

Humanized mice to study the role of lymphocyte trafficking in HIV dissemination

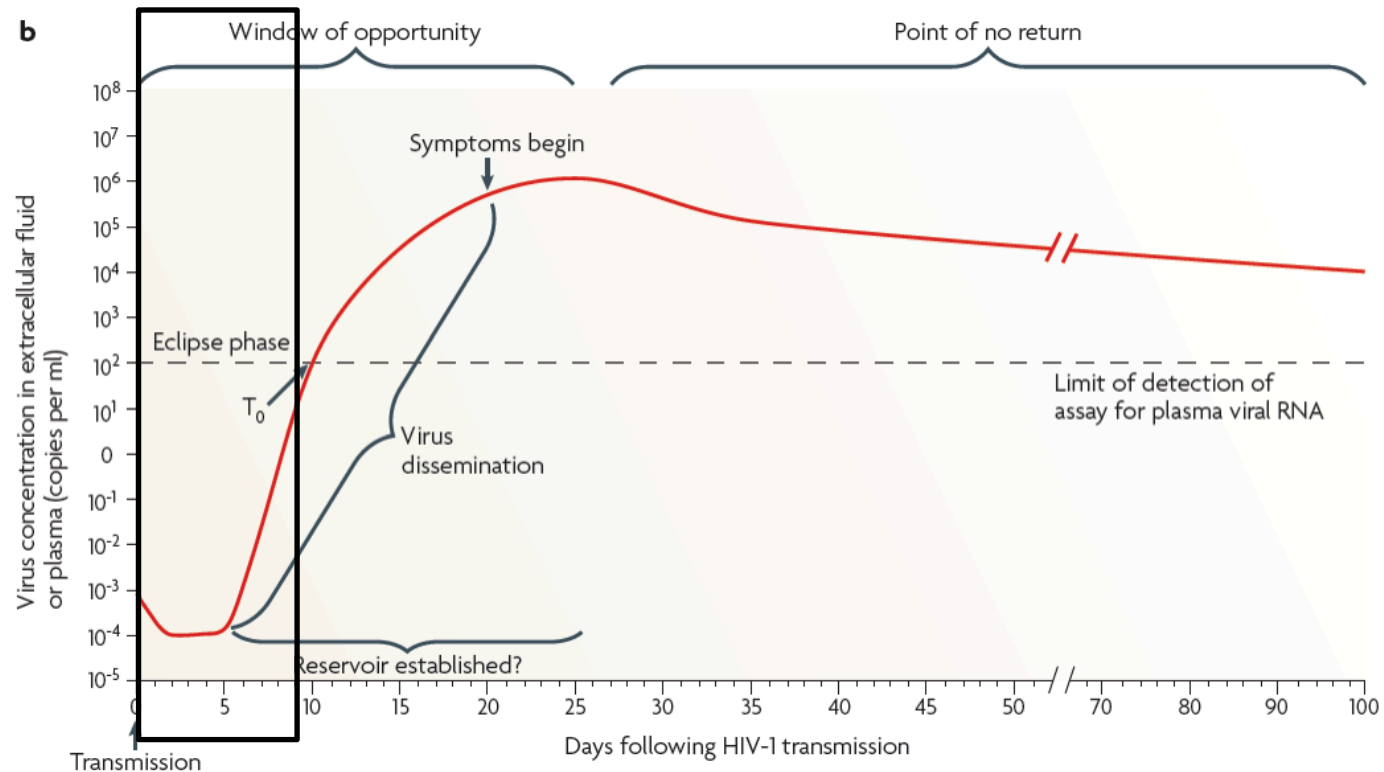
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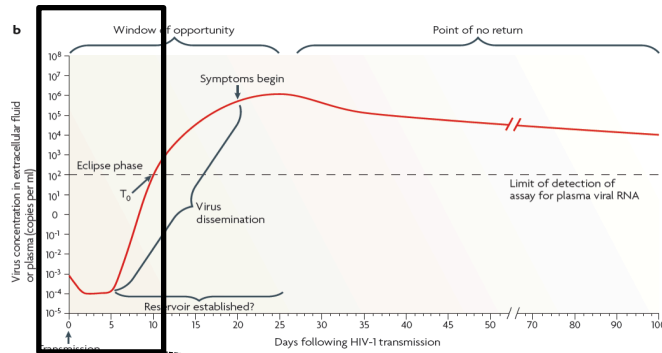
Fundamental events in acute HIV infection



McMichael & Haynes Nat Rev immunol 2010

Need a deeper understanding of the earliest events and immune responses to HIV-1 infection, especially at mucosal sites.

Early events in SIV transmission



Genital tract mucosa

Lymph nodes

Distant tissues

viremia



SIV IVAG

Infection of founder
CD4⁺ CCR5⁺ T cell

Dissemination

Systemic infection

hours

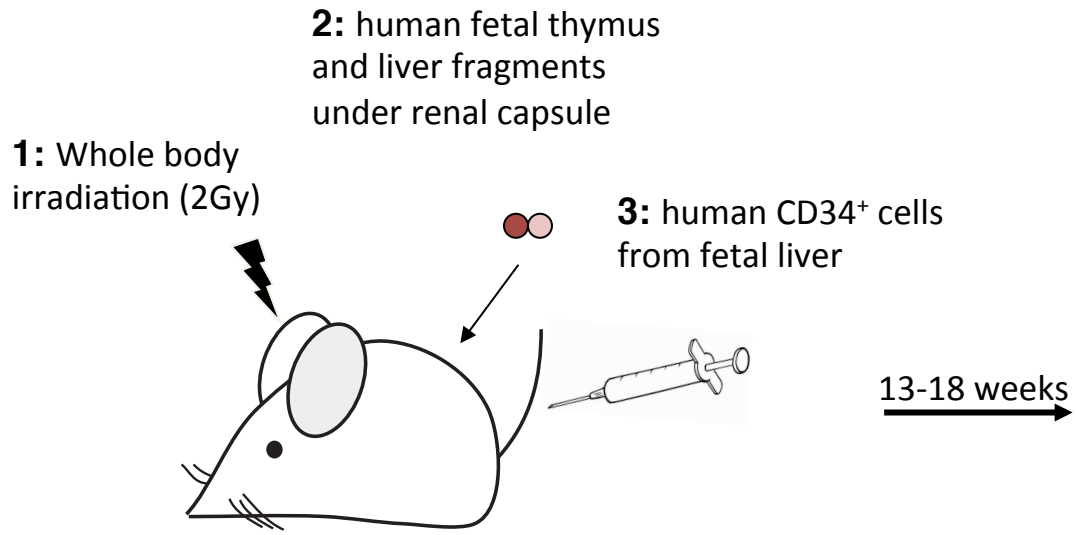
days

week 1

Window of opportunity:
days

Does Paradigm holds true for HIV transmission ?

Humanized Bone marrow/Liver/Thymus (BLT) mice



NOD-*Scid* (NS)
NOD-*Scid* /IL2R γ c^{-/-}(NSG)

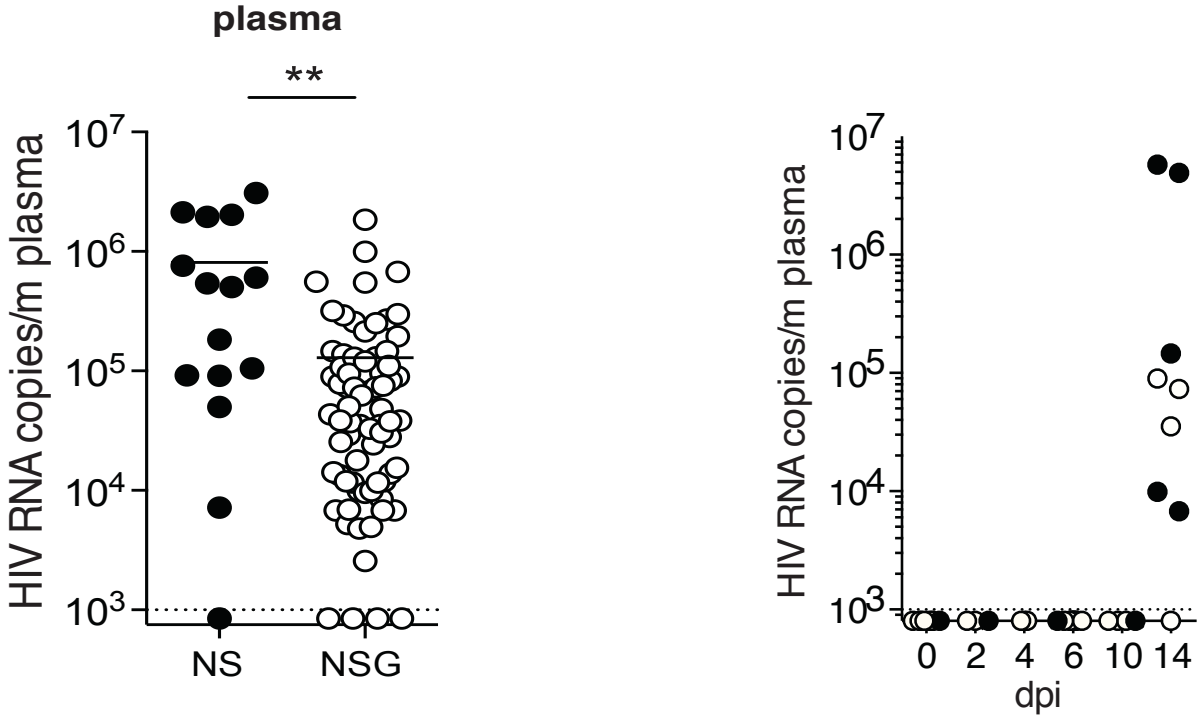
Inclusion criteria:

- > 40% human CD45⁺
- > 30% human CD3⁺,
- ≥ 200 CD4⁺ T cells/ μ l peripheral blood.

Intravaginal (IVAG) HIV infection

Atraumatic application

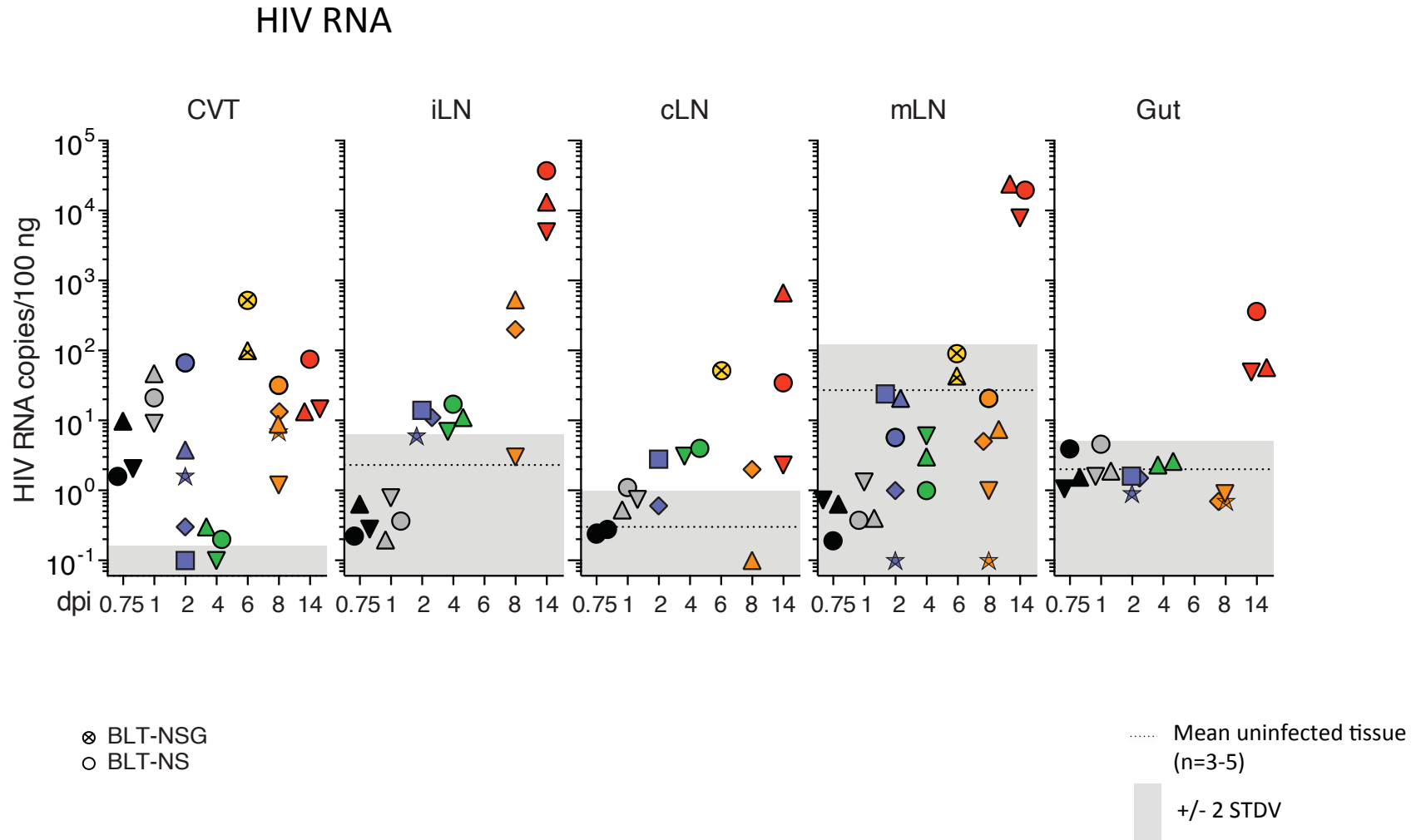
10^5 TCID₅₀ HIV-1_{JR-CSF}



n=90 total, 13 batches

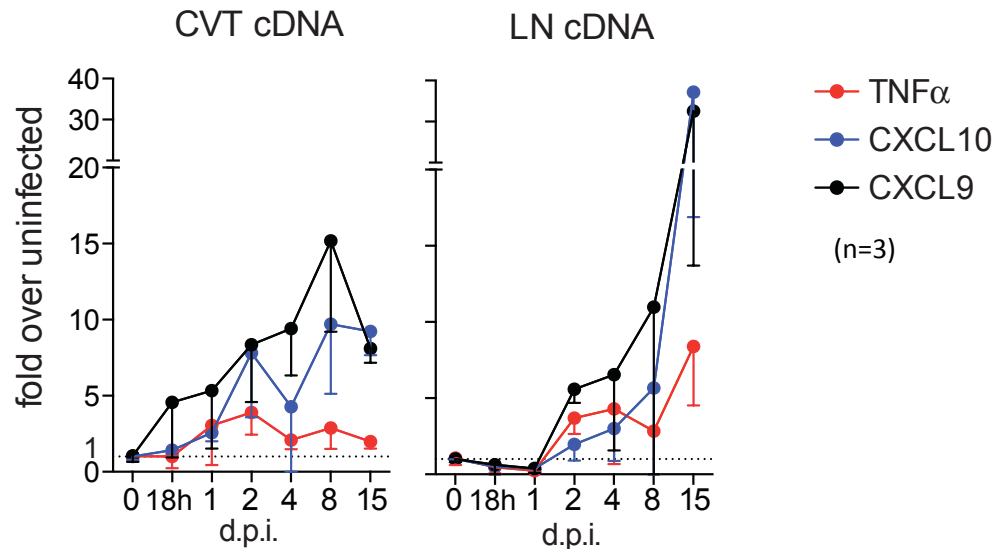
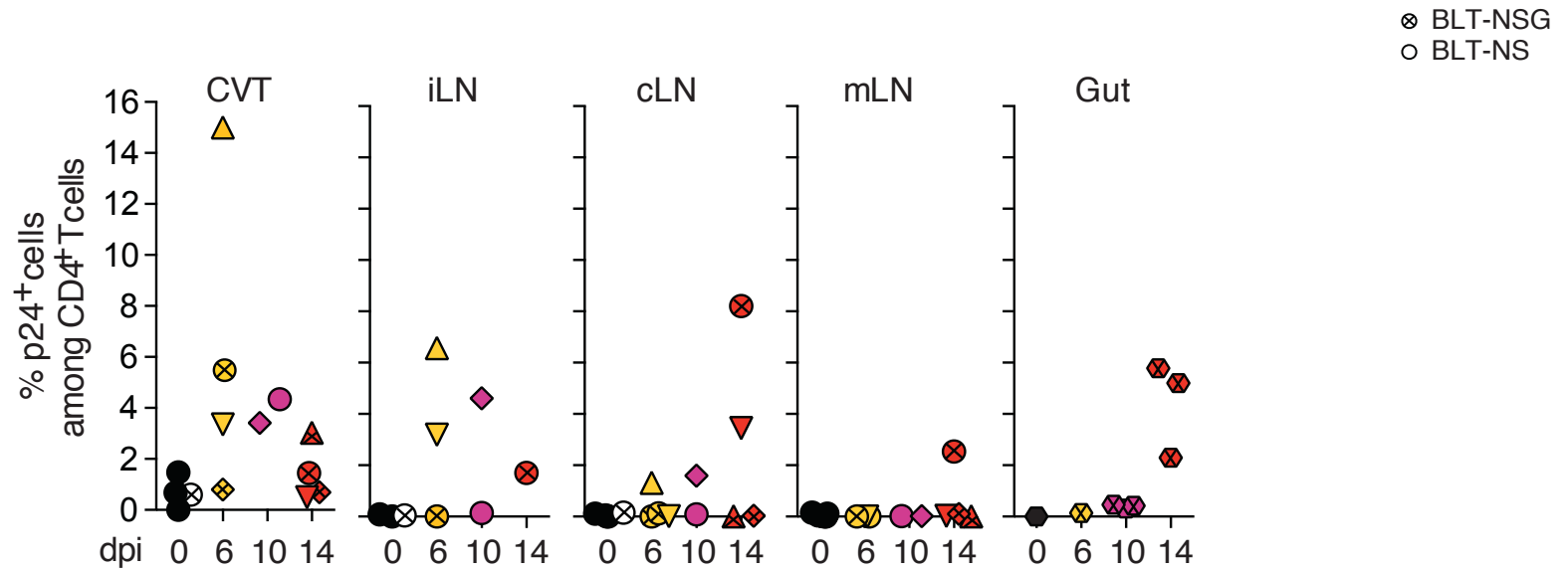
Infection rate: 96% at 14 dpi

