

Role of T follicular helper cells in HIV-1 persistence

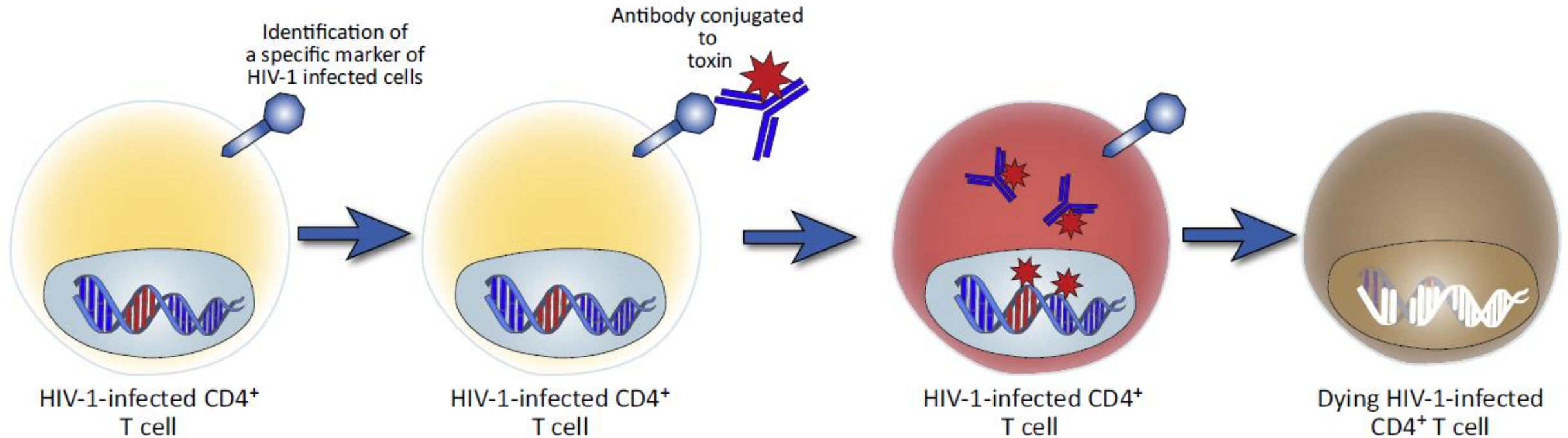
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Identification and characterization of the HIV reservoir

- The therapeutic implications of identifying specific HIV reservoir(s) are tremendous because it may influence the design of interventional therapies targeting the elimination the HIV reservoir

To identify marker(s) to specifically target HIV-1 infected cells using immunotherapy



Identification of HIV reservoirs

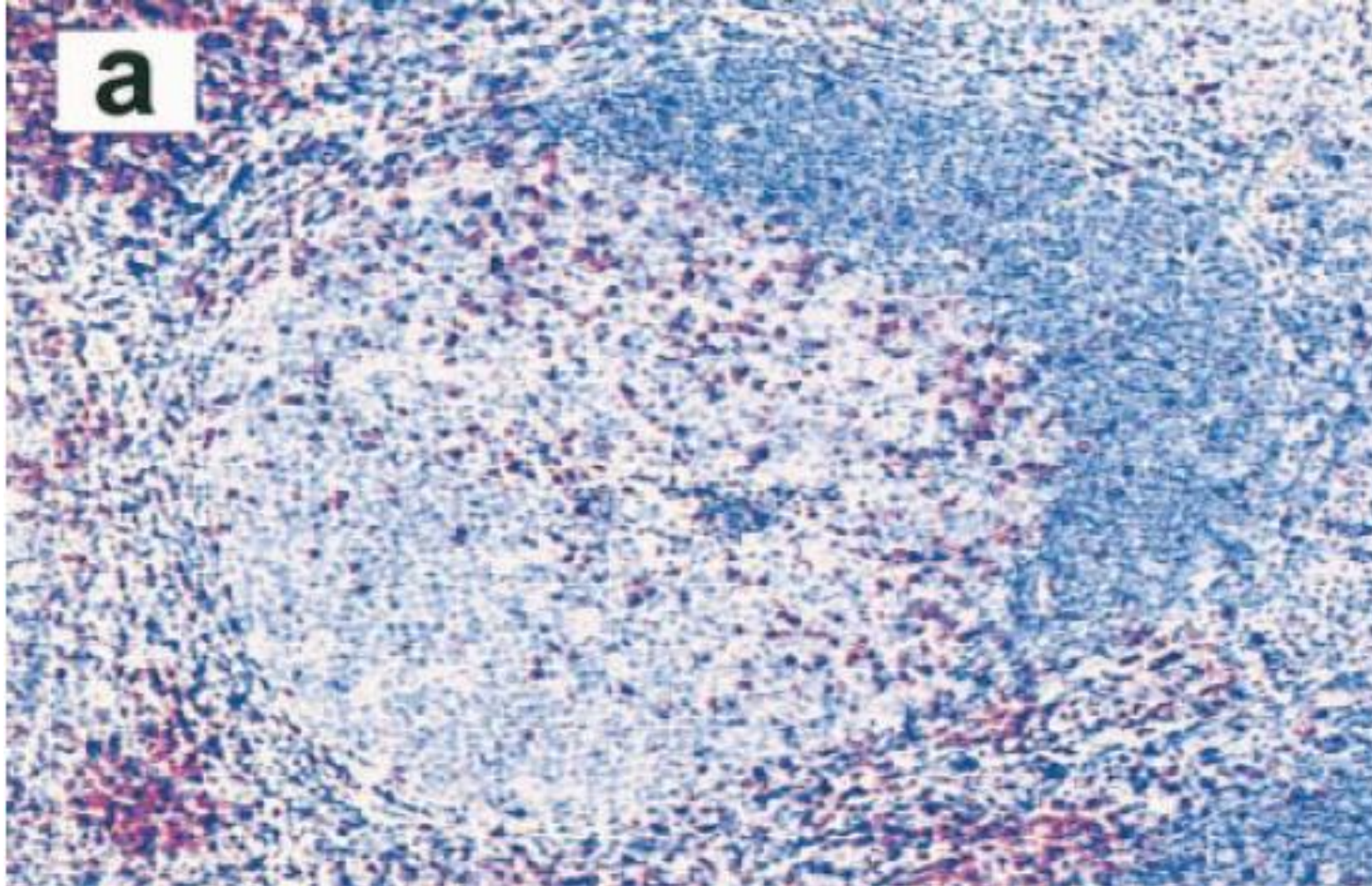
Marker	Reference	Year
Central Memory	Chomont <i>et al.</i> , Nat Med	2009
CD2	Iglesias-Ussel <i>et al.</i> , J Virol	2013
PD-1, Lag-3, TIGIT	Fromentin <i>et al.</i> , Plos Pathog.	2016
CD32	Descours <i>et al.</i> , Nature	2017
CCR6	Gosselin <i>et al.</i> , AIDS	2017
CTLA-4 (SIV)	McGarry <i>et al.</i> , Immunity	2017
CD30	Hogan <i>et al.</i> , Plos Pathog	2018
CXCR3	Banga <i>et al.</i> , Frontiers in Immunol.	2018

Lymphoid organs are the primary anatomical compartments for HIV replication and spreading

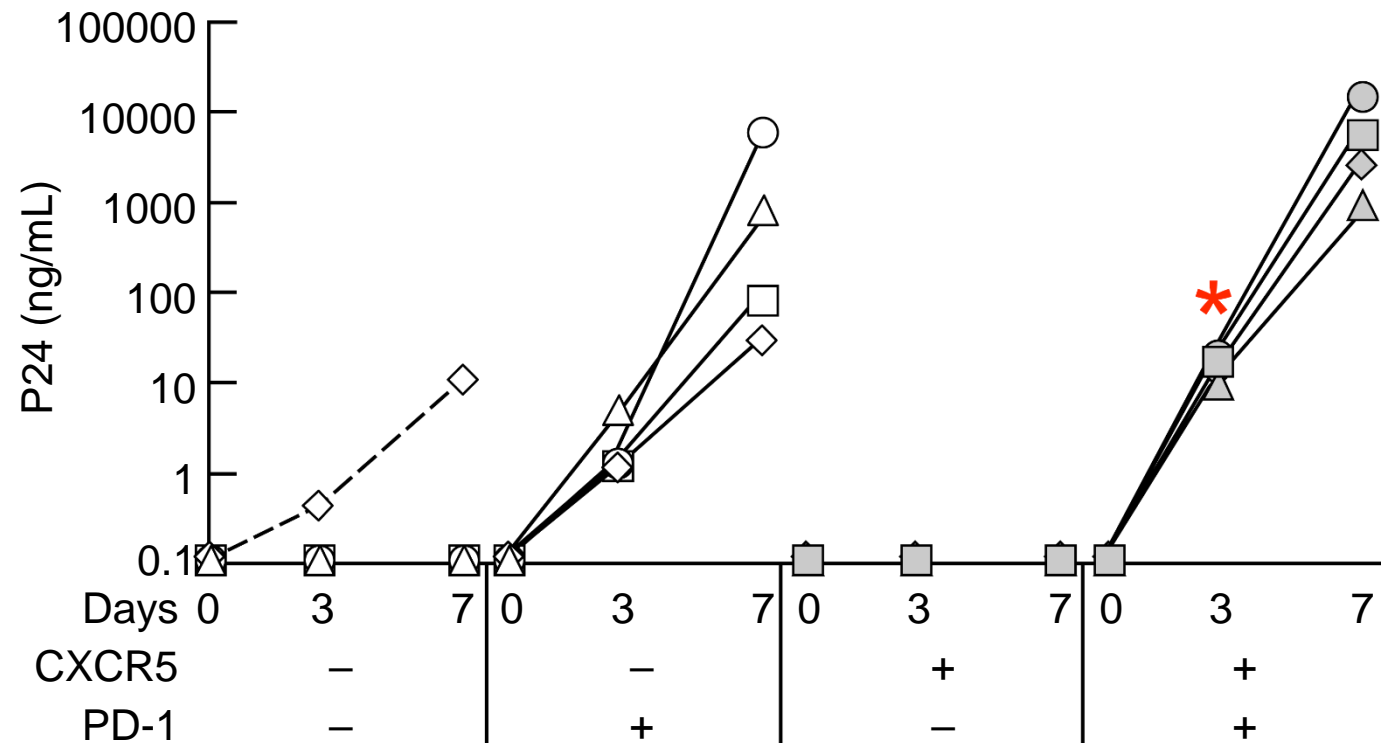
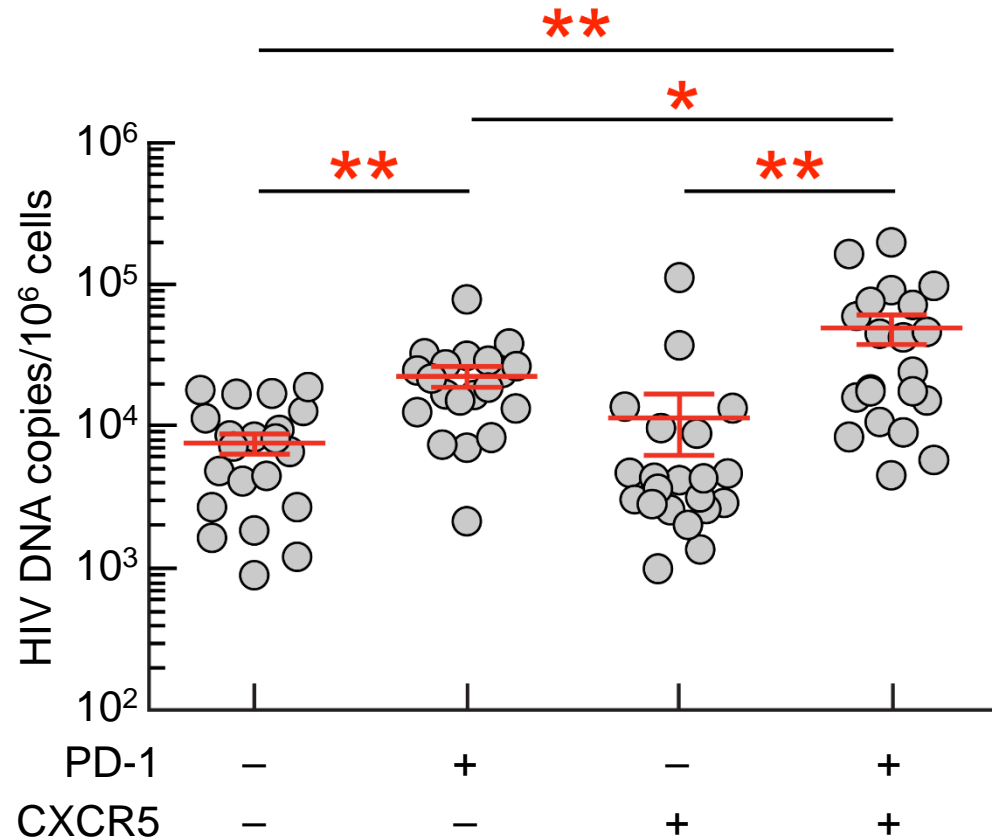


