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Humanized Mice for Studying HIV Persistence in Long-Lived Tissue-Resident Macrophages

Amélie Cattin[1,2], Tram NQ Pham[3], Natalia F. Rosario[2], Laurence Raymond-Marchand[2], Olga Volodina[3], Frédéric Dallaire[3], Jonathan Dias[1,2], Jean-Victor Guimond[4], Natacha Patey[4], Elie Haddad[4], Éric A. Cohen[1,3] and Petronela Ancuta[1,2].

[1]Département de microbiologie, infectiologie et immunologie, Faculté de médecine, Université de Montréal, Montréal, Québec, Canada
[2]Centre de recherche du CHUM, Montréal, Québec, Canada
[3]Institut de recherches cliniques de Montréal, Montréal, Québec, Canada
[4]CHU Sainte Justine, Montréal, Québec, Canada

Conflict of Interest Disclosure
I have no conflicts of interest

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Université de Montréal

CRCHUM CENTRE DE RECHERCHE

amelie.cattin@umontreal.ca

BACKGROUND

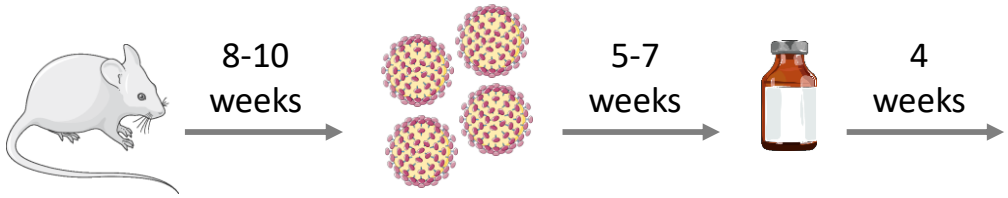
The contribution of myeloid cells to HIV reservoir persistence during antiretroviral therapy (ART) remains controversial. Recent advances revealed the existence of two pools of tissue resident-macrophages (TRM):

- **long-lived (LL-TRM):**
  - -self-renewal capacity
  - -derived from embryonic stem cells of the yolk sac and the fetal liver
- **short-lived (SL-TRM):**
  - -derived from bone-marrow monocytes

Although the presence of LL-TRM in the brain, liver, lungs and dermis is well-established, recent studies demonstrated the existence of LL-TRM in multiple other tissues including blood vessels and heart. In contrast, gut-associated lymphoid tissues are mainly infiltrated by monocyte-derived SL-TRM.

Our previous studies demonstrated that **blood monocytes and colon SL-TRM rarely carry HIV-DNA reservoirs in ART-treated people living with HIV**. Our capacity to investigate HIV persistence in myeloid cells is limited by difficulties in accessing deep tissues from PLWH. Humanized mice (hu-mice) represent appropriate models for HIV reservoir studies.

EXPERIMENTAL APPROACH



Bone marrow/liver/thymus (BLT) hu-mice
NOD-scid IL2Rγnull background

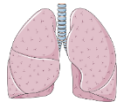
HIV challenge
200,000 $TCID_{50}$ NL4.3-ADA-GFP via intraperitoneal injection or vaginal inoculation

ART
Emtricitabine (FTC)
Tenofovir (TDF)
Raltegravir (RAL)

- Phenotyping
- Sorting:
  - CCR2+ SL-TRM
  - CCR2- LL-TRM
  - CD4+ T-cells
- Proviral HIV-DNA PCR