HIV dissemination following IVAG infection

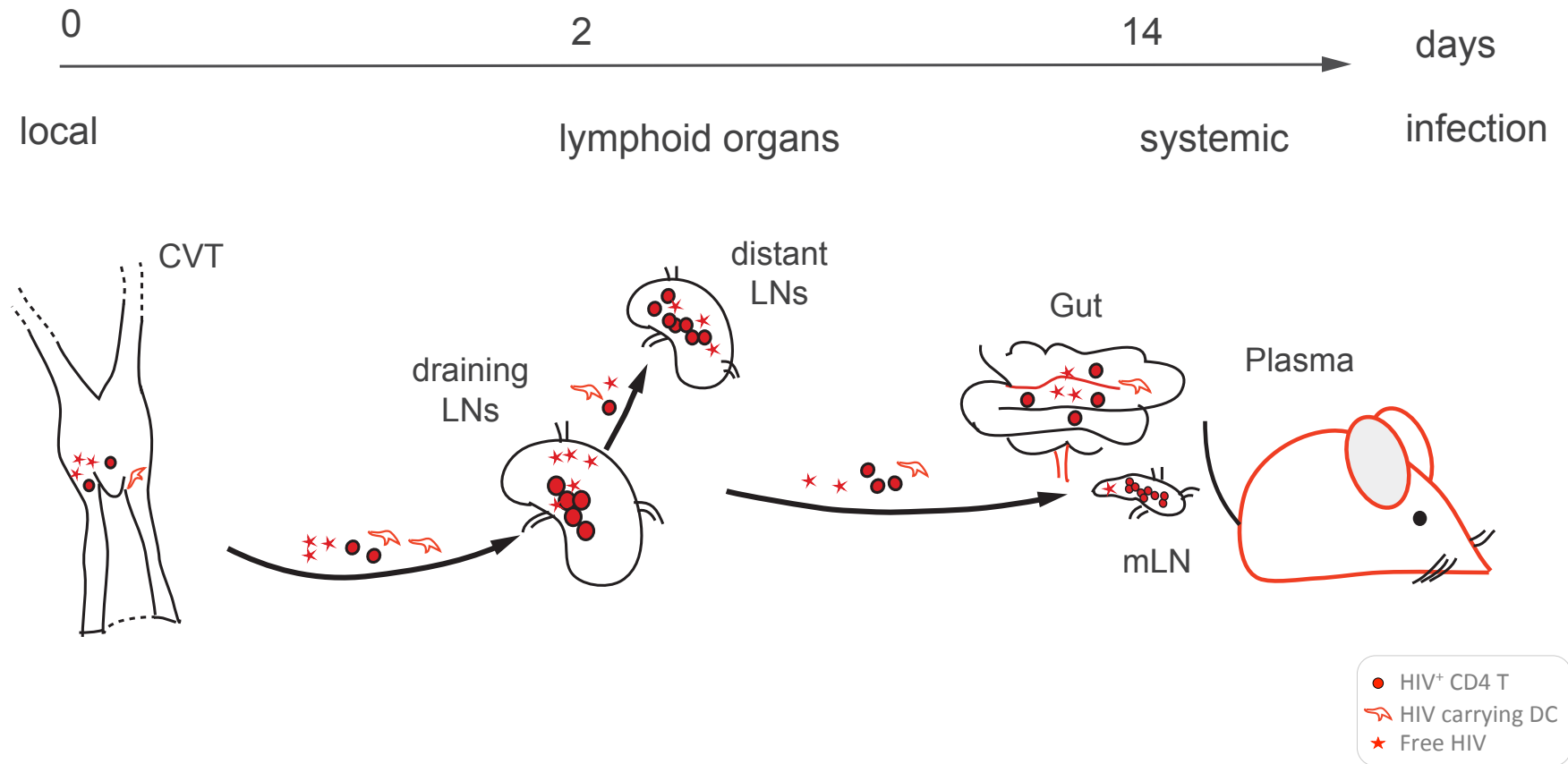


CVT: cervico-vaginal tissue

HIV dissemination following IVAG infection

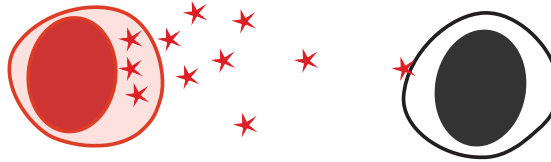


HIV dissemination in BLT mice

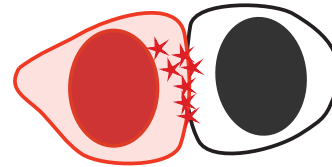


HIV transmission

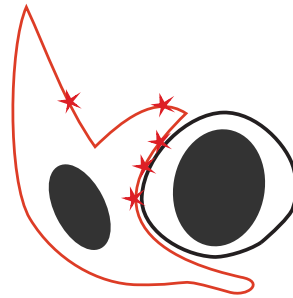
Free virus to cell



Infected cell to cell



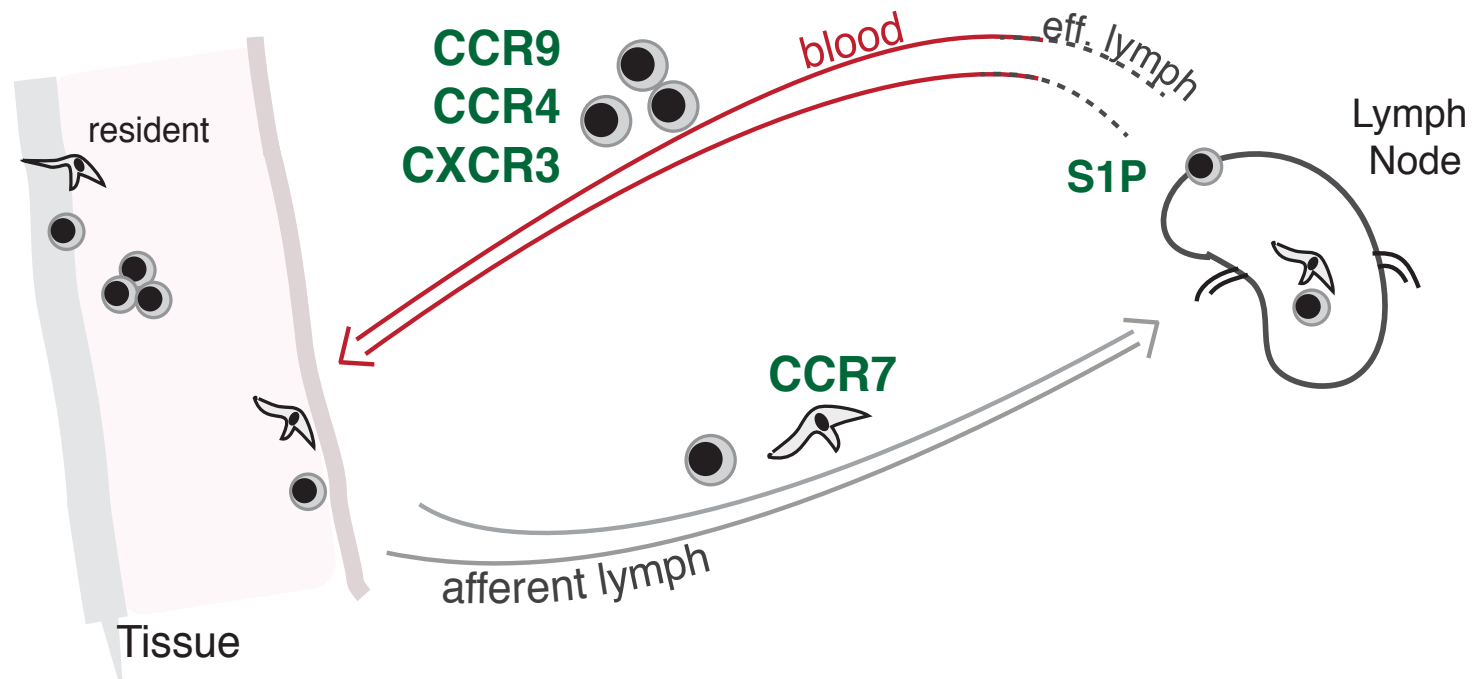
HIV carrying-cell to cell



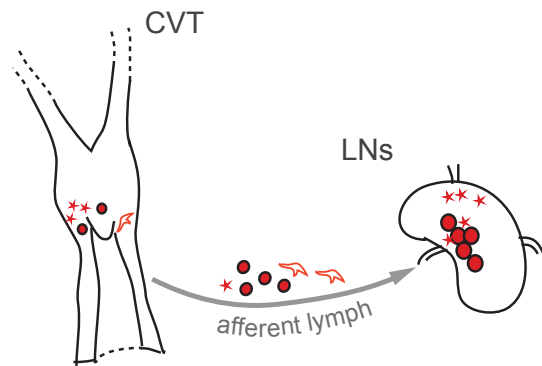
Cell-to-cell is more efficient than free virus-to-cell transmission *in vitro*

*Dimitrov J Virol 1993, McDonald Science 2003, Jolly J Exp Med 2004,