Adapted from Pantaleo *et al.*, Nature 1993

In germinal centers a new CD4 T-cell subset was discovered and named follicular helper T (Tfh) cells

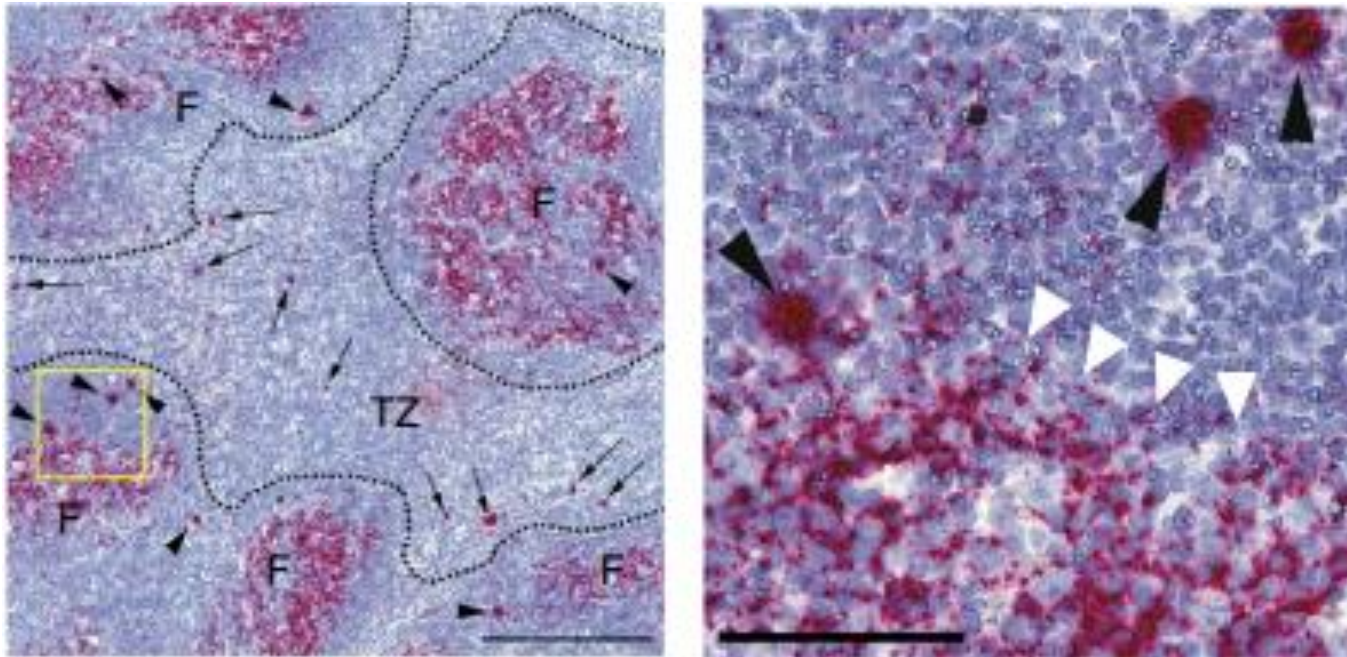


Tfh and CXCR5-PD-1⁺ CD4 T-cell populations support active HIV replication and production in viremic HIV-1 infected individuals

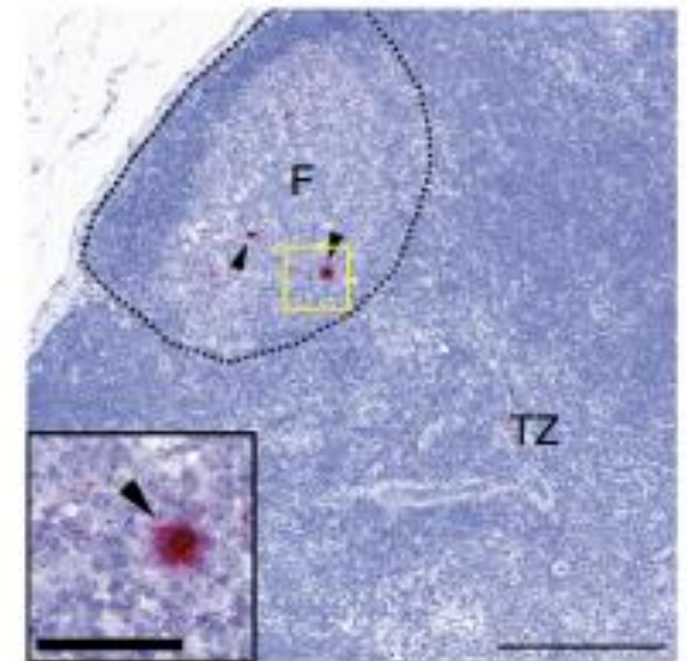


Productive SIV infection in Tfh cells within B cell follicles of elite controller macaques

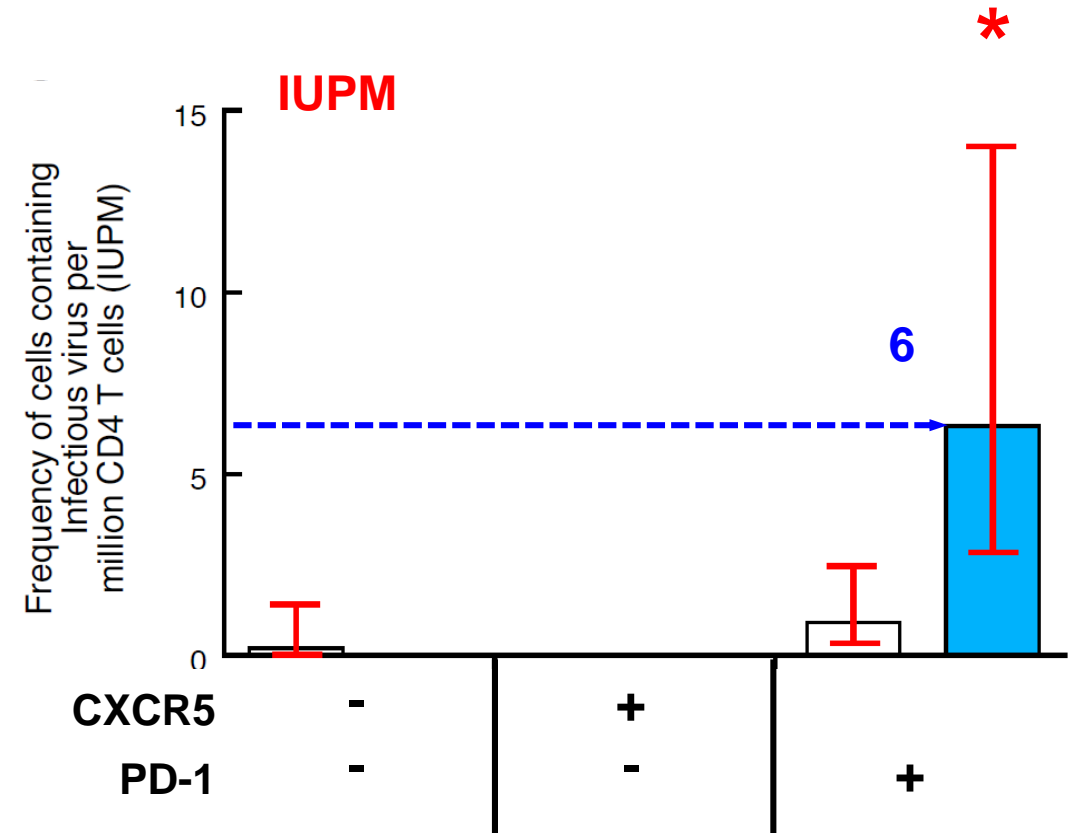
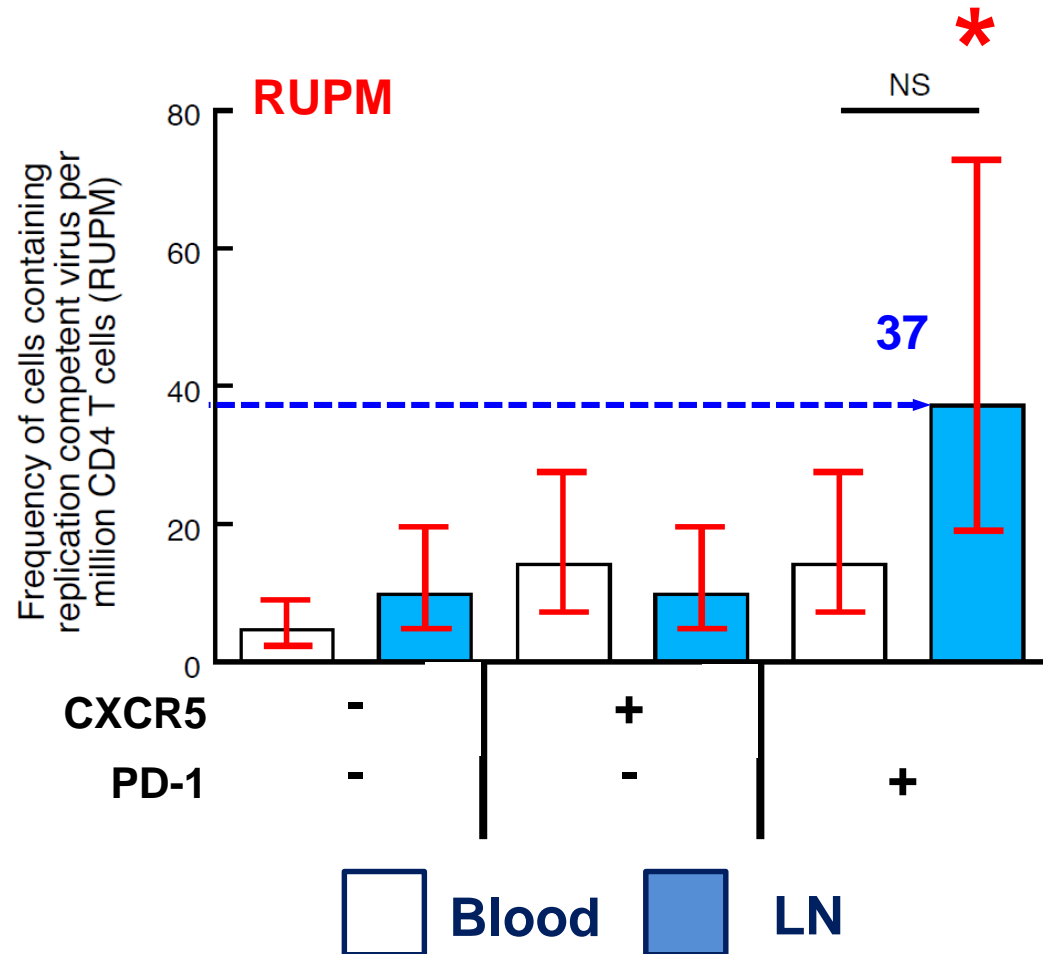
Chronically SIV-infected progressor macaque



