

Small animal models and cell-associated transmission

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Rationale

- Allows infection with HIV rather than surrogates
- Lower cost
 - More robust experimental group sizes
- Abundant rather than scarce and threatened primate species

Small animal models of cell-associated HIV-transmission

- FIV (feline immunodeficiency virus)
- Humanized immunodeficient mice
 - SCID-hu-PBL
 - BLT
 - Rag-hu

FIV

Isolation of a T-lymphotropic virus from domestic cats with an immunodeficiency-like syndrome.

Pedersen NC, Ho EW, Brown ML, Yamamoto JK.
Science. 1987 Feb 13;235(4790):790-3.

FIV similarities to HIV

- Immune deficiency disease, neurological disease, wasting
- Present in the semen (cell free and cell assd.)
- CD4 tropic, CD4 depleting
- High genetic diversity
- Mucosal transmission

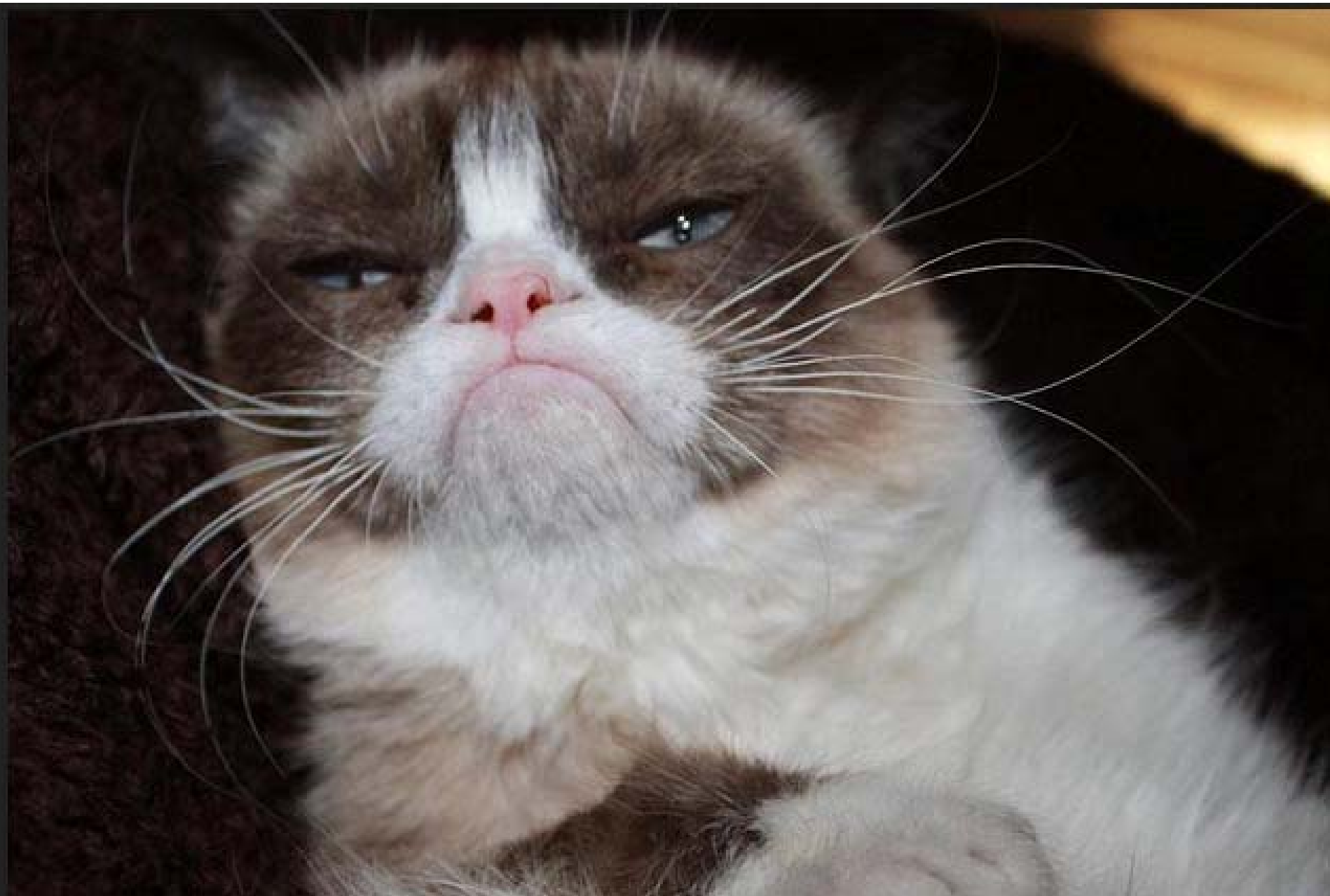
FLV and mucosal transmission

- First lentivirus vaginal rectal, and oral transmission models (presented data in 1988)
- First test of a topical microbicide to prevent transmission
- Description
 - fresh cell inoculum (PBMC cultured in IL-2)
 - Subsequent models used and cryopreserved cell stock or T-cell line