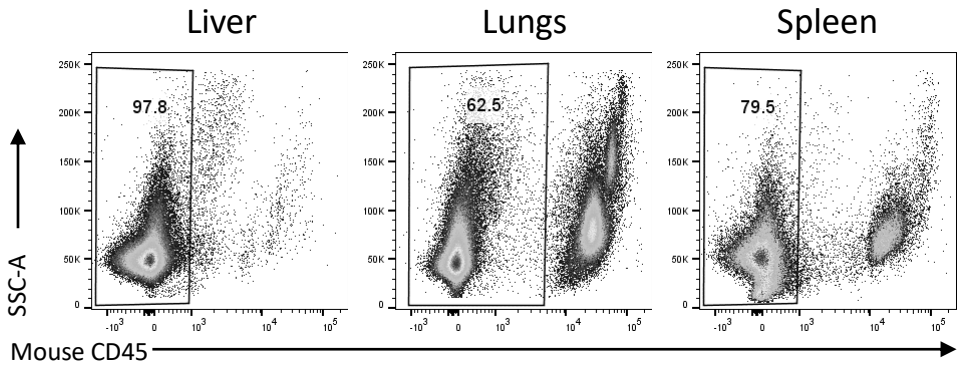

liver

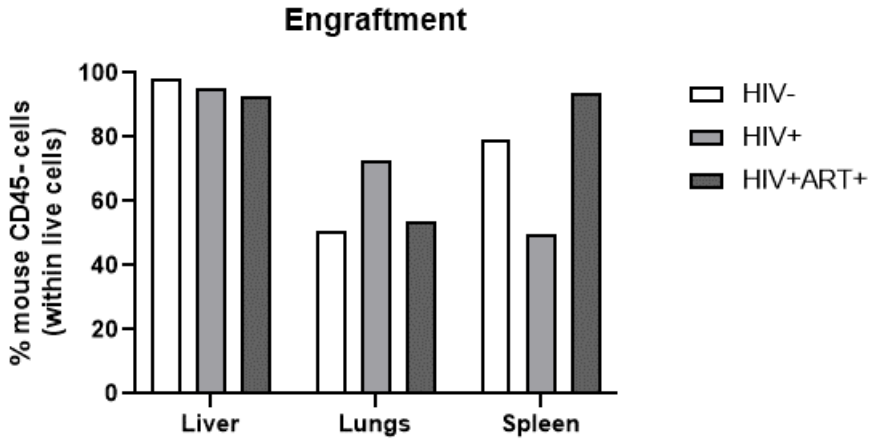

Spleen
In progress


lungs

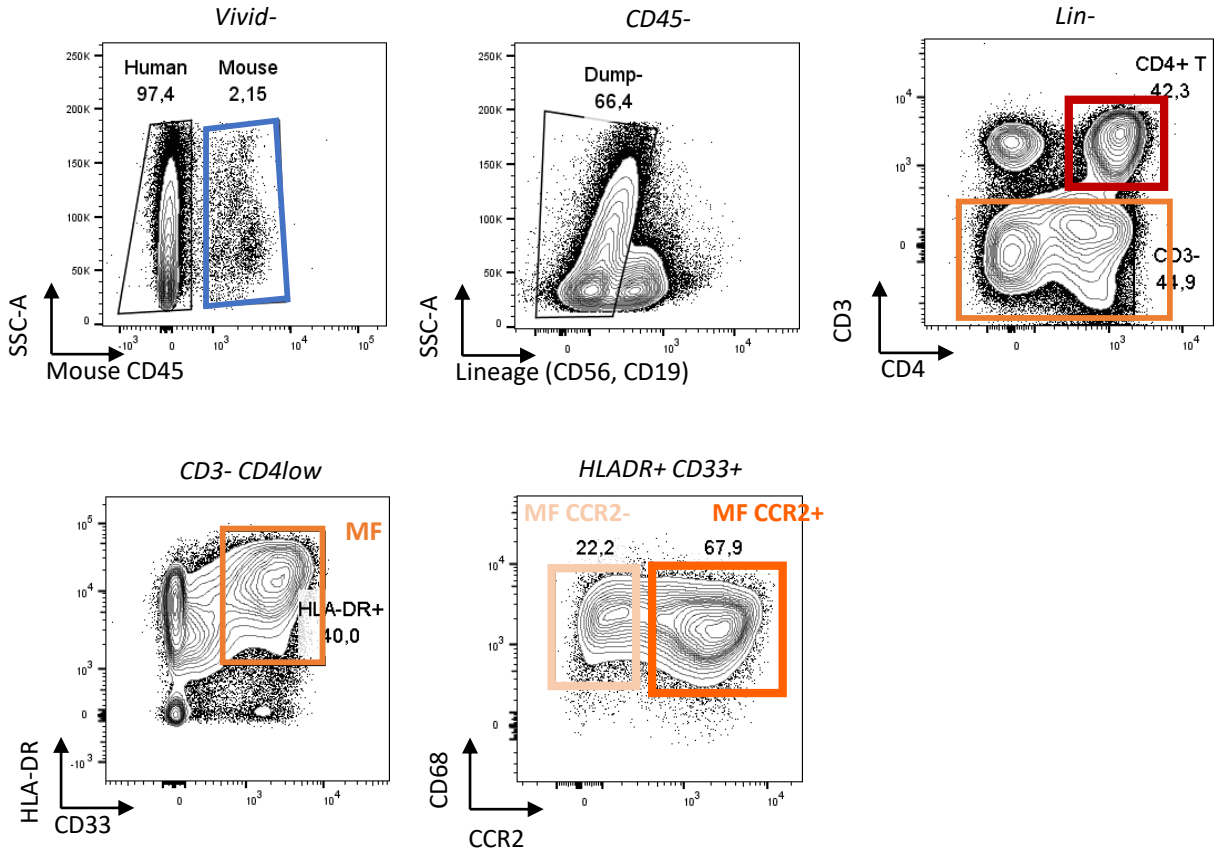
RESULTS

1. Engraftment of human cells in processed hu-BLT samples





2. Gating strategy: representative strategy on liver cells

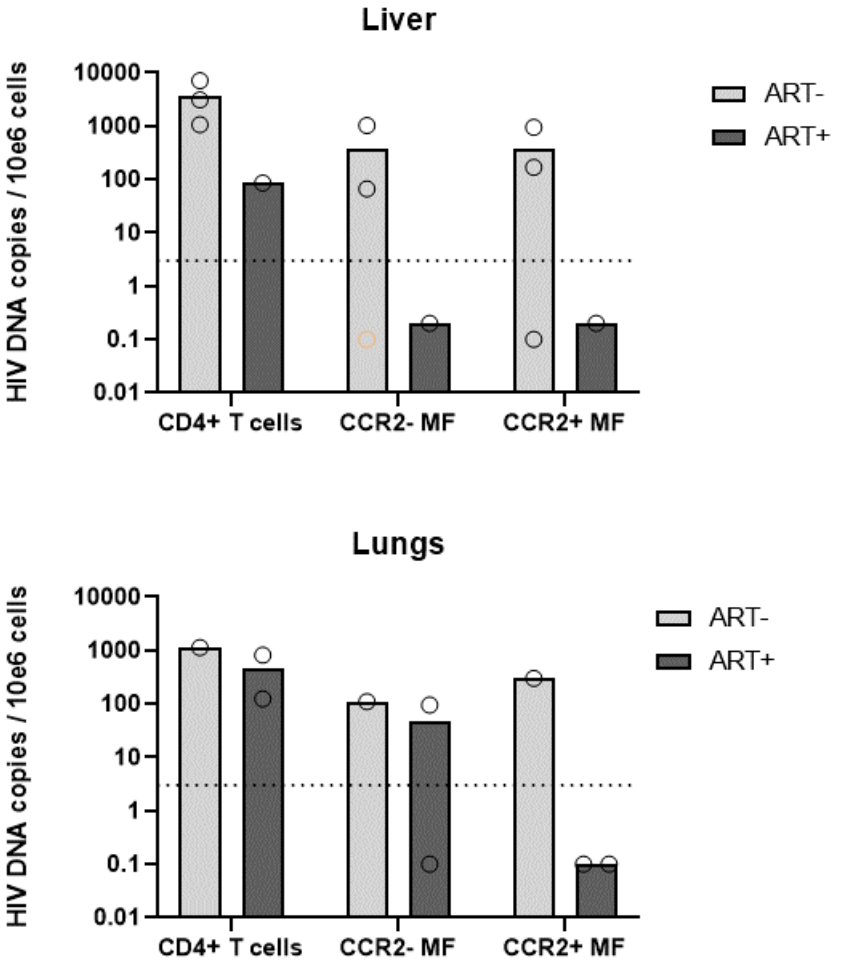


4 populations sorted:

- Mouse CD45+ cells
- CD4+ T cells
- CCR2- MF
- CCR2+ MF

RESULTS

3. Integrated HIV-DNA in liver and lung-infiltrating cells



-------- *Limit of detection*

CONCLUSION

Human myeloid cells were identified as cells expressing a mCD45-CD3-CD4lowCD33+HLADR+CCR2+/CCR2- phenotype

In **HIV+ untreated mice:**

→ integrated HIV-DNA was detected in both CCR2+/CCR2- myeloid cells and CD4+ T-cells from the liver and lungs

In **HIV+ ART-treated mice:**

→ integrated HIV-DNA was detected in CD4+ T-cells from the liver and lungs and in CCR2- myeloid cells from the lungs

→ It was not detected in both CCR2+/CCR2- from the liver and CCR2+ myeloid cells from the lungs

These results provide preliminary evidences on the contribution of LL-TRM *vs* SL-TRM to HIV reservoir persistence during ART in the lungs.