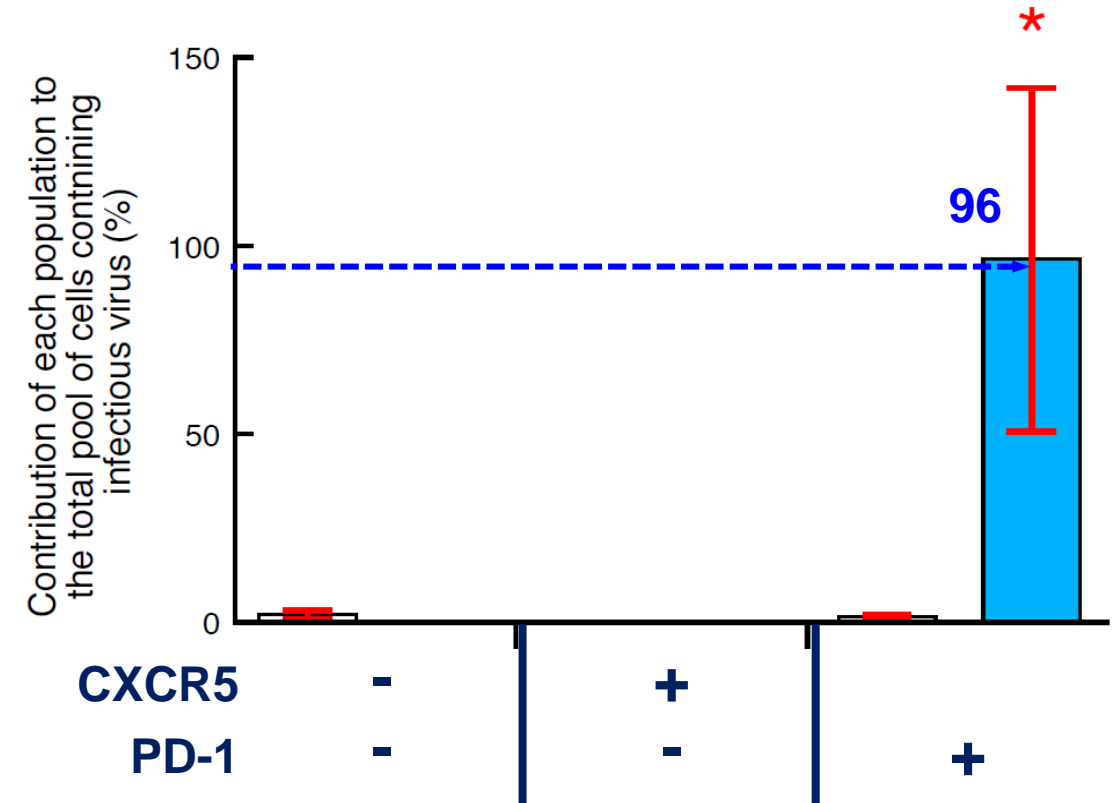
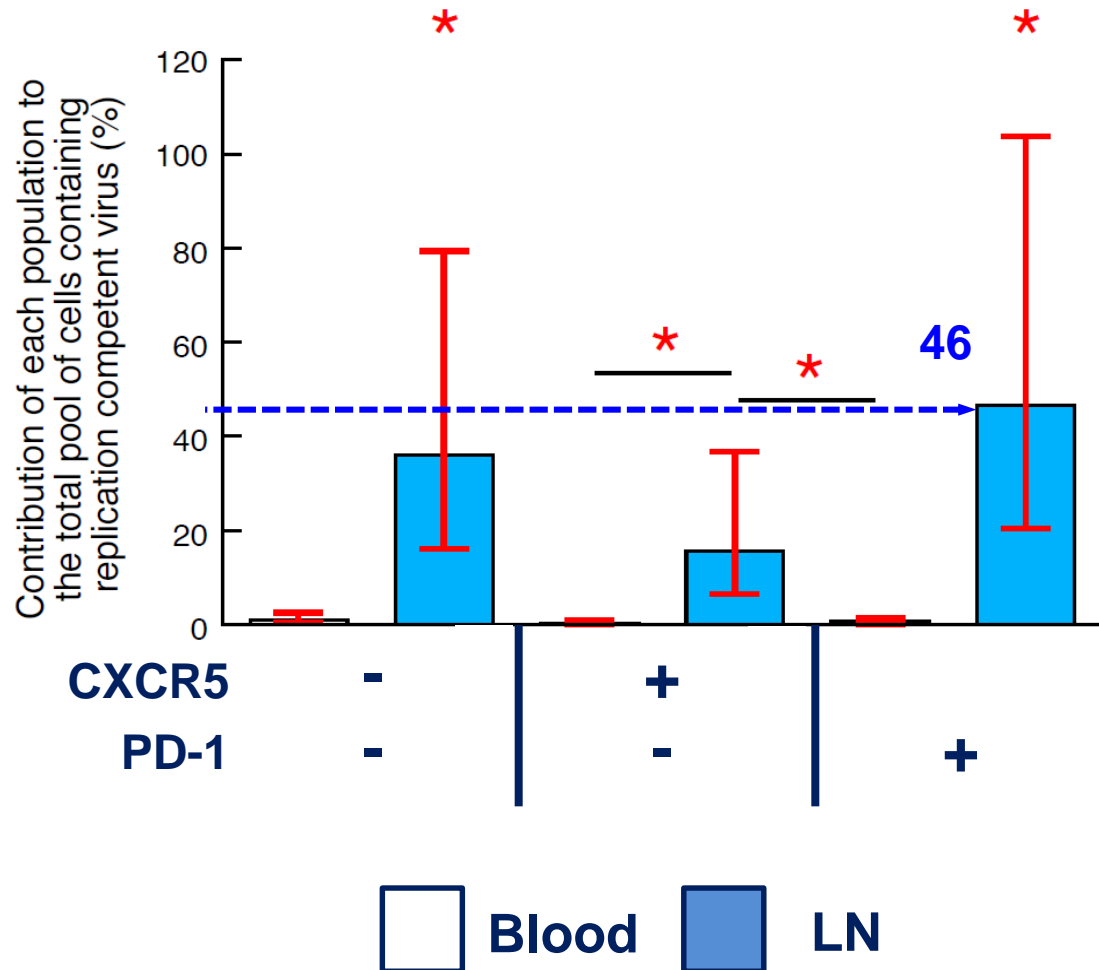
Elite controller macaque



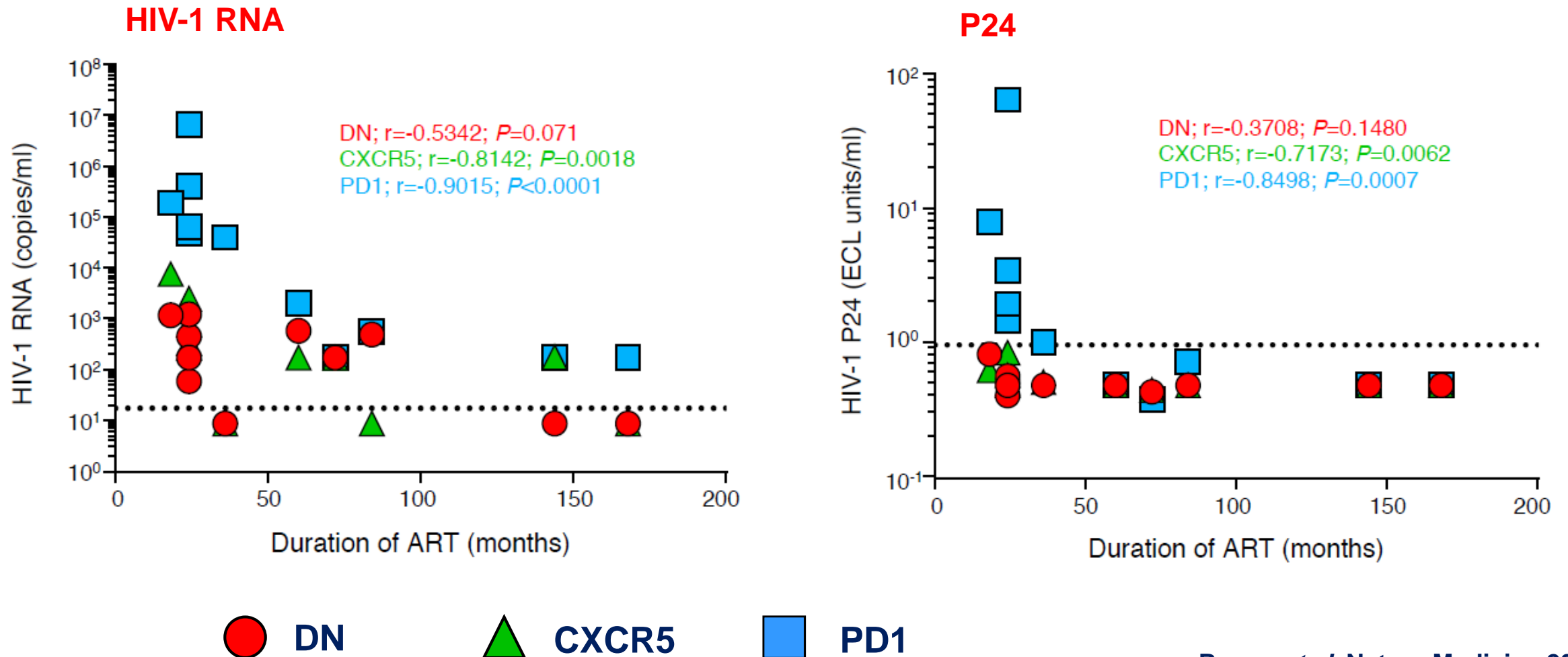
LN PD-1⁺/Tfh cells are enriched in cells containing replication competent virus



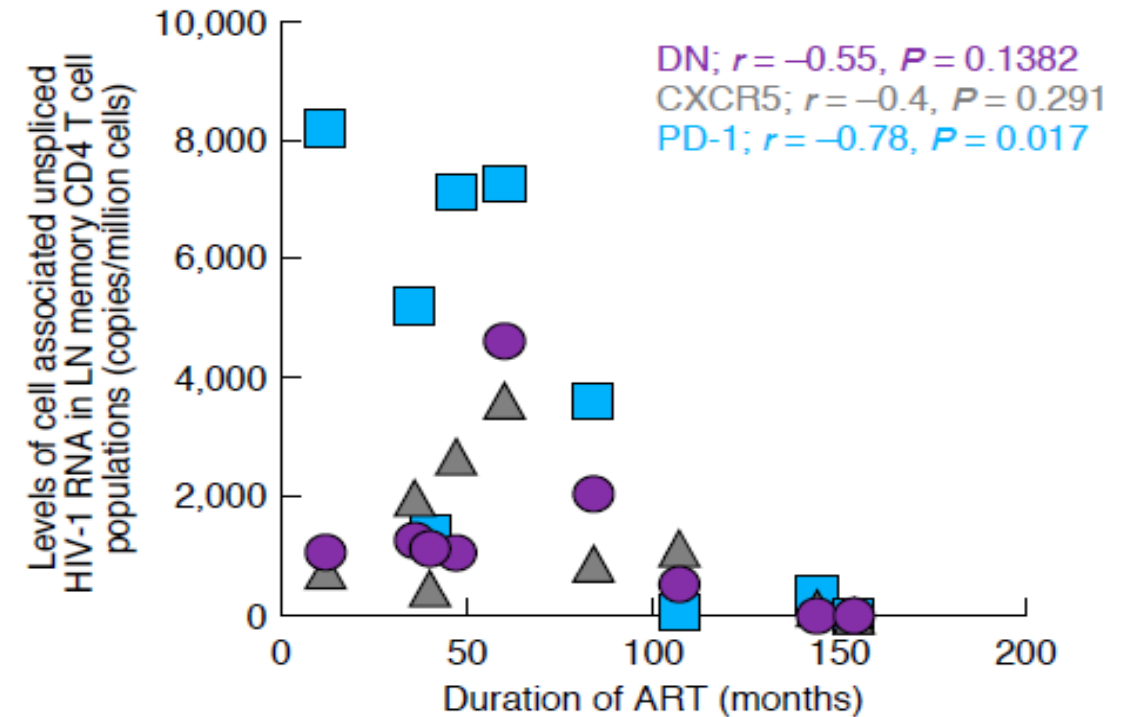
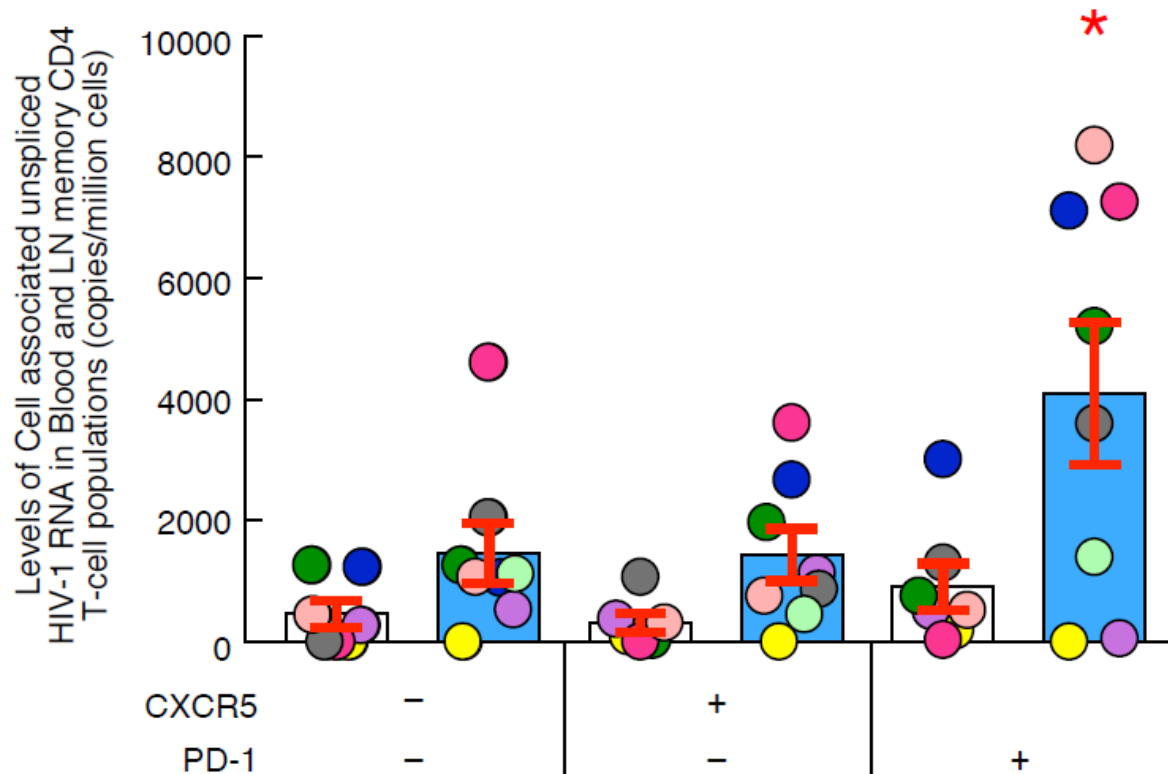
LN PD-1⁺ CD4 T cells contribute the most to the total pool of cells containing replication competent virus