 - Subsequent models showed cell-free inoculum also transmits
 - 10^6 cells
 - Threshold $\sim 10^4$ for detectable infection
 - 100-1000 cells can induce a latent infection

Limitations of the FIV model

- Cost lower than primates but still substantial
- Relatively limited immunological knowledge and reagents
- Animal rights objections as strong or stronger than for primates



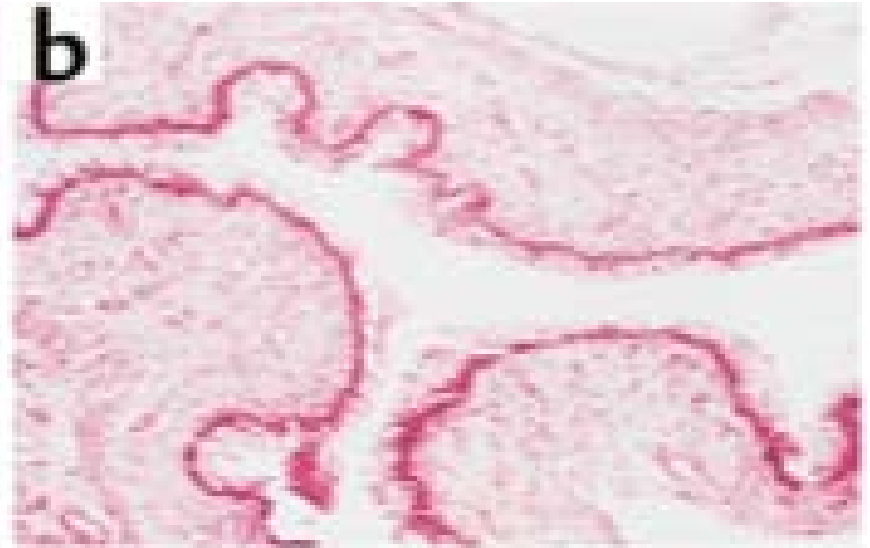


Immunodeficient mouse models



Estrus mouse

DP-treated mouse



Human Vagina

Human Cervix

HIV inoculum	Number of mice from which HIV-1 was cultured/ Number of mice exposed to HIV-1
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HIV-1_{Ba-L}-infected HuPBMCs

1.00 × 10 ⁶ cells	56/66 ^A
0.25 × 10 ⁶ cells	4/5 ^A
0.10 × 10 ⁶ cells	4/9
0.05 × 10 ⁶ cells	1/5
0.01 × 10 ⁶ cells	0/9

HIV-1_{Ba-L} cell-free virus

1.0 × 10 ^{6.5} TCID ₅₀	0/7
1.0 × 10 ⁶ TCID ₅₀	0/5
1.0 × 10 ⁵ TCID ₅₀	0/5

CCR5-utilizing strains of HIV-1 are transmitted vaginally in HuPBL-SCID mice^A

HIV inoculum	Number of mice from which HIV-1 was cultured/ Number of mice exposed to HIV-1
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HIV-1_{Ba-L}(R5)-infected HuPBMCs

