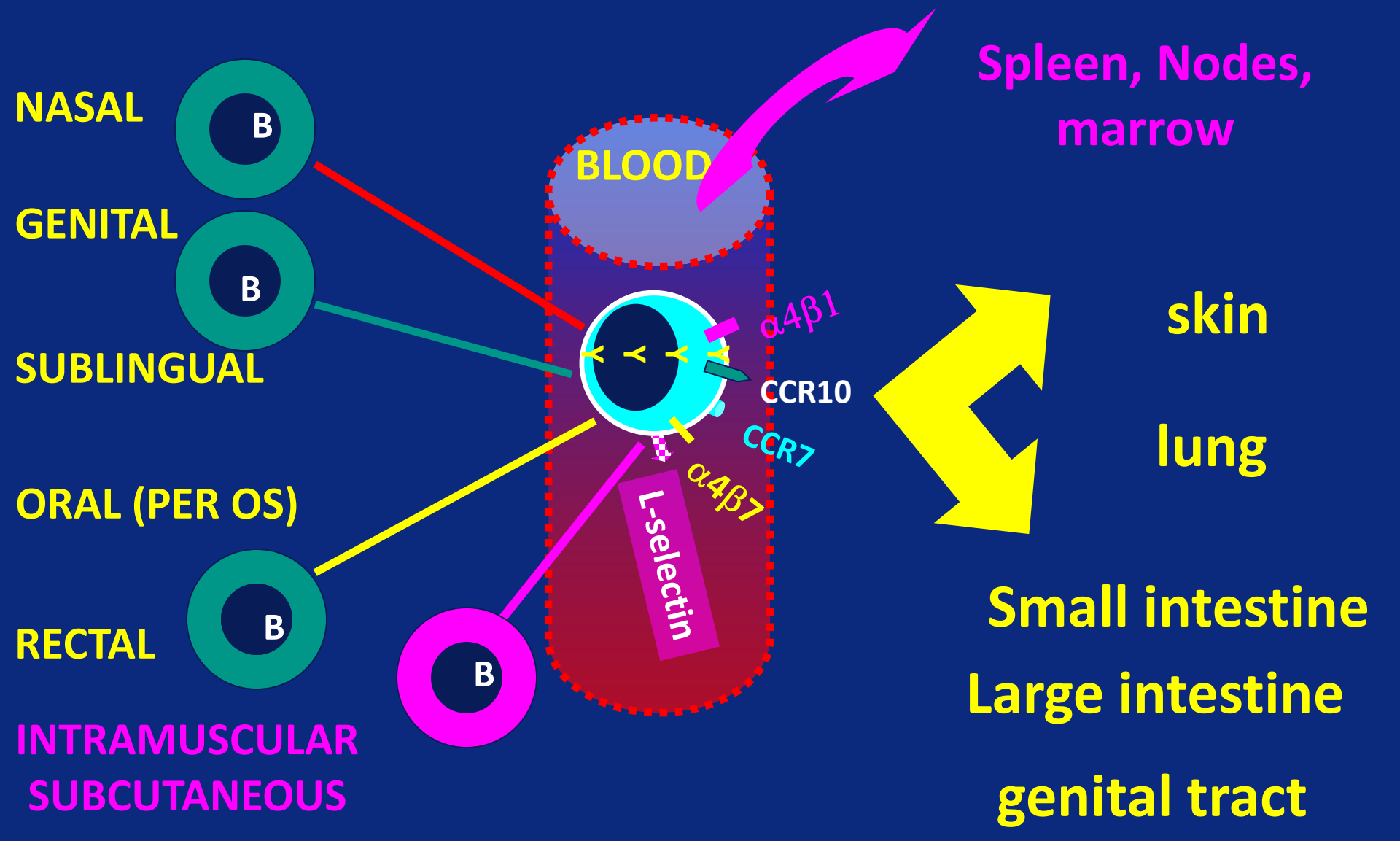
- How/where to administer?