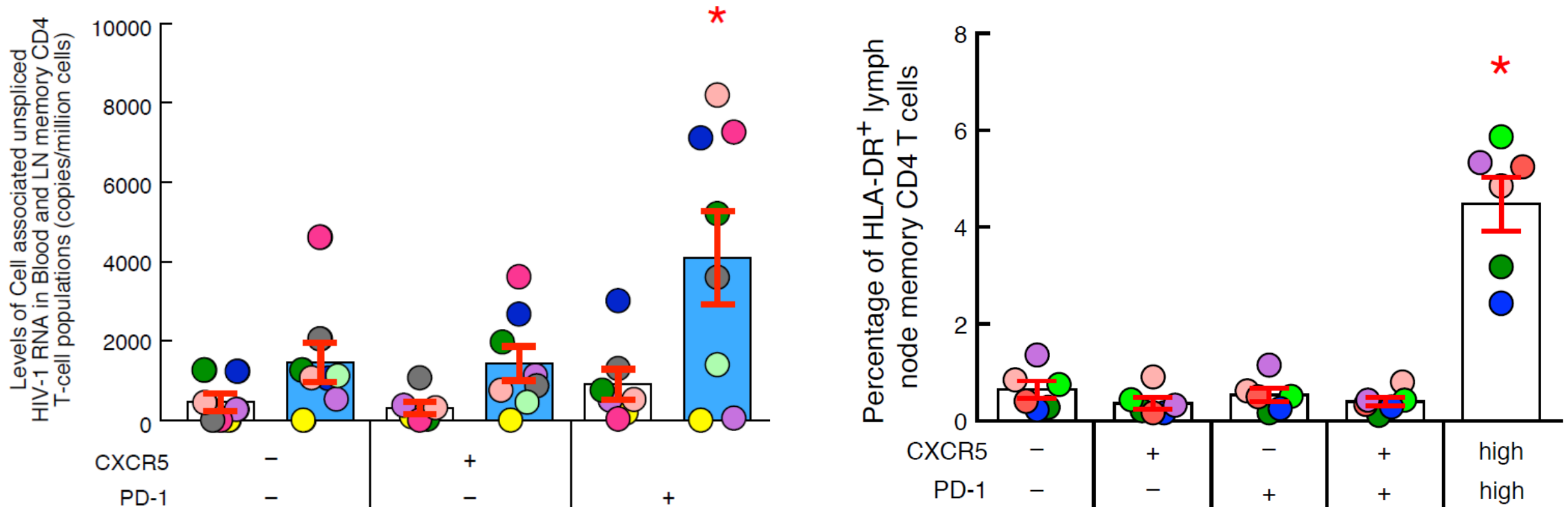
Levels of HIV Replication in LN PD-1⁺/Tfh cells negatively correlate with the duration of treatment of ART treated aviremic subjects



Increased levels of HIV cell associated RNA in LN PD-1⁺/Tfh cells of ART Treated Aviremic Patients

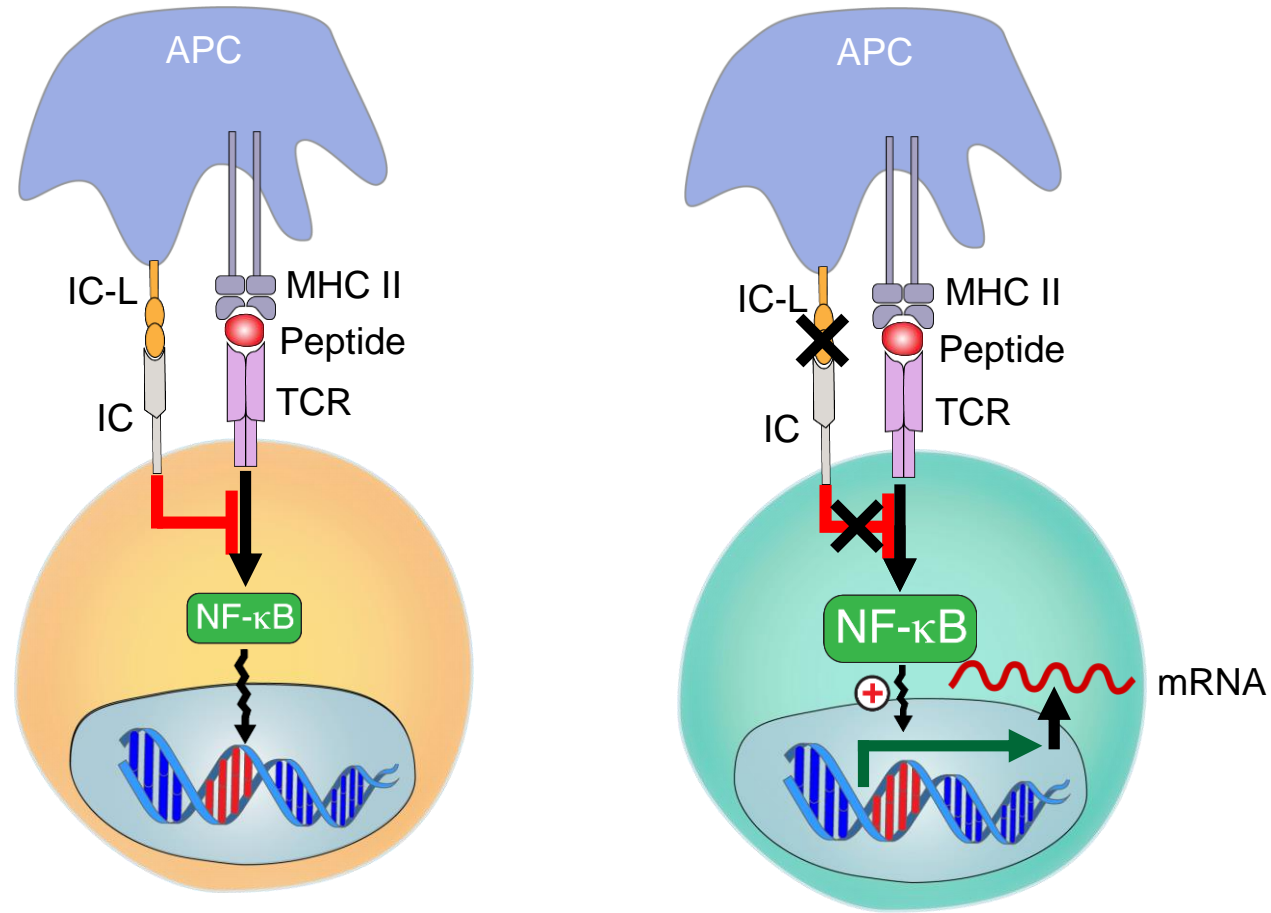


Active transcription occurs preferentially within PD-1⁺/Tfh cells likely because of their greater state of activation



- Indicating that B-cell follicles might be anatomical sanctuaries for active and persistent transcription in both HIV/SIV infected individuals

Hypothesis: IC/IC-L interactions may be reduced in LN microenvironment



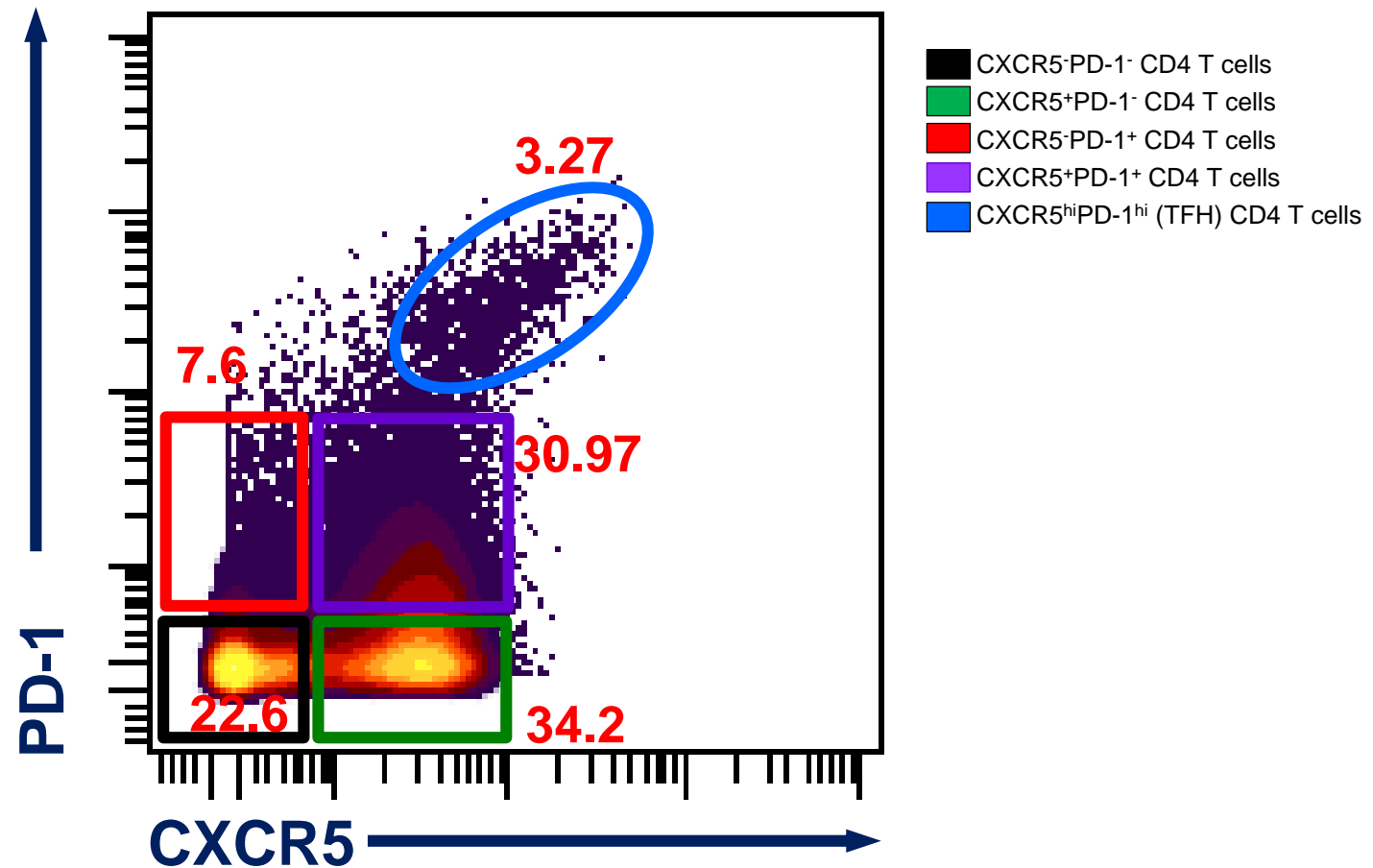
Latently infected CD4 T cell

Infected Tfh cell

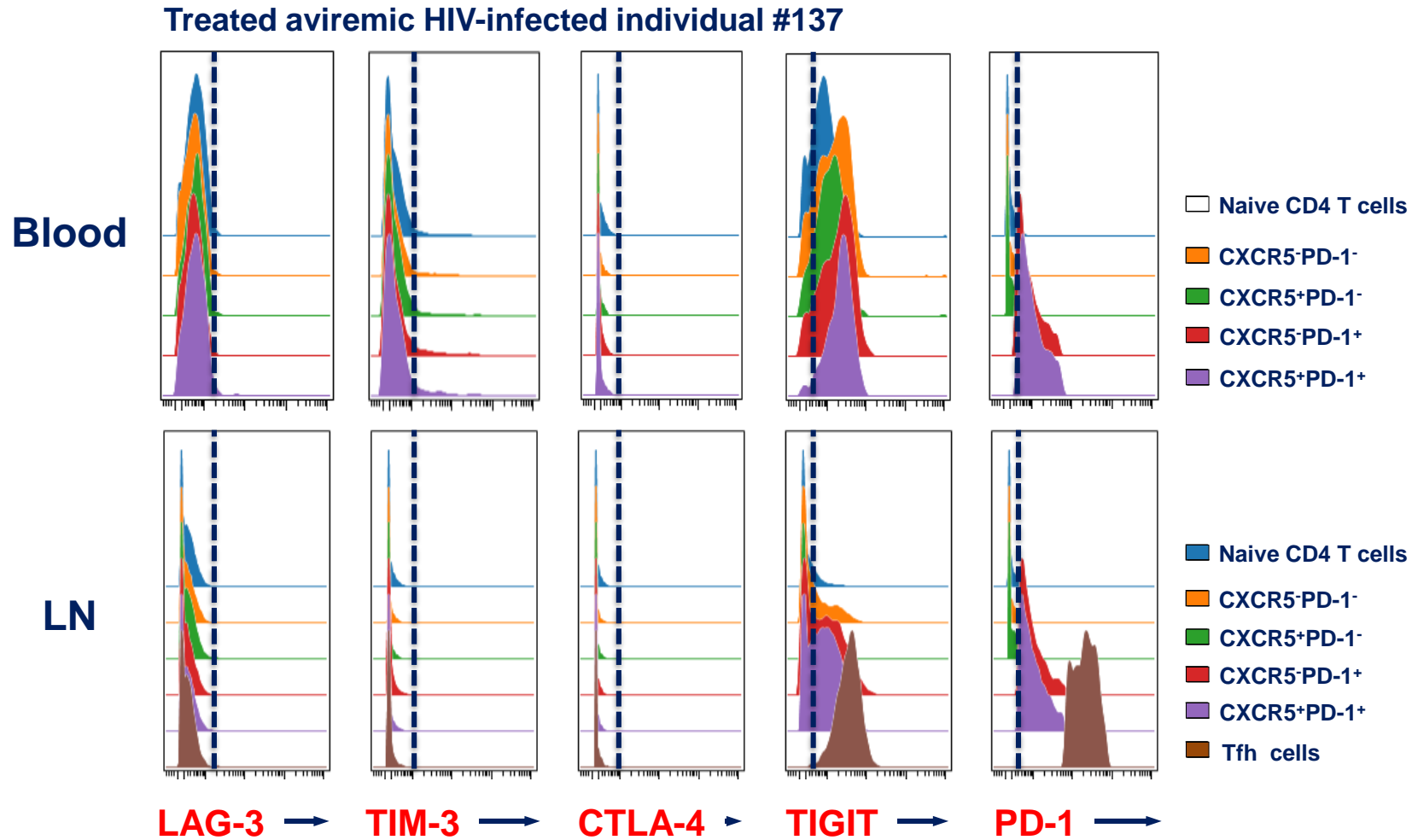
IC molecule expression on blood and LN CD4 T-cell populations