1.00 × 10 ⁶ cells	5/5 ^B
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0.25 × 10 ⁶ cells	<u>4/5^B</u>
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0.05 × 10 ⁶ cells	1/5
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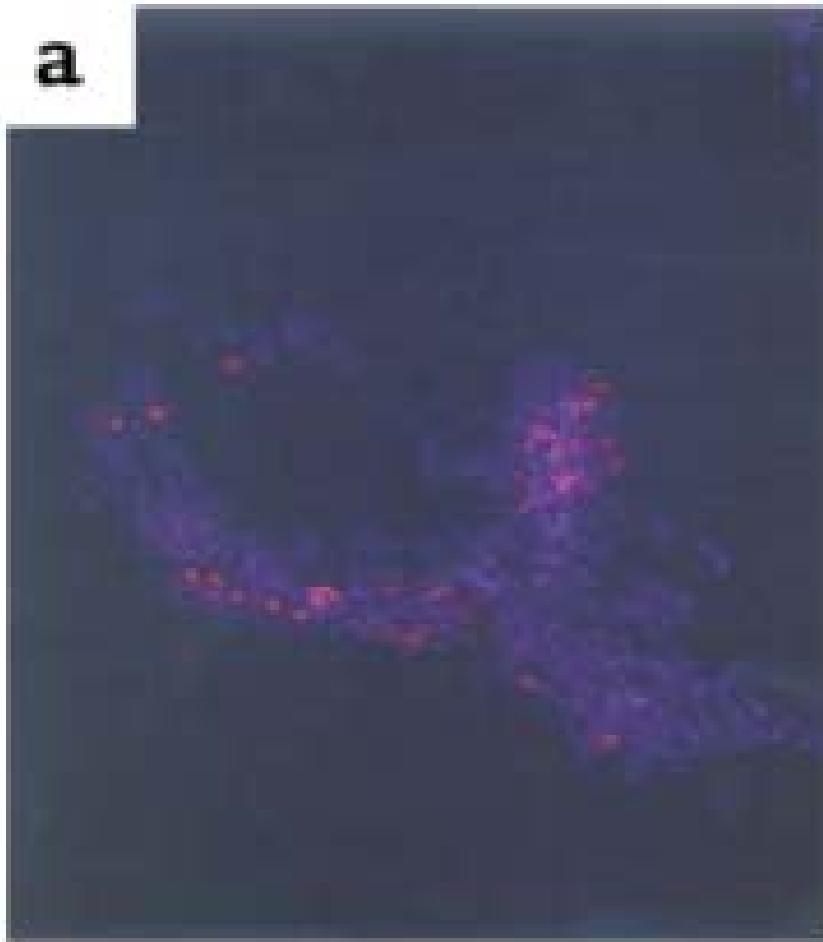
HIV-1_{MN}(X4)-infected HuPBMCs