→ 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)

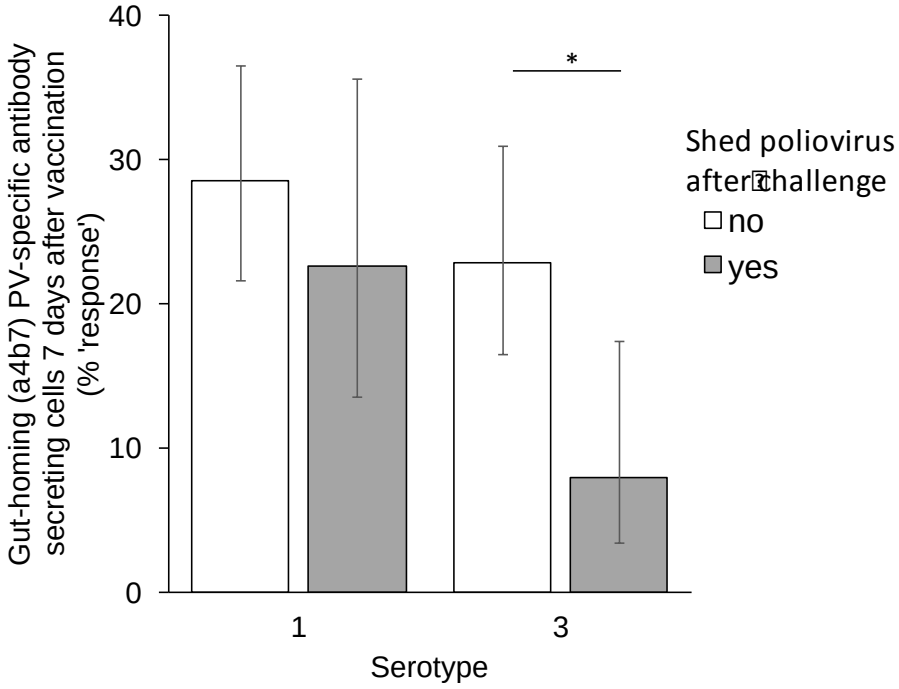
TRACKING MUCOSAL ANTIBODY RESPONSES IN BLOOD!



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

Antibody Secreting Cells (ELISPOT)

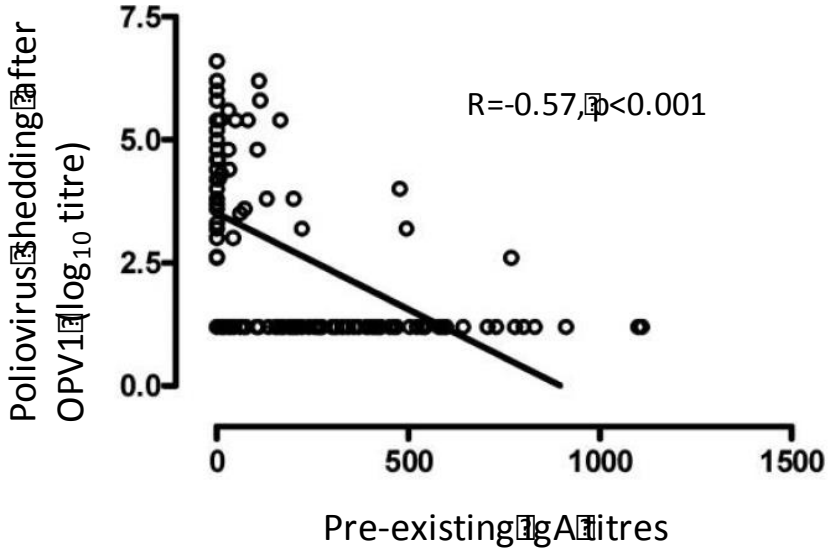
OPV & IPV immunised children



Dey et al. *PLoS ONE* 2016

Serum IgA (ELISA)

Adults, naturally immune & IPV immunised



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

Cecil Czerkinsky

Institut de Pharmacologie Moléculaire & Cellulaire
CNRS-INSERM
Sophia-Antipolis
France

czerkinsky@ipmc.cnrs.fr

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