Treated aviremic HIV-infected individual #137

Gated on LN CD3⁺CD4⁺CD45RA⁻ cells

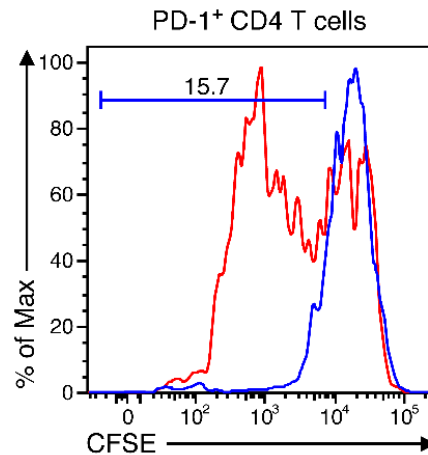
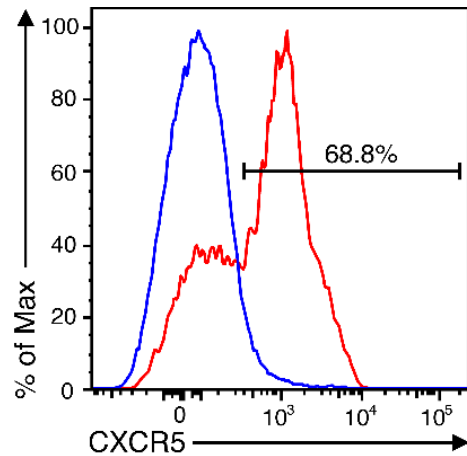
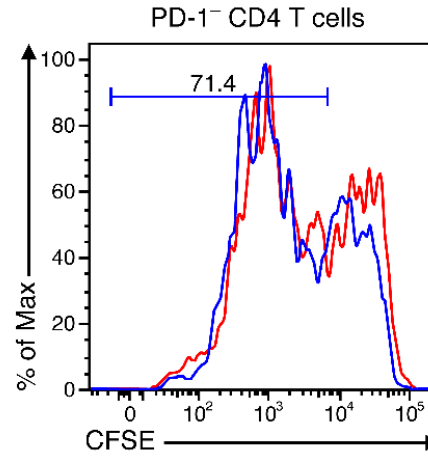
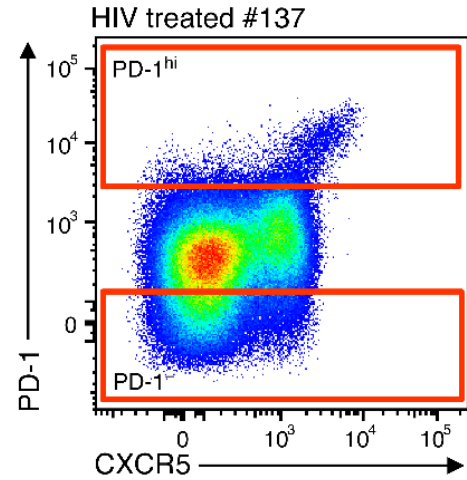


IC molecule expression on blood and LN CD4 T-cell populations



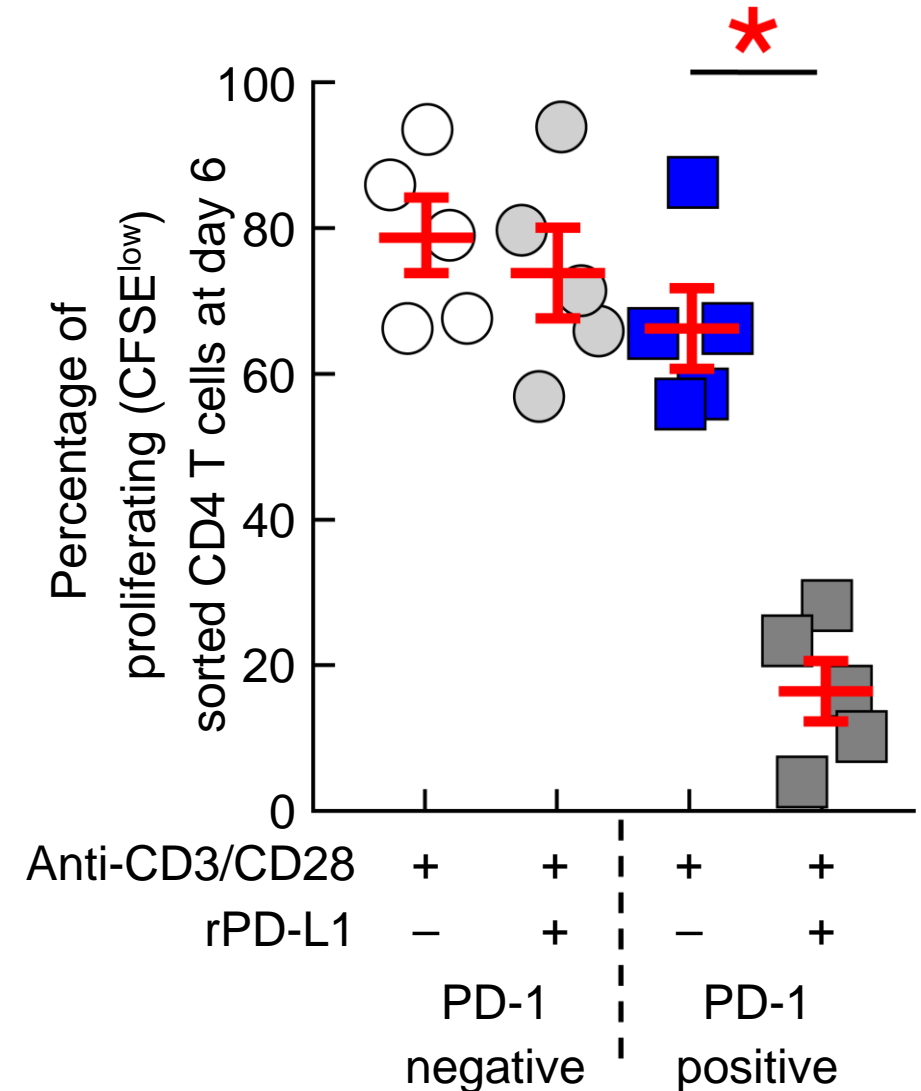
➤ TIGIT and PD-1 are the 2 main IC molecules expressed on blood and LN CD4 T-cell populations

IC/IC-L interaction modulates TCR signaling of LN PD1⁺/Tfh cells

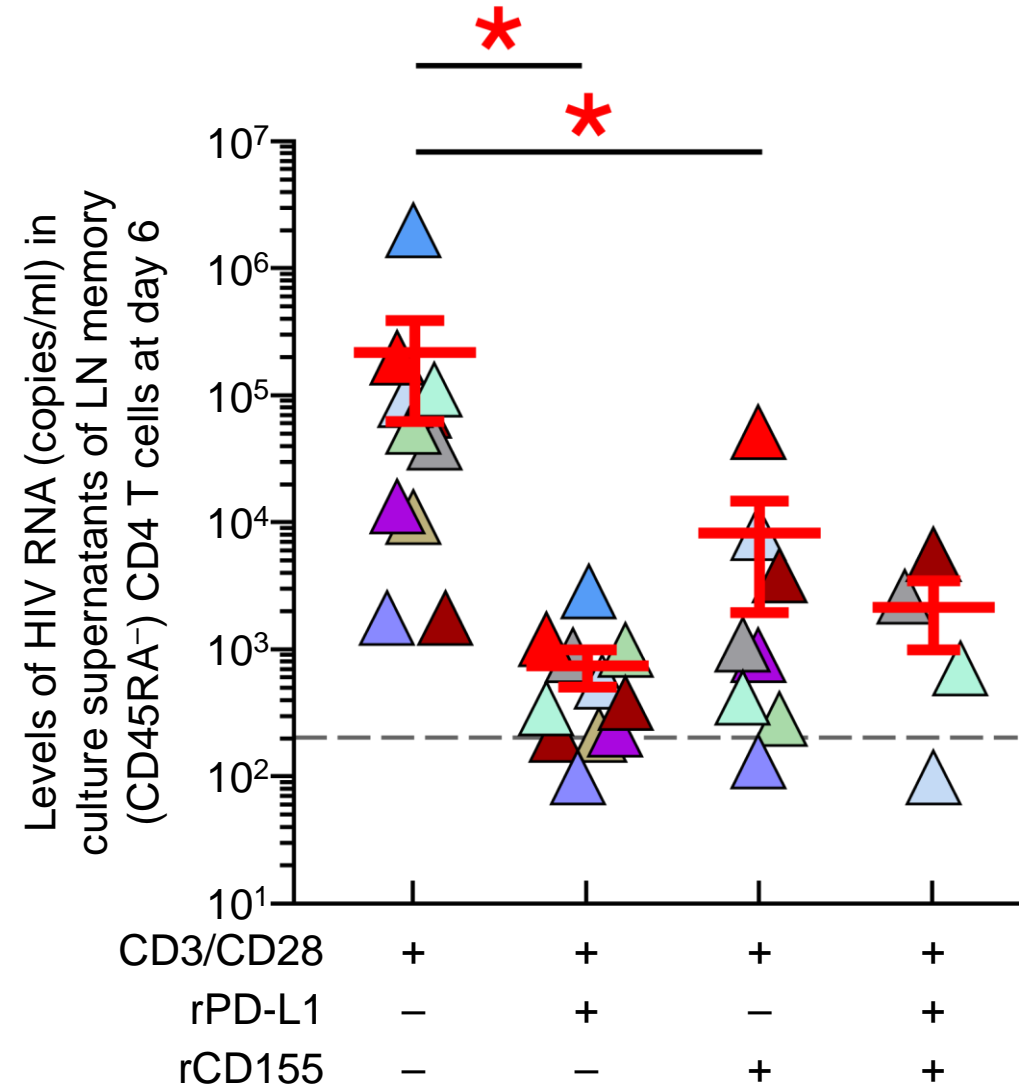
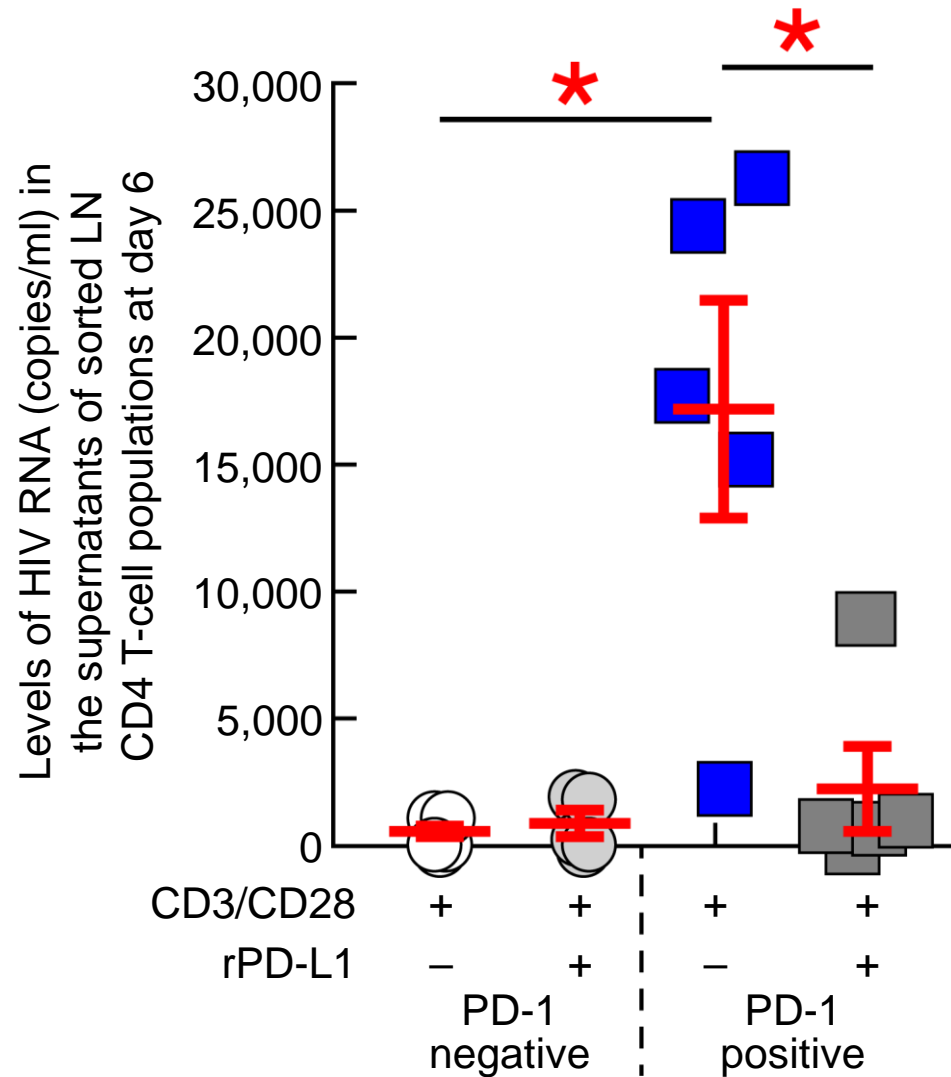