Chen J Virol 2007, Sourisseau J Virol 2007, Dale Immunological Reviews 2013*

Immune cell trafficking

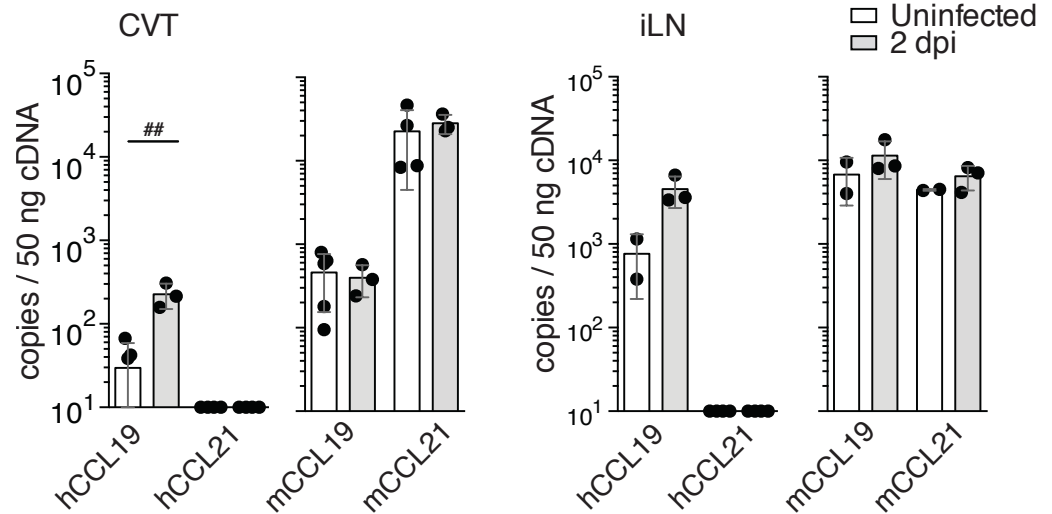


Role of leukocyte trafficking in HIV dissemination? – CCR7

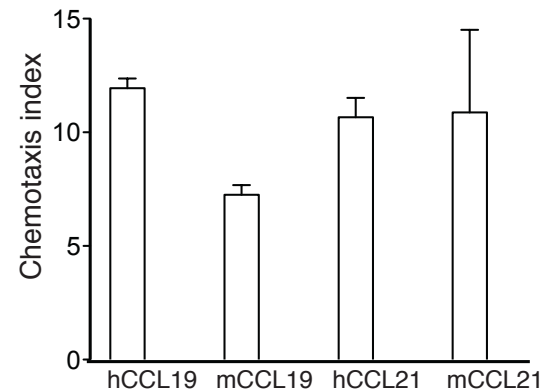


CCR7?

murine ligands >> human ligands in tissues



Human CCR7 respond to murine ligand *in vitro*

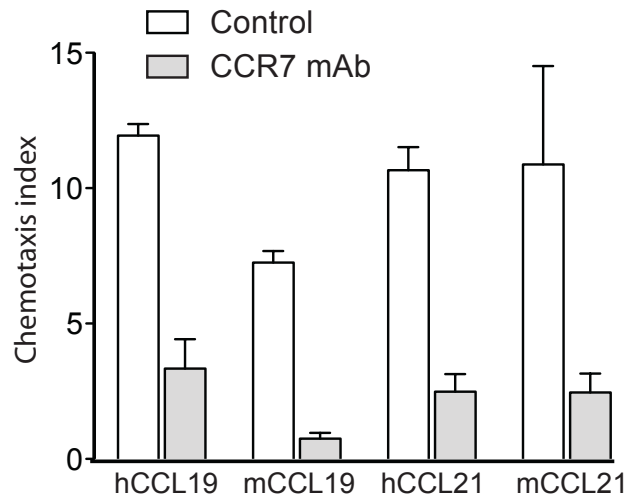


Human T cells, 100 nM chemokine

Anti-human CCR7 mAb (α CCR7)

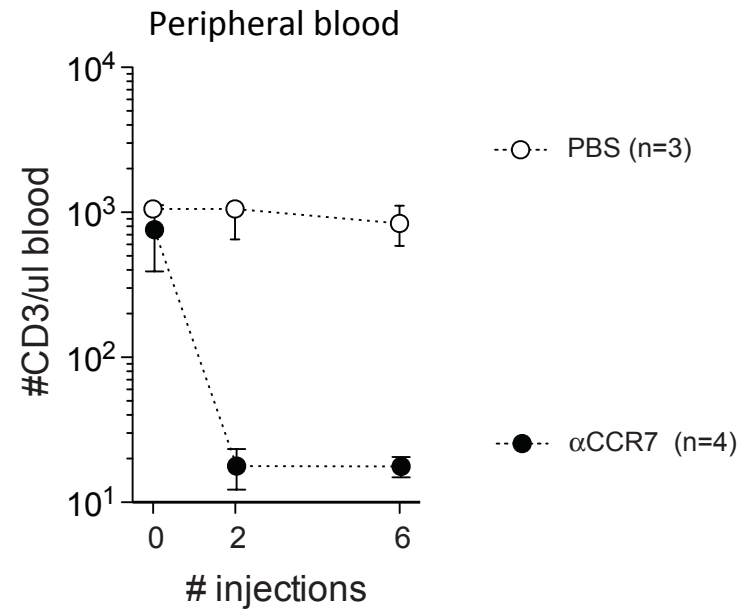
- α CCR7:**
- mutant, no N-linked glycosylation,
 - impaired Fc receptor binding & ADCC