1.00 × 10 ⁶ cells	1/5
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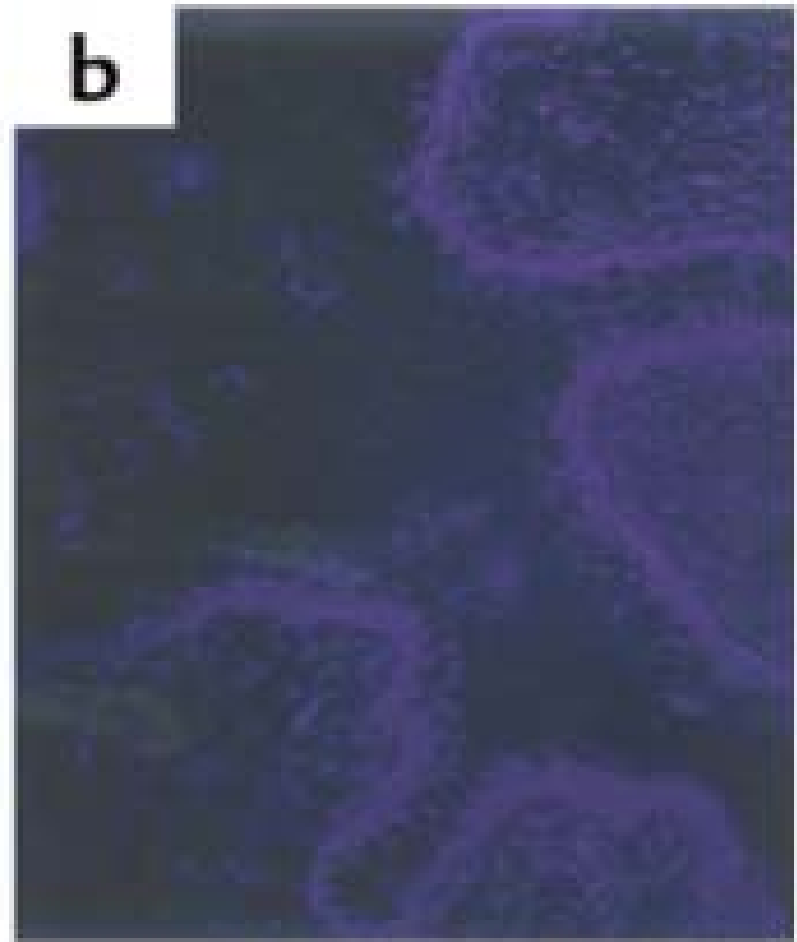
0.25 × 10 ⁶ cells	0/5
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0.05 × 10 ⁶ cells	0/5