— Naïve (CD45RA⁻) CD4 T cells

— PD-1^{hi} CXCR5^{hi} (Tfh) CD4 T cells

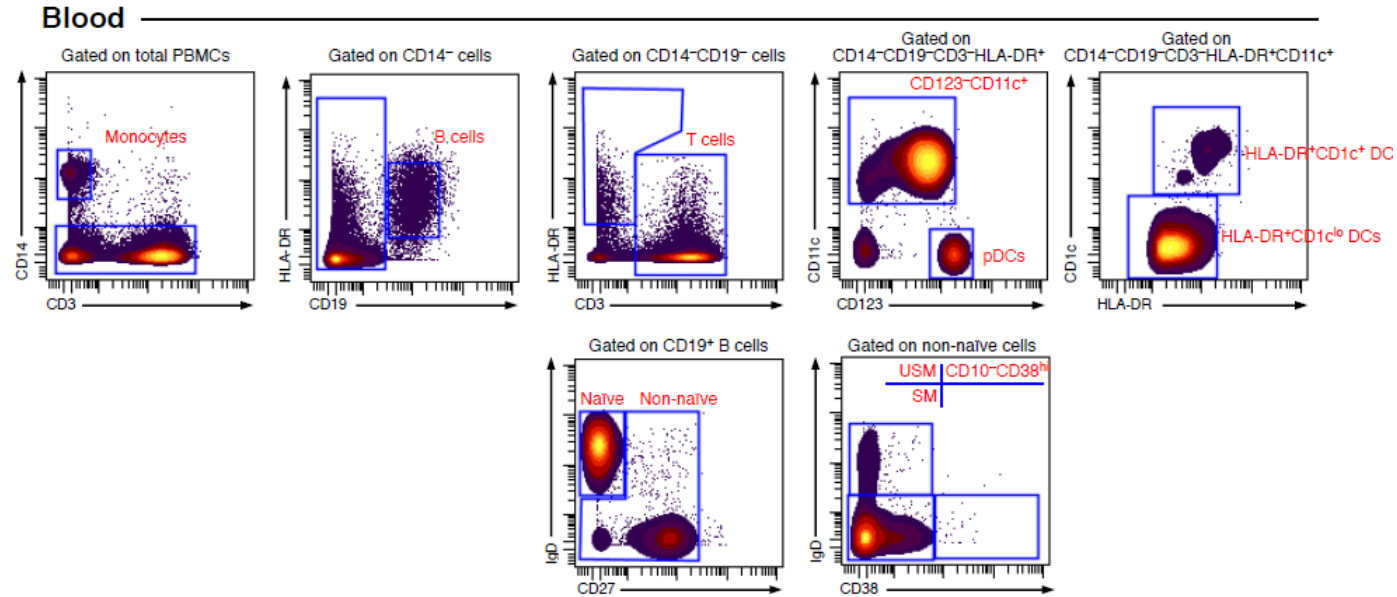


IC/IC-L interaction modulates HIV transcription/production from LN PD1+/Tfh cells