In vitro



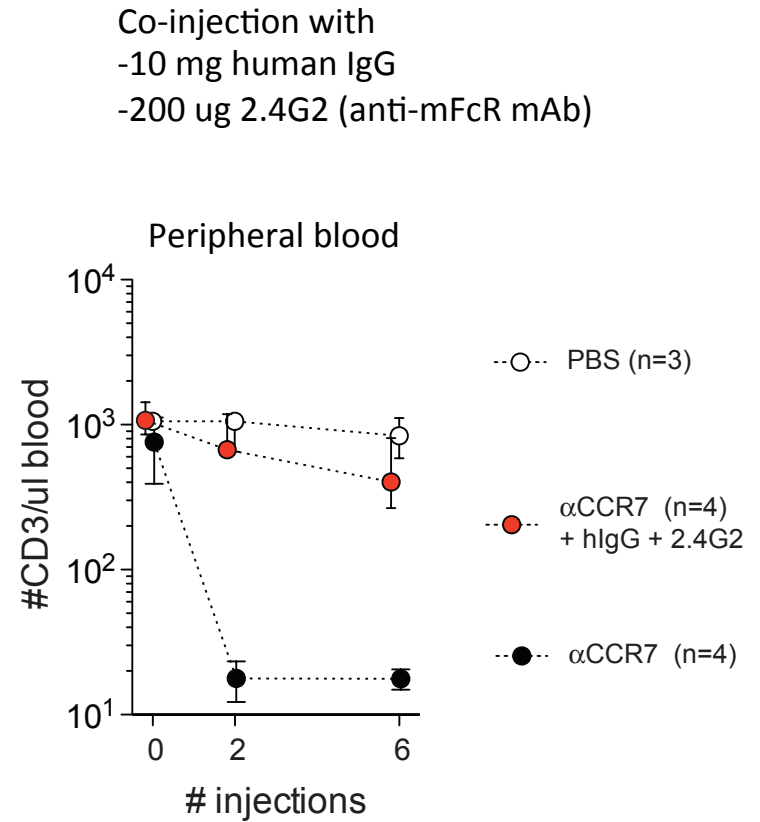
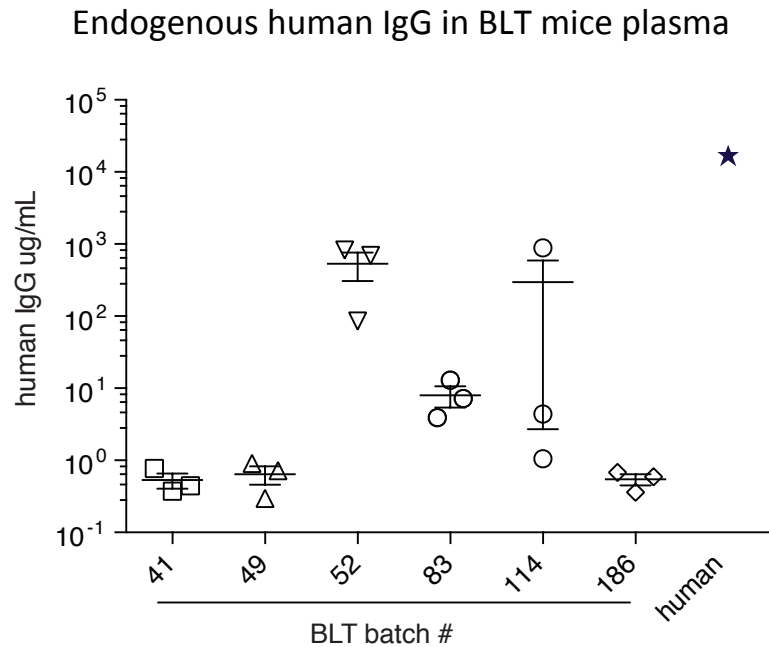
Human T cells
100 nM chemokine

In vivo

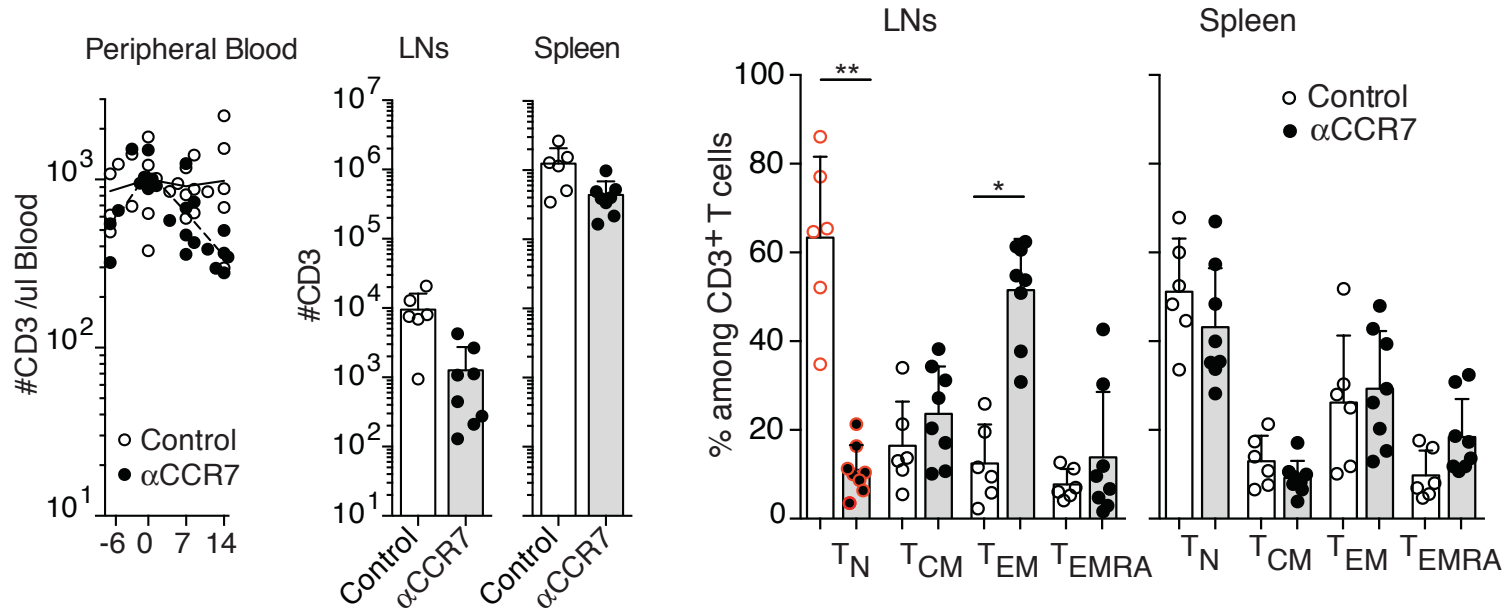
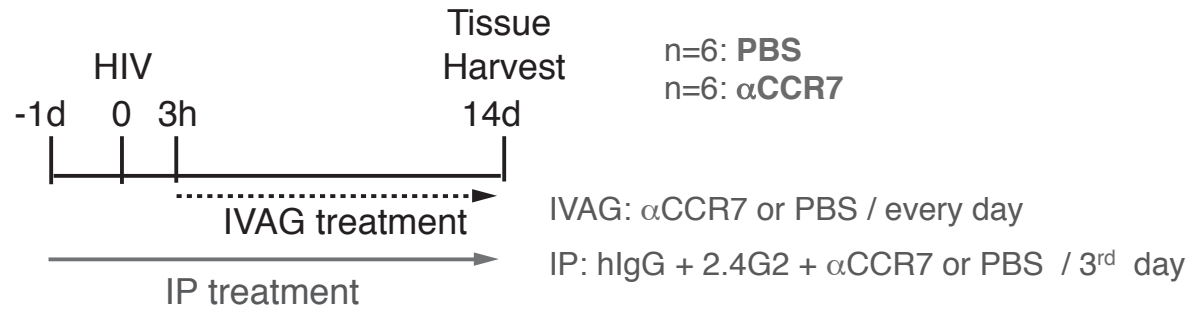


Anti-human CCR7 mAb (α CCR7)