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FISH detection of human cells



Peritoneum



Vagina

BLT Mouse Model

- Humanize immunodeficient mice:
 - NOD/SCID mice
- Transplant with human immune cells

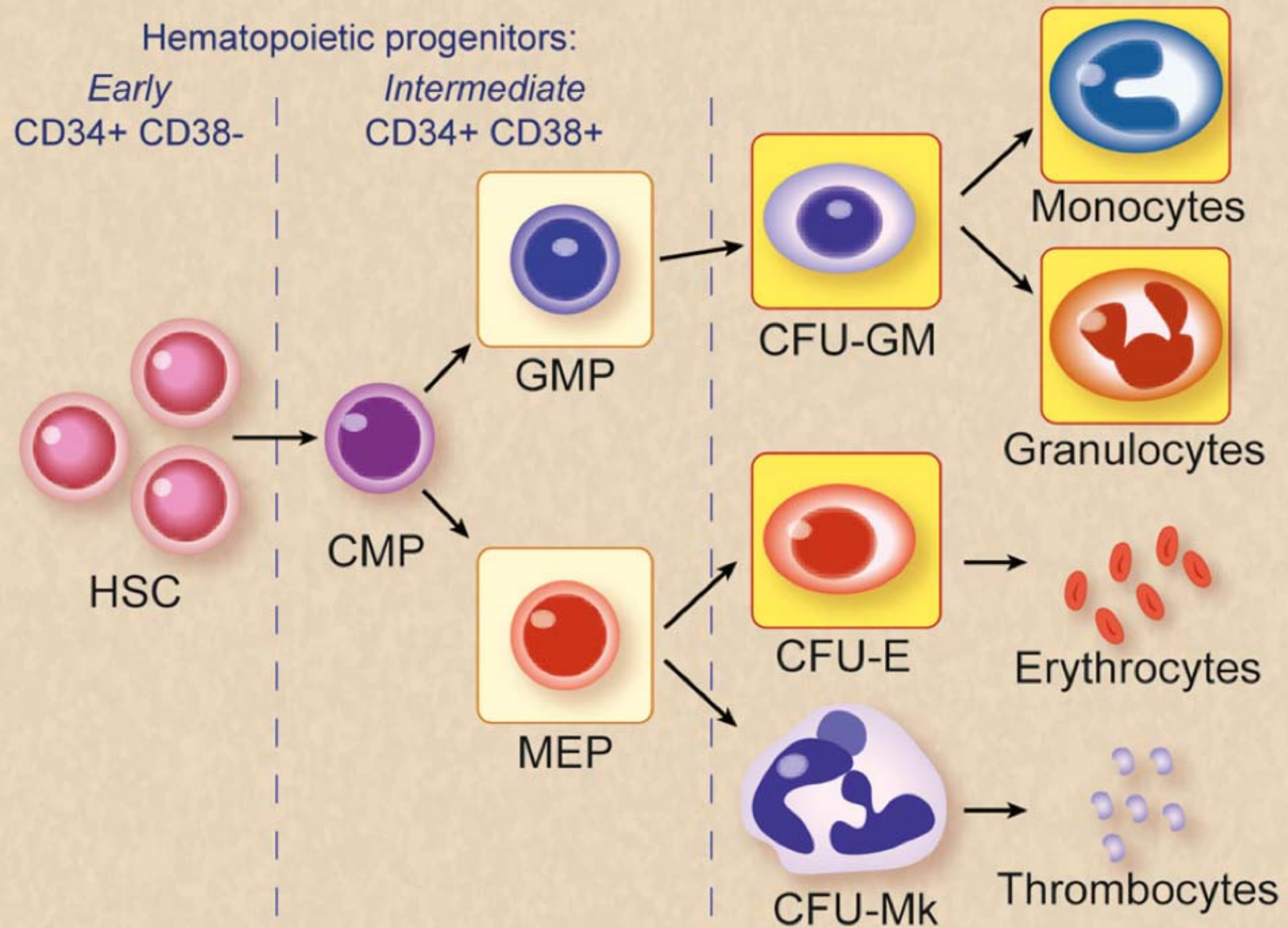
Hematopoietic progenitors:

Early

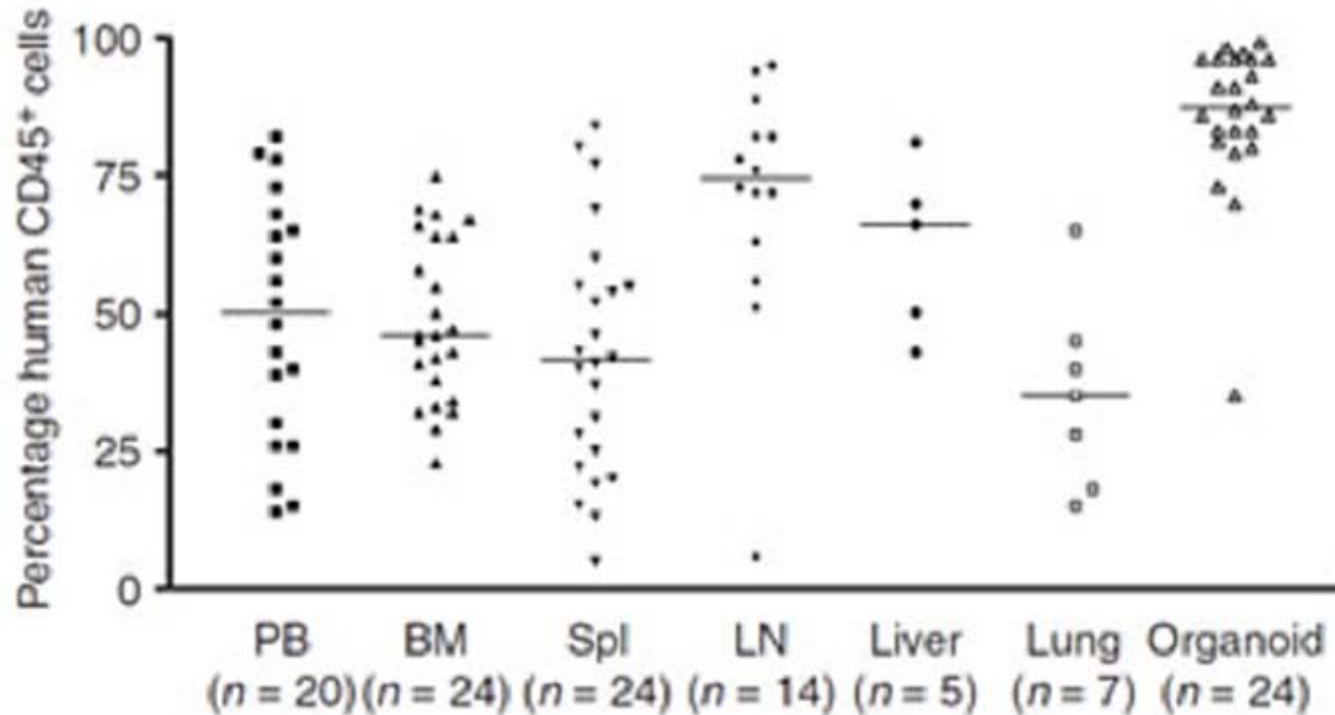
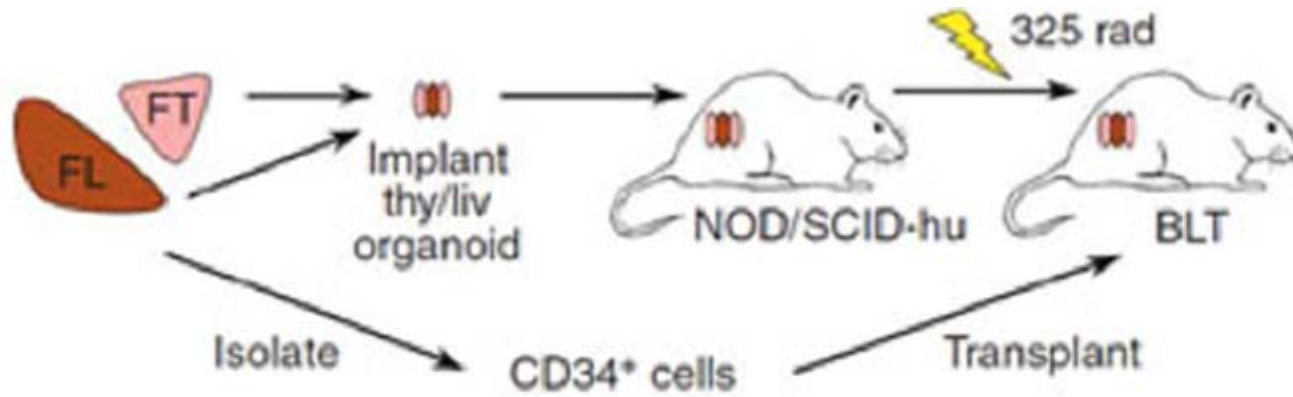
CD34+ CD38-

Intermediate

CD34+ CD38+



BLT mouse model



Human cell engraftment in BLT

- Cell types
 - CD4, Mono/mac, Dendritic, NK
- Locations
 - Lymph nodes, thymus, marrow
 - Intestines, female reproductive tract

Cell-associated transmission in BLT

- Cell free HIV-1, readily transmits both vaginally and rectally
- Recent data from Garcia et al with infected cells
 - Cell-associated transmitted vaginally in BLT model
 - Topical tenofovir ineffective
 - Systemic tenofovir and emtricitabine only marginally effective
 - Topical maraviroc and VRC03 were effective

Rag-hu HIV model (Akkina et al)

- Mice: BALB/c Rag2^{null/null} gamma chain^{null/null}
- Inject $\sim 10^6$ fetal human liver CD34+ cells into liver (radiation pretreatment, but no surgery required)
- Screen for engraftment at 10-12 wk
 - Select mice with >60% engraftment
- Cell-free virus: 3000 TCID₅₀ HIV-1 BaL typically infects 100% of controls
- Cell associated inoculum of HIV-2 was highly infectious (Akkima, unpublished)

Summary

- Cell free transmission of HIV-1 and HIV-2 occurs in diverse small animal models
- SCID-hu model (refractory to cell-free virus) shows infected cells can travel to distant sites
 - Non-accessible to topicals?
- Mouse models have advantages of higher efficiency and statistical rigor, and experiments with HIV rather than SIV or SHIV
- Primates likely more closely mimic immune and mucosal environments