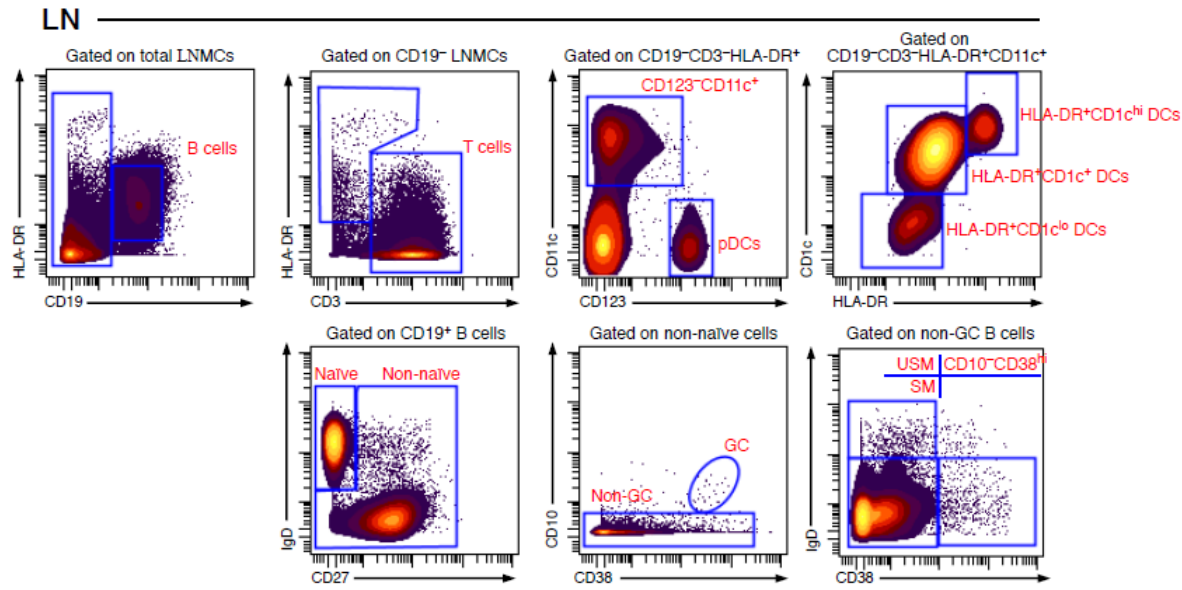


IC-ligand expression on blood and LN cell populations

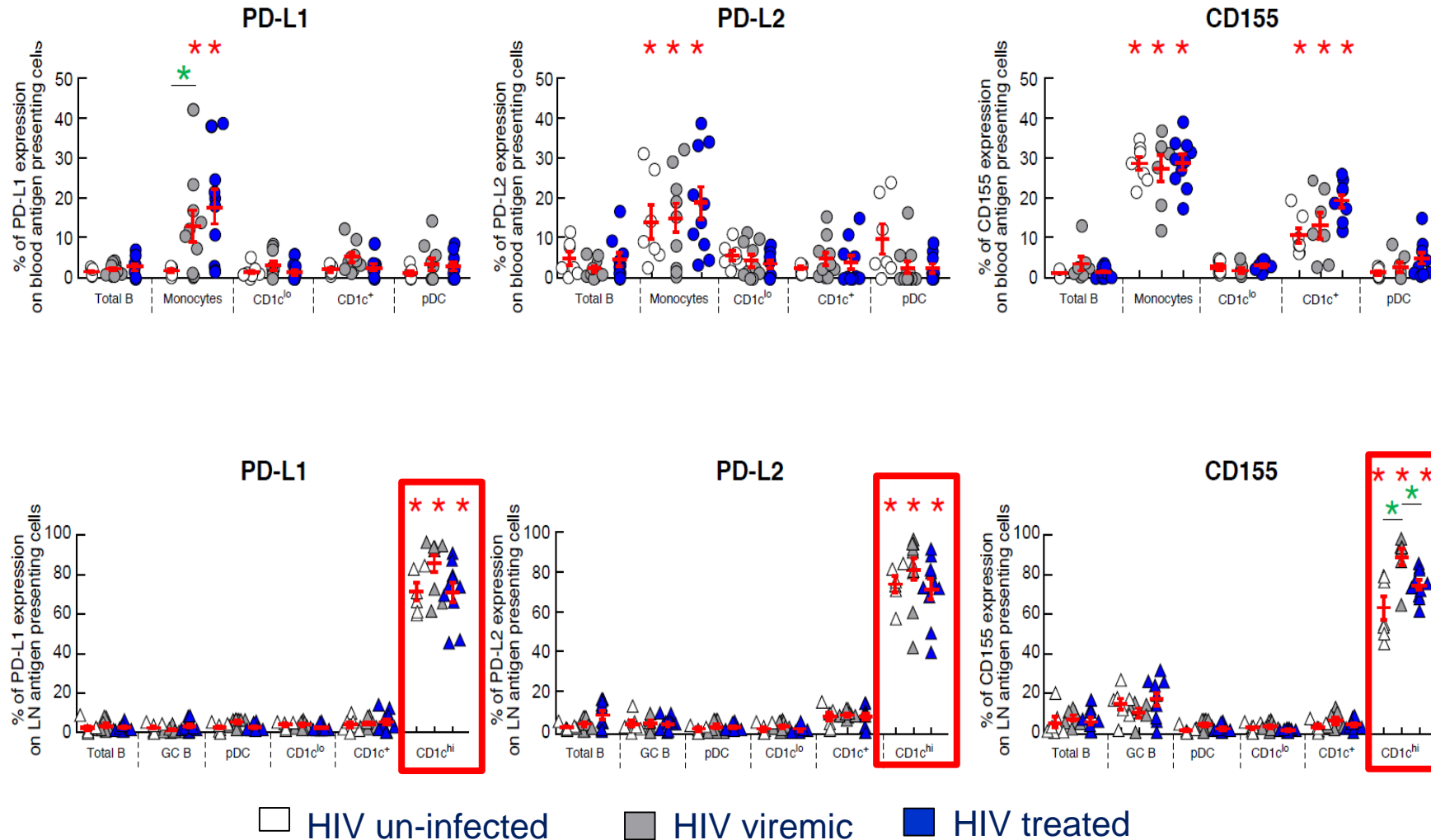
Blood



LN

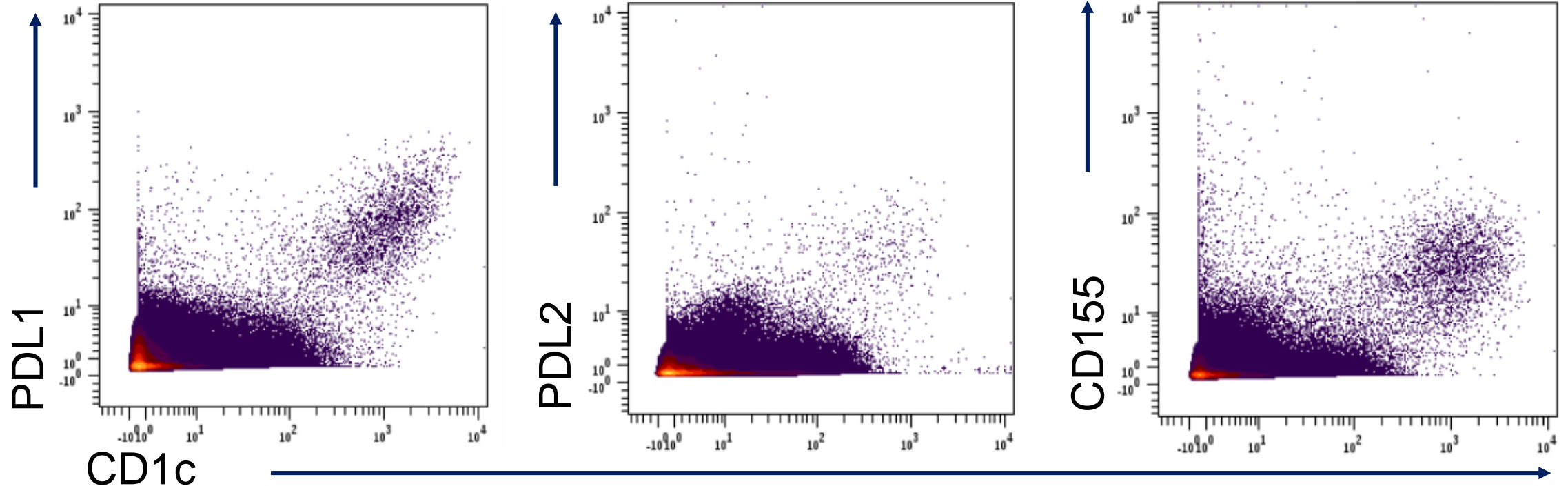


IC-Ls are predominantly expressed on LN myeloid $CD1c^{hi}$ DCs

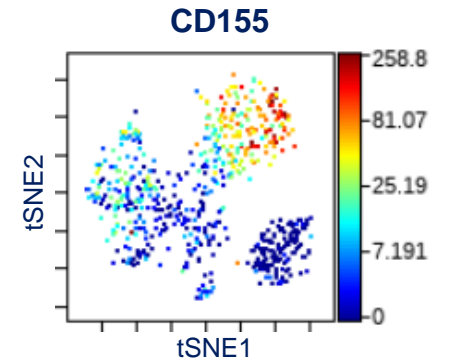
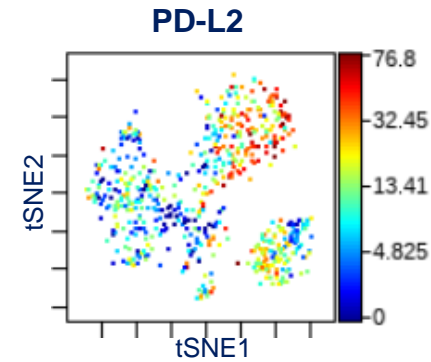
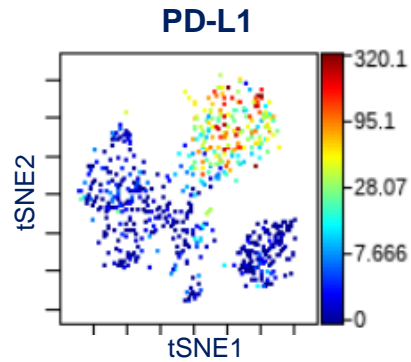
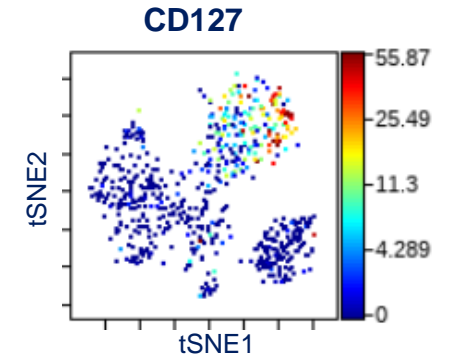
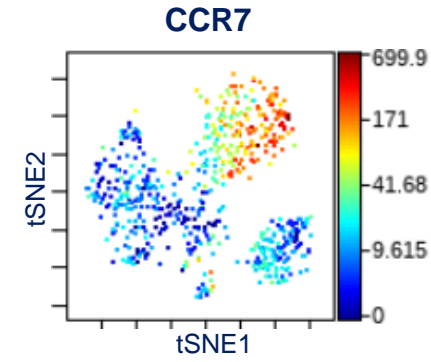
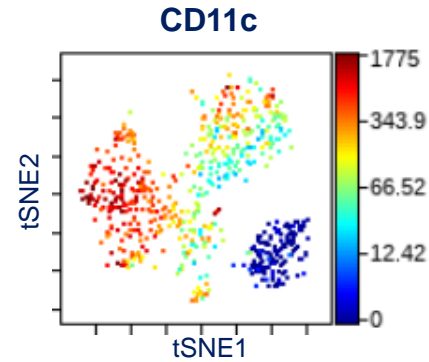
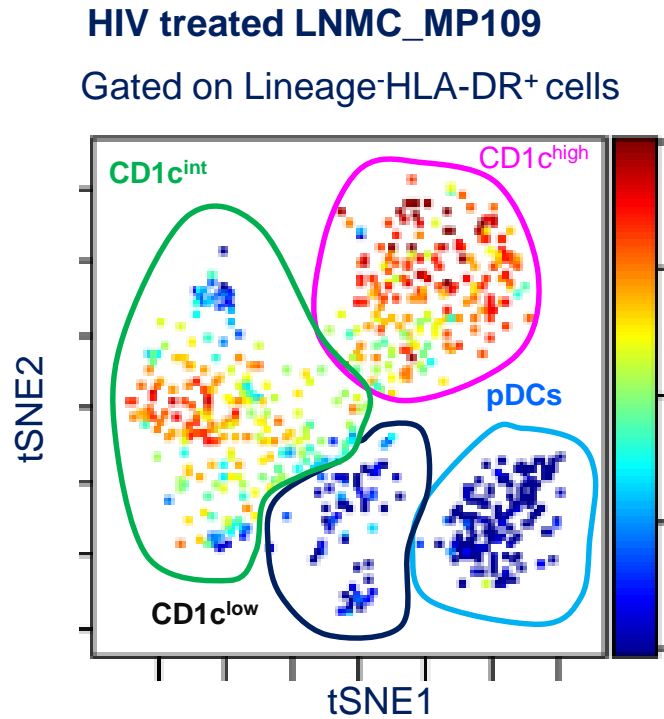


IC-Ls are primarily expressed on LN myeloid $CD1c^{hi}$ DCs

Treated aviremic HIV-infected individual

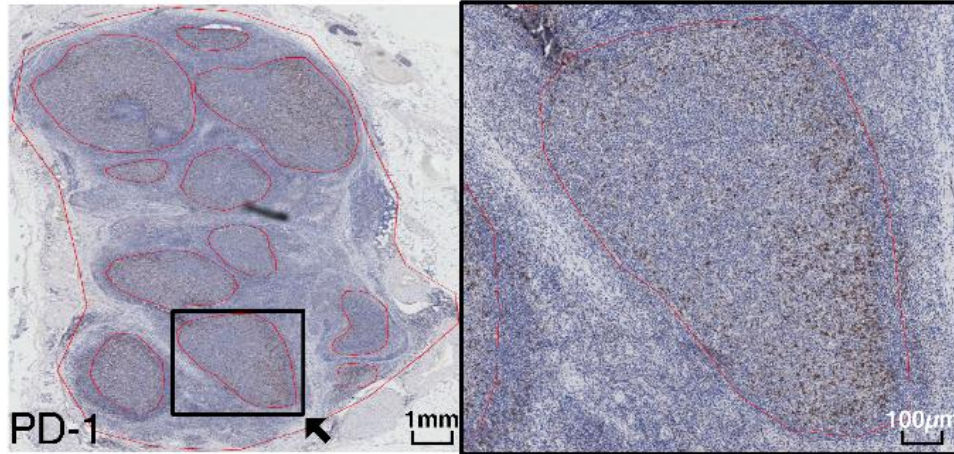


LN myeloid $CD1c^{hi}$ DCs harbor markers of migratory DCs

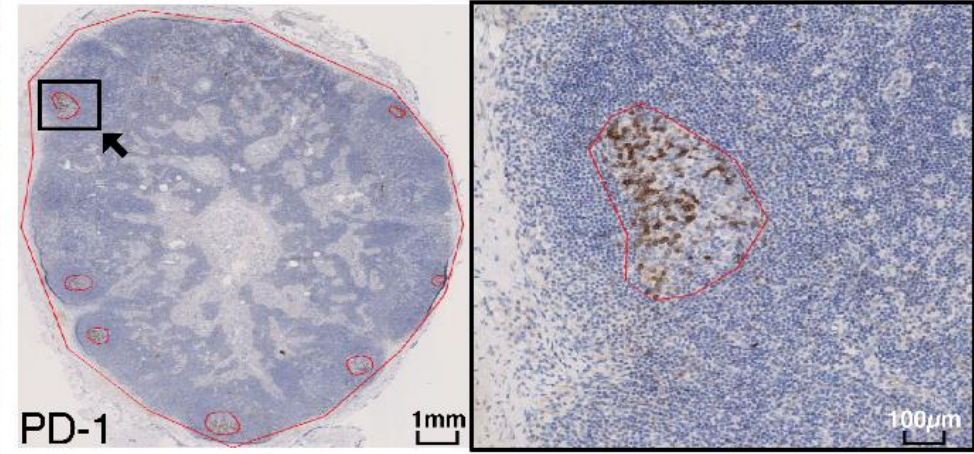


Do PD-1-expressing and PD-L1 expressing cells colocalize?