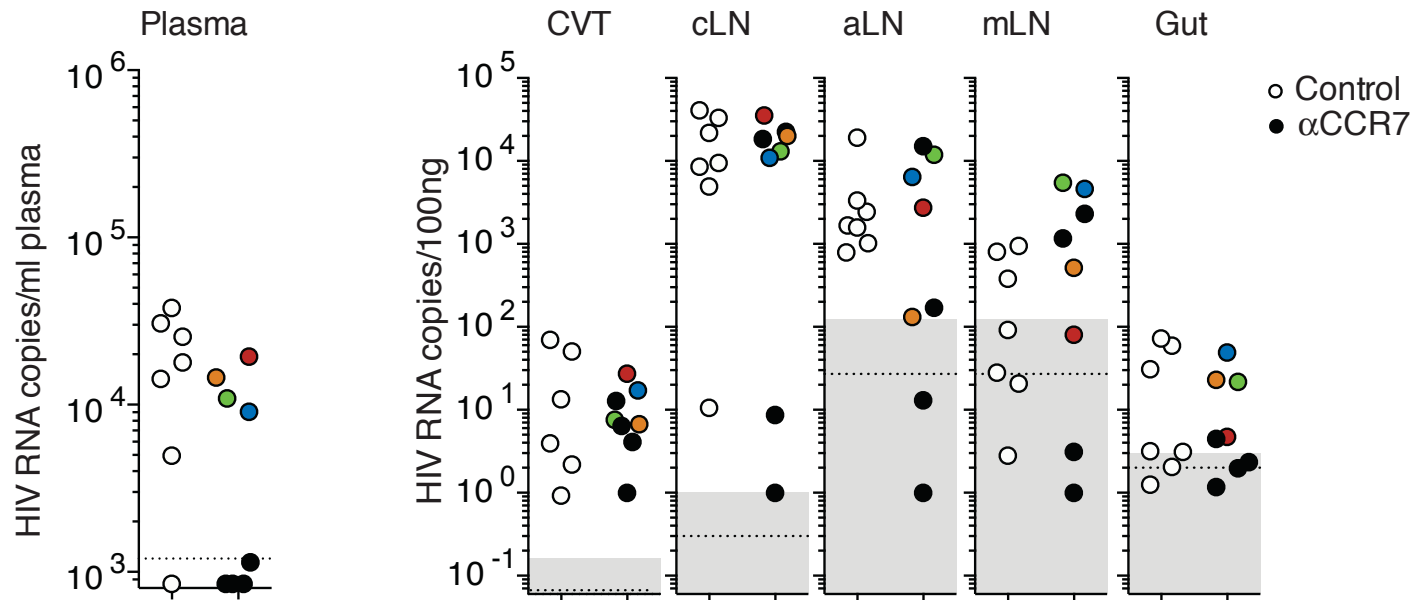
Would the low level of endogenous hIgG impact depletion of targeted cells by α CCR7?



Effect of anti-CCR7 mAb (α CCR7) on HIV dissemination

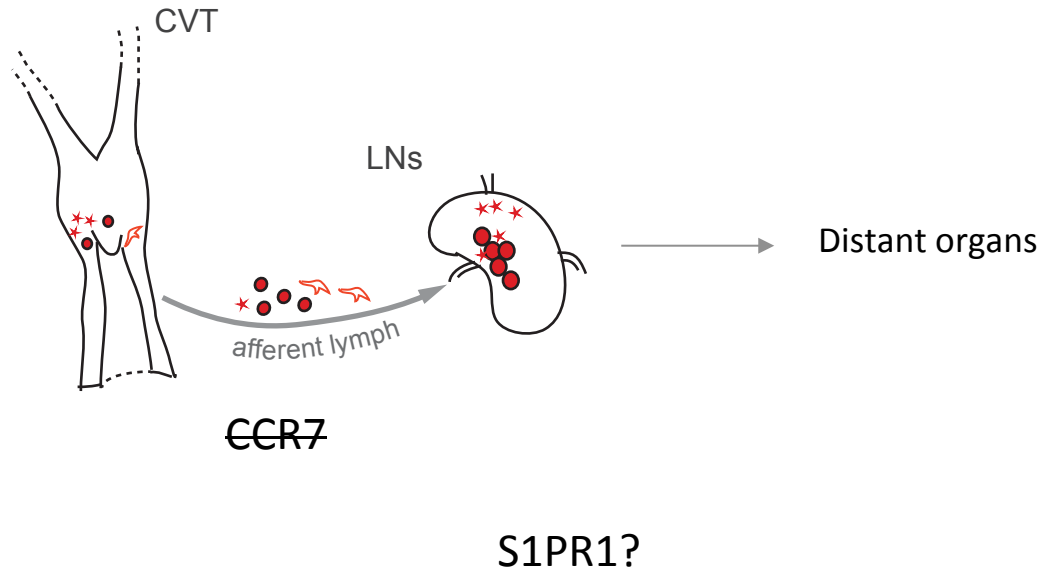


Effect of anti-CCR7 mAb (α CCR7) on HIV dissemination



CCR7 blockade does not inhibit HIV dissemination

Role of leukocyte trafficking in HIV dissemination? – S1PR1



Leukocyte trafficking from tissues to the LN during inflammation

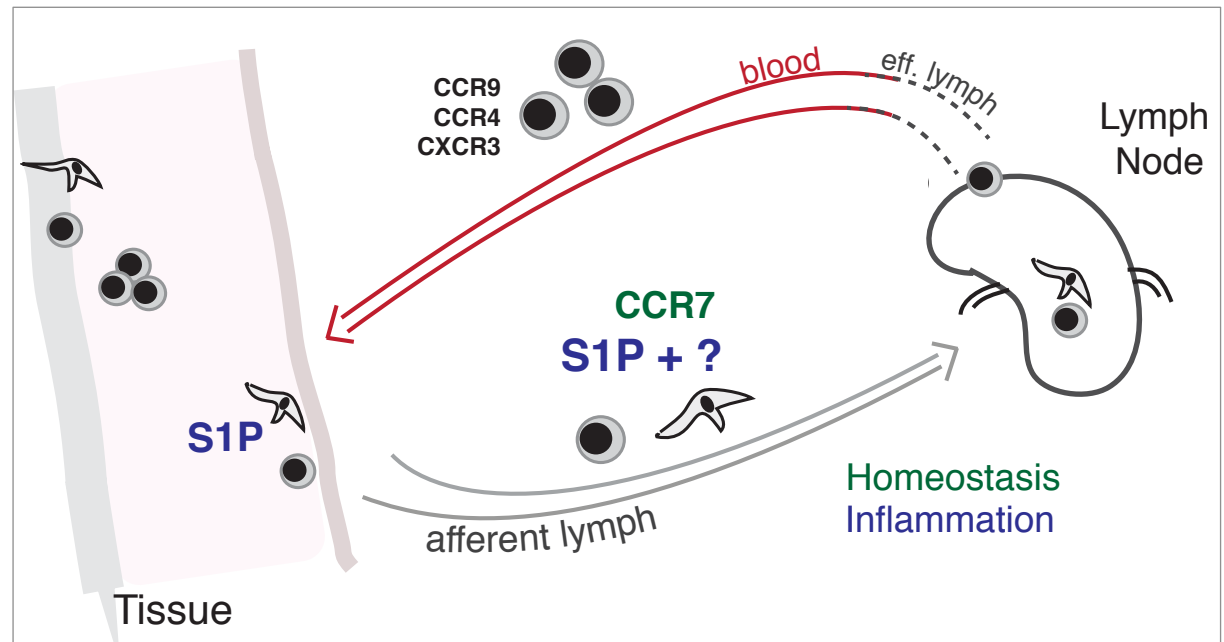
CCR7 blockade partially inhibits T cell egress from tissue.

Sphingosine 1-phosphate receptor 1 (S1PR1) participates in T cell egress from peripheral tissues into afferent lymphatics.

Ledgerwood, Nat Immunol 2008
Brown, J Immunol 2010.

Yersinia pestis-infected DCs trafficking from tissue to secondary lymphoid organs is largely dependent on S1PR1.

St John et al., Immunity 2010



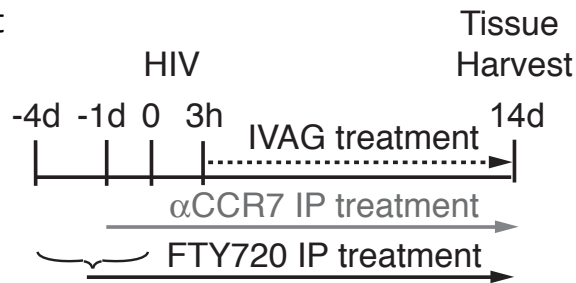
S1PR1 signaling is required for T cells to exit lymph nodes and enter the blood.

Cyster et al. Annu Rev Immunol 2012.

Role of S1PR1 in HIV spread from the CVT to the LN ?

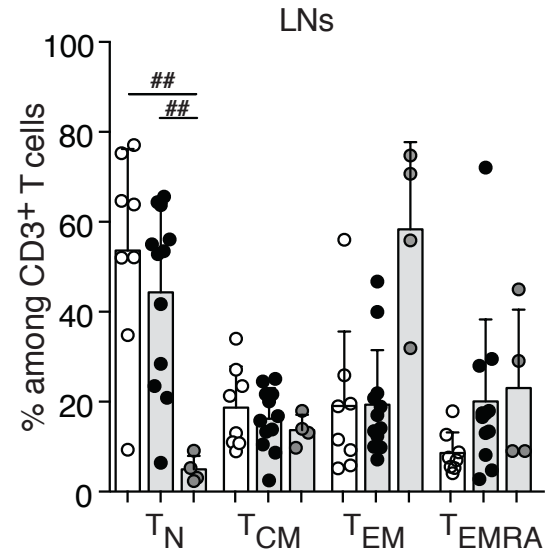
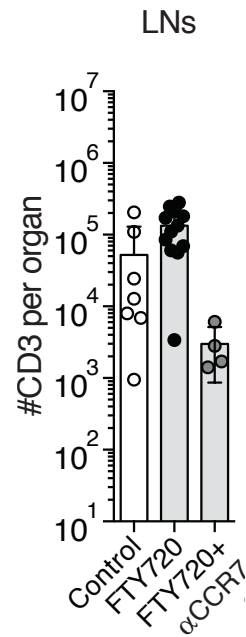
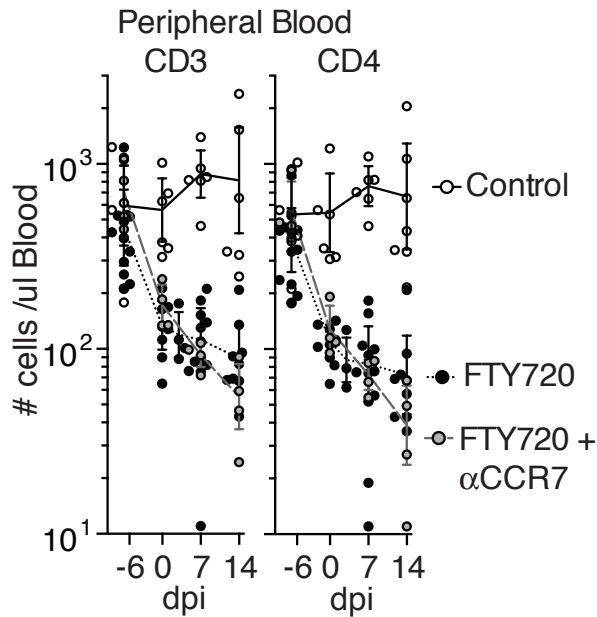
Effect of S1PR1 blockade on HIV dissemination

FTY720: S1PR1 antagonist

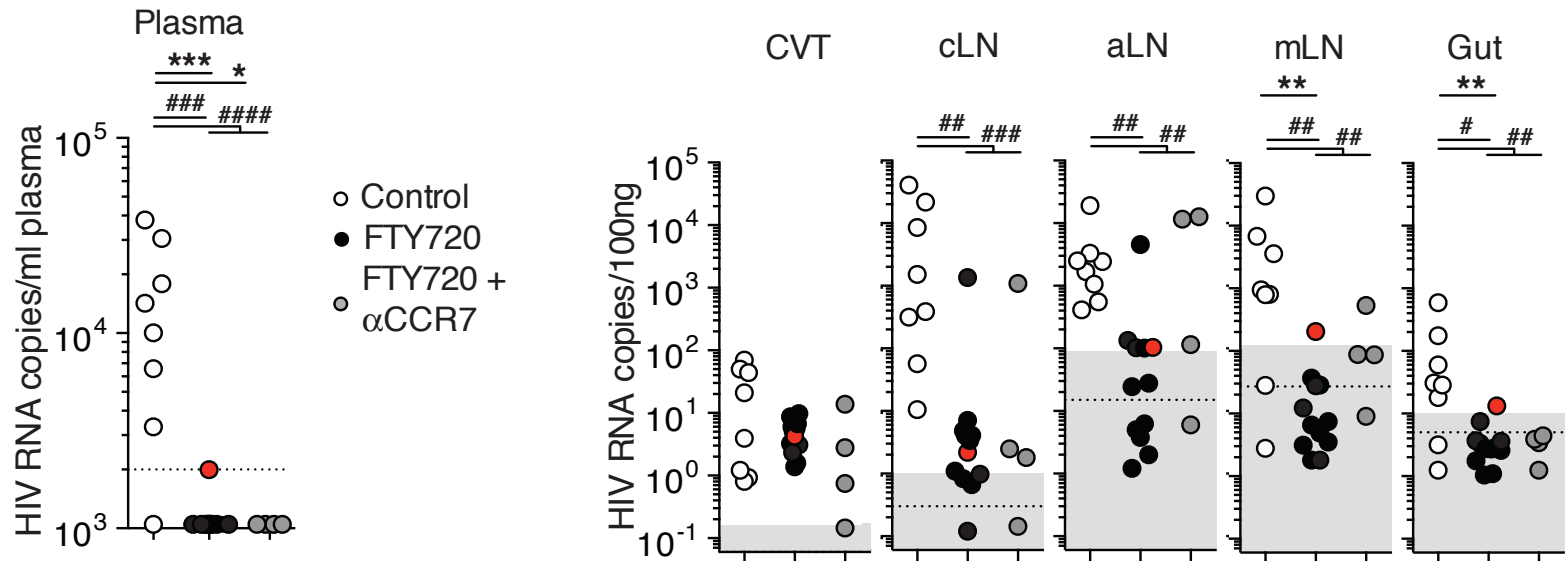


n=7: PBS
 n=12: FTY720 (Fingolimod)
 n=4 : FTY720+ α CCR7

IP: FTY720 every day \pm α CCR7 / 3rd day
 IVAG: FTY720 \pm α CCR7 every day



Effect of S1PR1 blockade on HIV dissemination

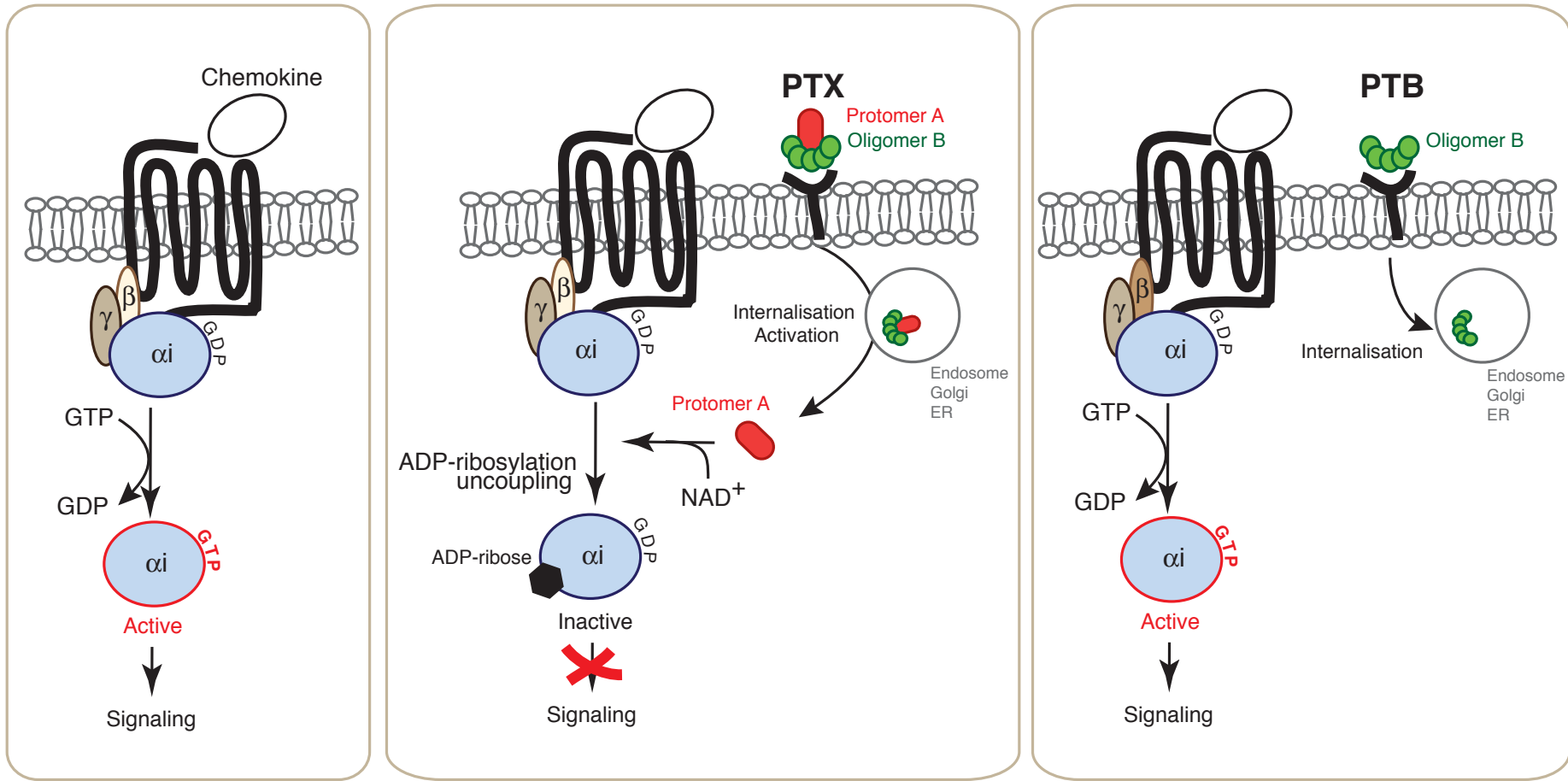


- S1PR1 blockade inhibited HIV spread to the Gut and viremia
- S1PR1 blockade might interfere with viral dissemination to the LNs.

Are other chemoattractant receptors involved in HIV dissemination from CVT?

Pertussis toxin blocks all chemokine induced GPCRs

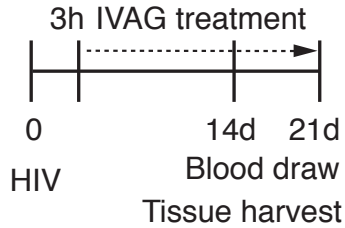
PTX: Protomer A (enz. act.) + **Oligomer B** (mb. Binding)



NAD⁺: Nicotinamide adenine dinucleotide

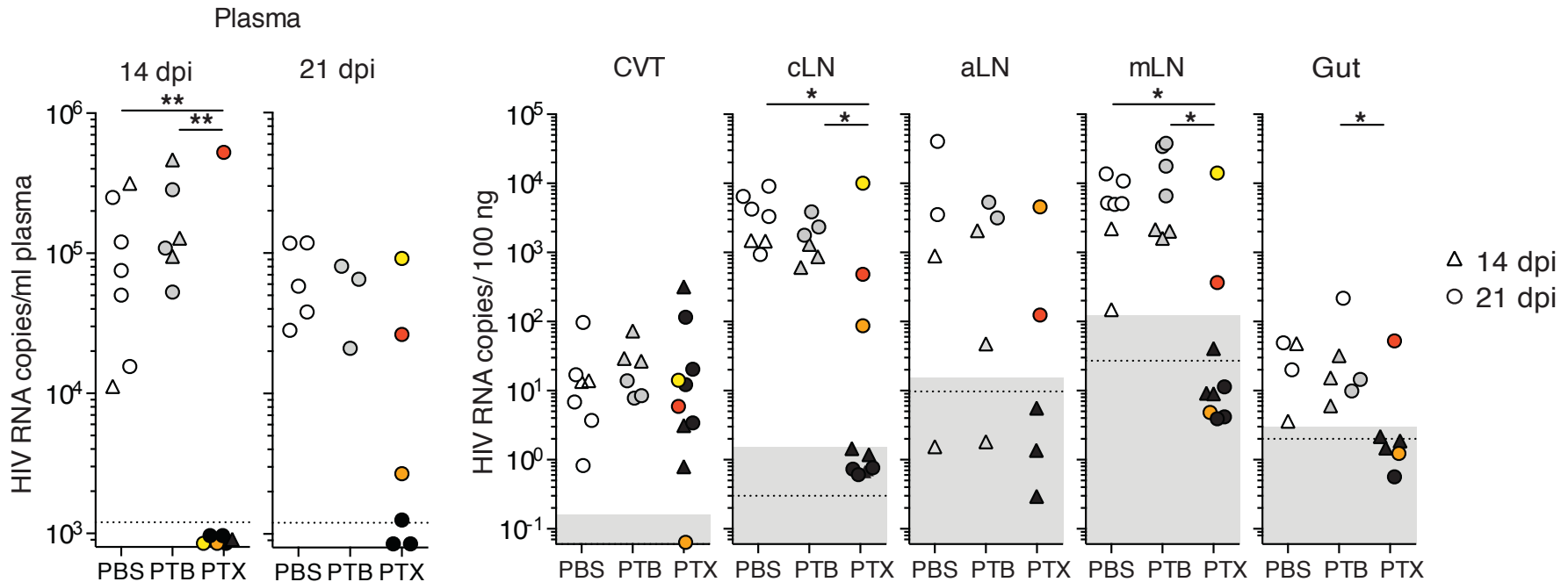
Effect of *Pertussis toxin* (PTX) treatment on HIV dissemination

PTX (A_1B_5): **Protomer A** (enzymatic activity) + **Oligomer B** (membrane binding)

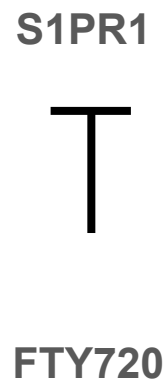
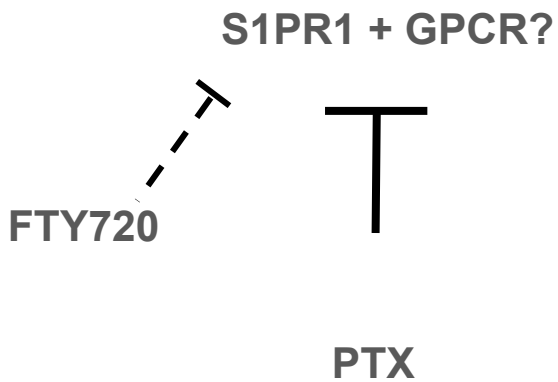
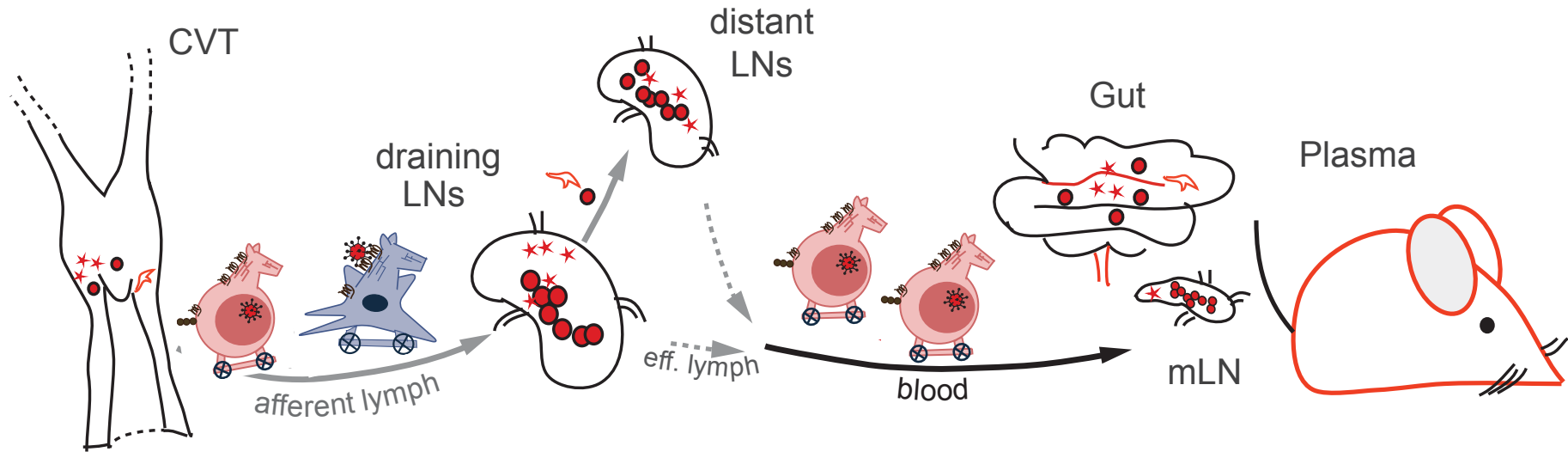


n=7: PBS
 n=9: PTX
 n=6: PTB

PTX: Pertussis toxin, everyday IVAG
PTB: Oligomer B, everyday IVAG



HIV hitchhikes a ride with leukocytes to disseminate



- HIV⁺ CD4 T
- ★ HIV carrying DC
- ★ Free HIV

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