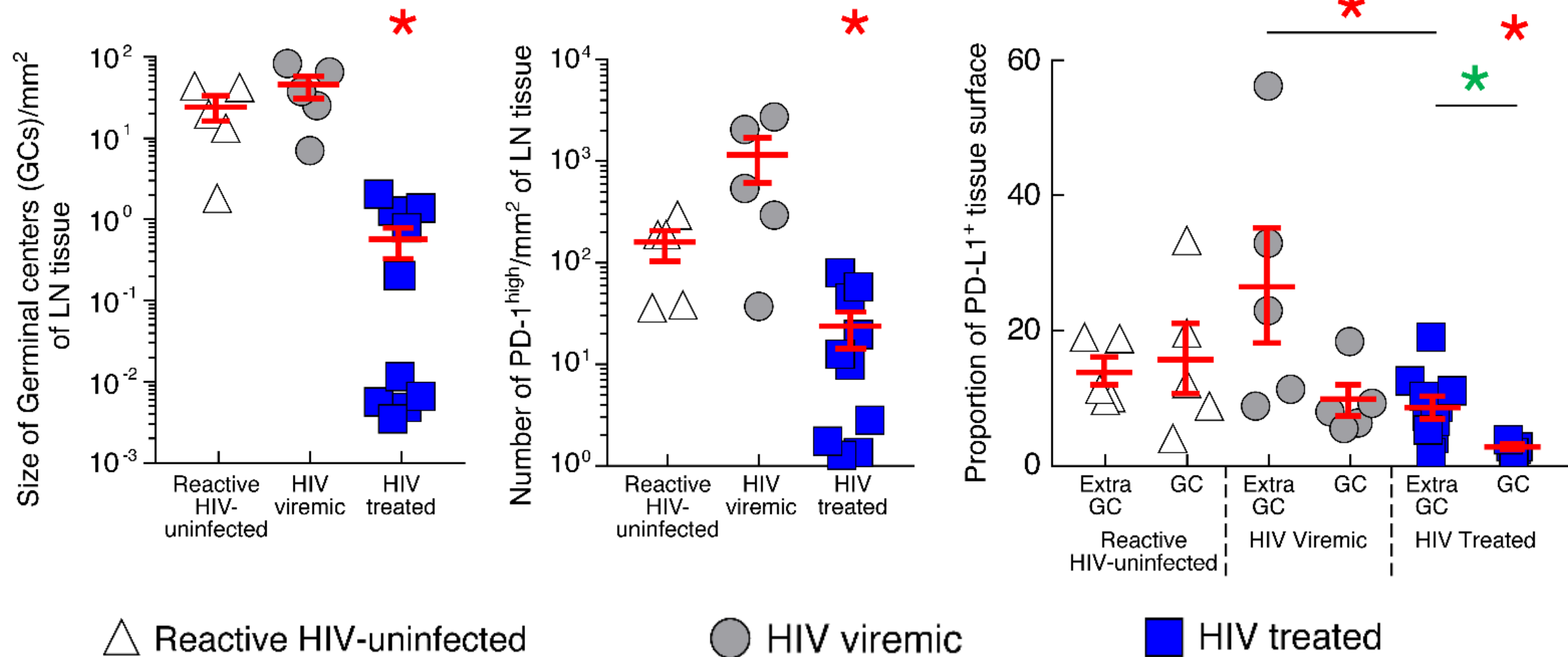
HIV viremic #177-1E



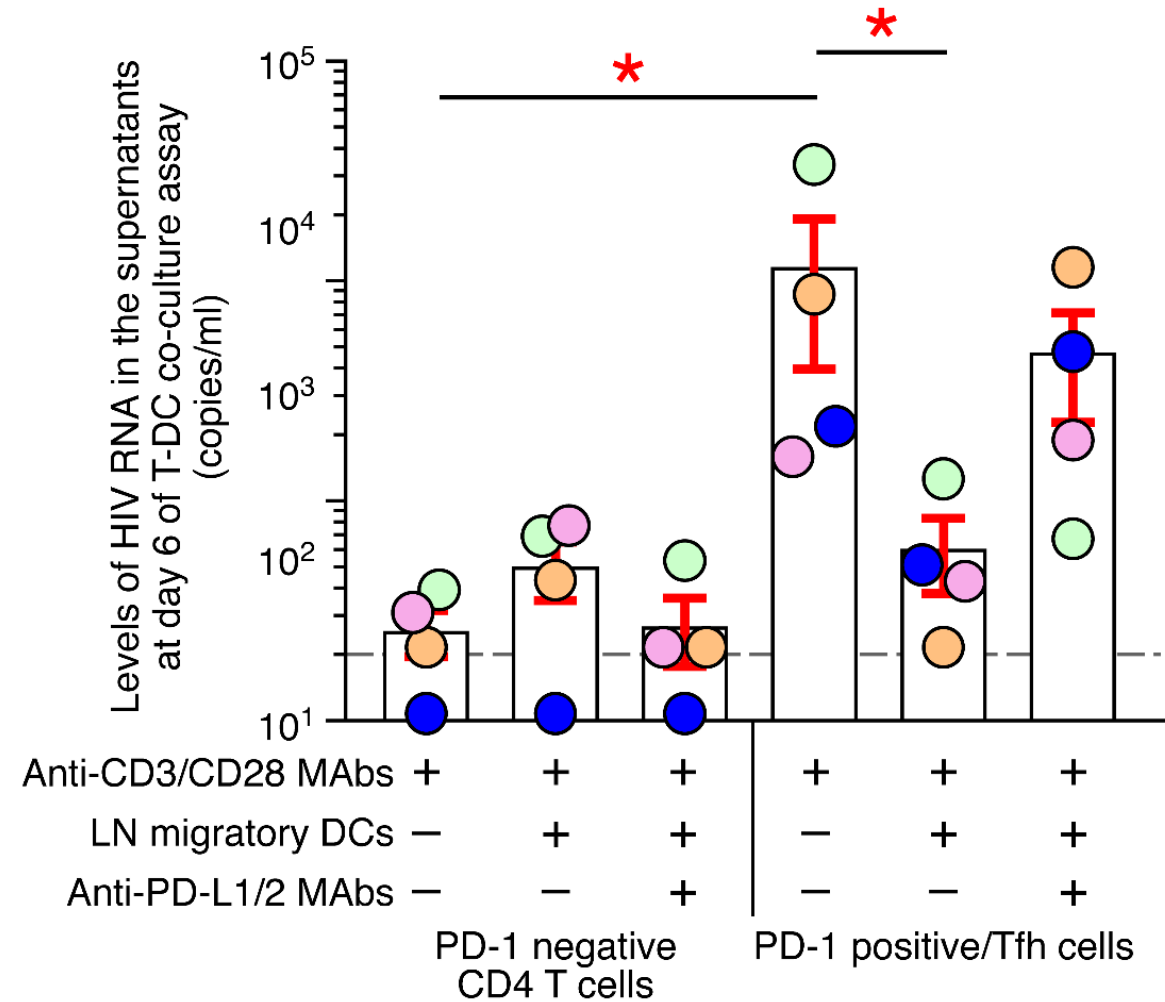
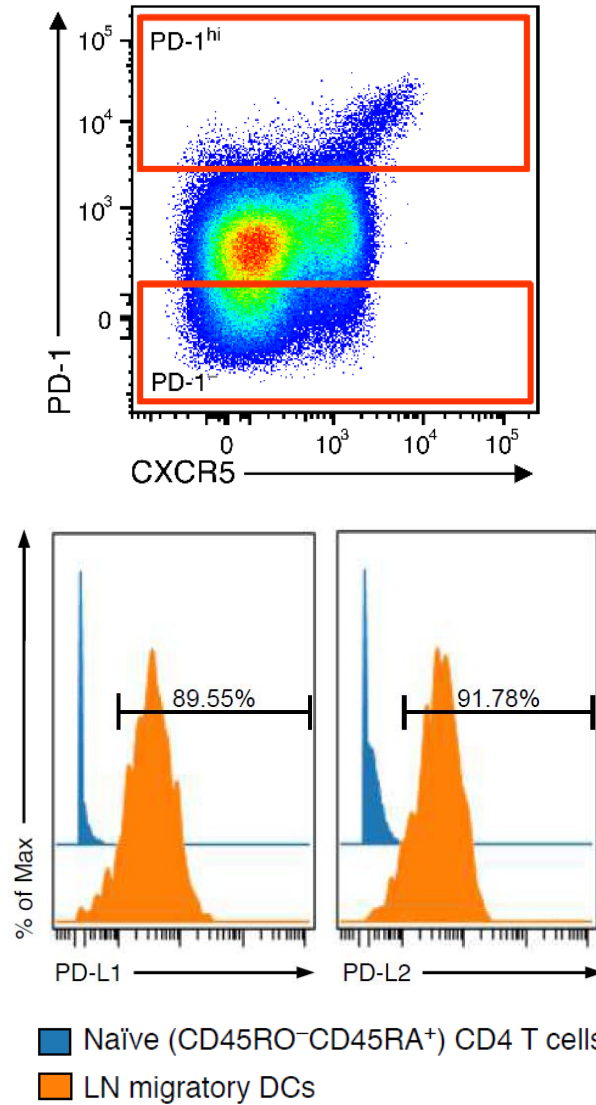
HIV treated #092-2



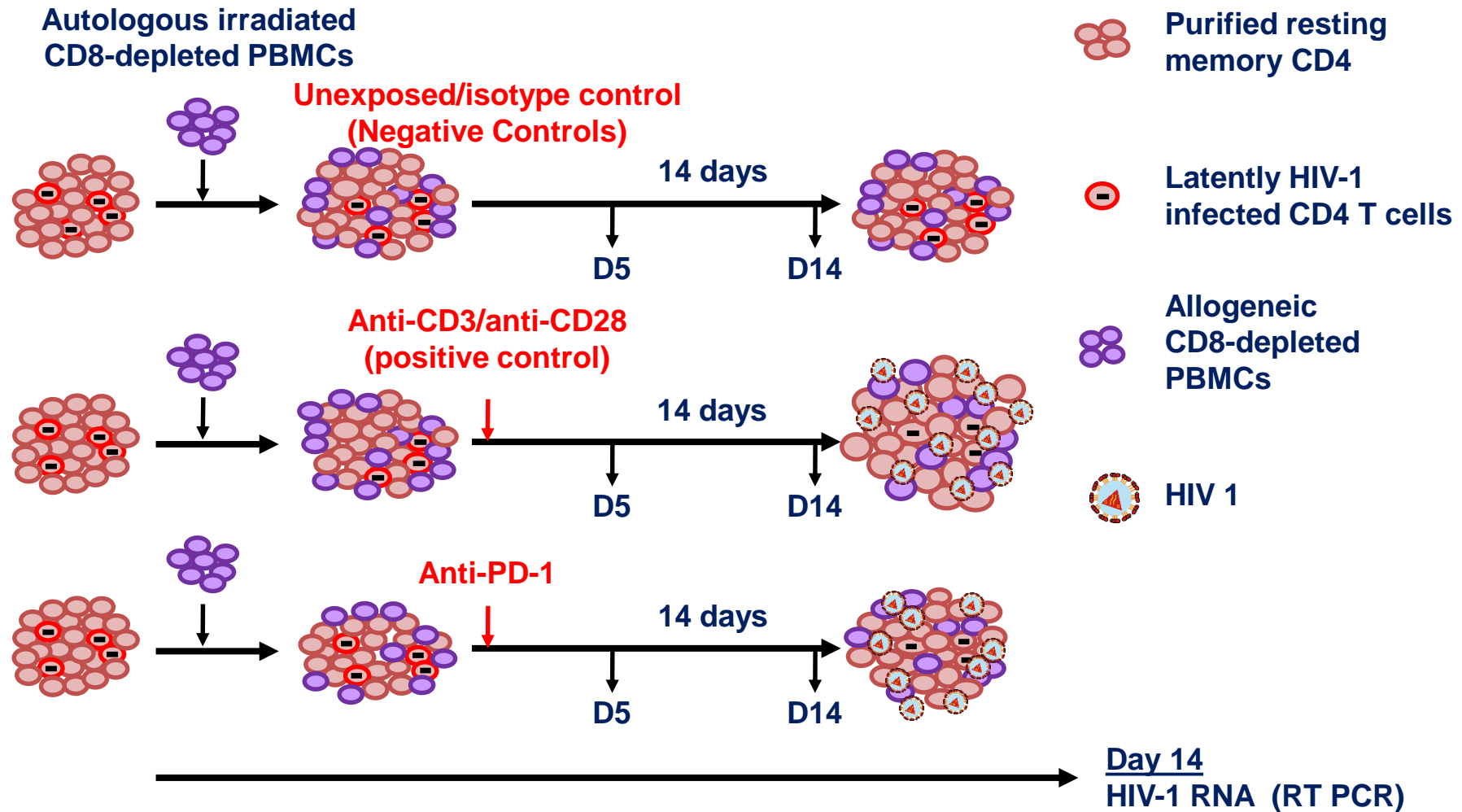
ART treatment initiation induces substantial changes in IC/IC-L expression



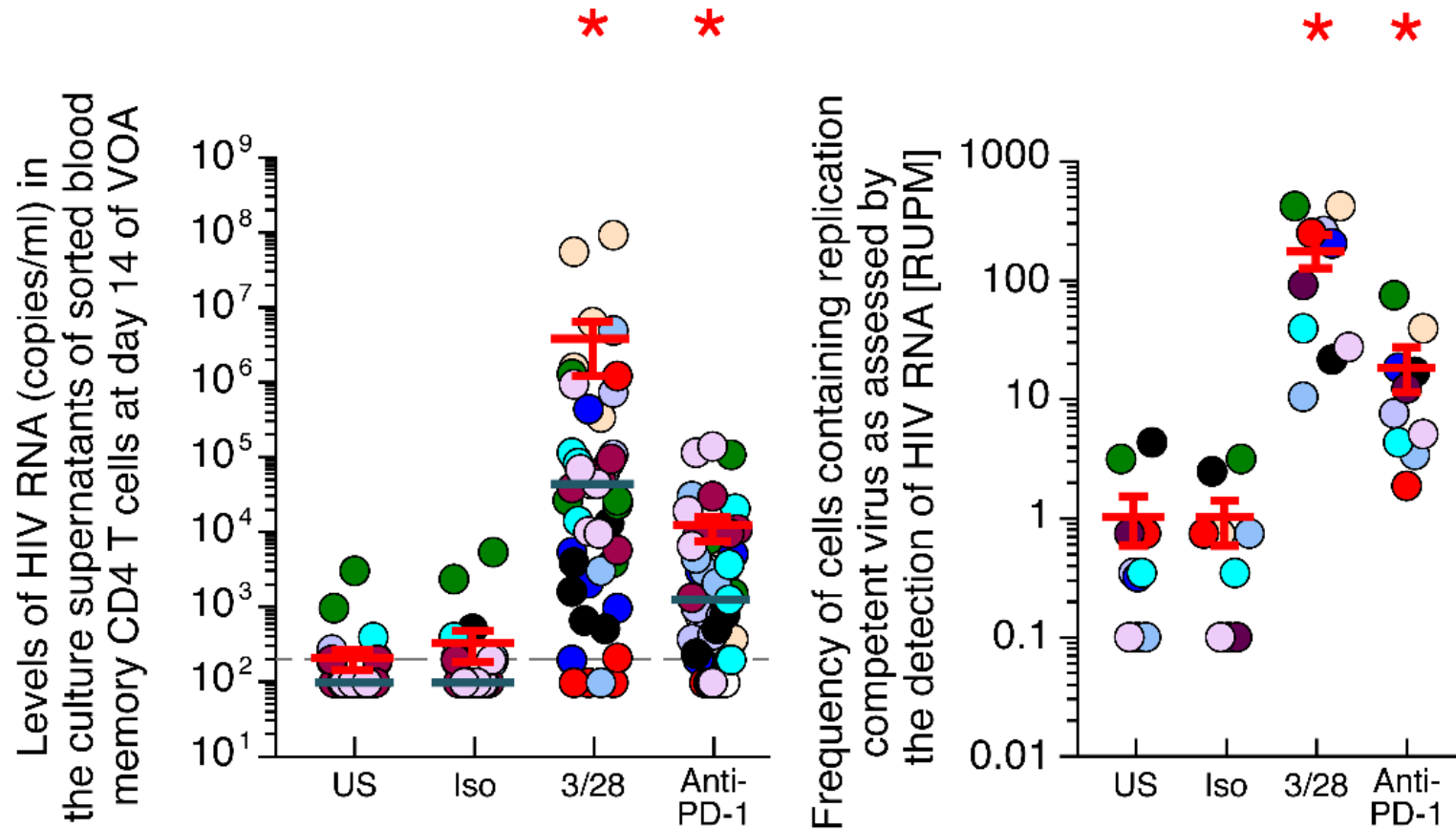
LN migratory DCs expressing IC-Ls modulate HIV transcription/production



Evaluation of anti-PD-1 MAbs efficiency to reactivate HIV-1 from latency



Anti-PD1 MAb Pembrolizumab reactivates HIV replication *in vitro*



➤ The RUPM frequency induced by anti-PD-1 MAbs corresponded to about 21% of the one induced by anti-CD3/anti-CD28 MAbs

Conclusions

- LN PD-1⁺/Tfh Cells are enriched in inducible replication competent HIV in treated aviremic HIV-infected subjects
- LN PD-1⁺/Tfh cells serve as the major source for active and persistent virus transcription after ART
- LN migratory DCs modulate HIV transcription / production *in vitro* through PD-1/PD-L interactions
- LN migratory DCs may more efficiently restrict HIV-1 transcription in the extra-follicular areas
- Anti-PD-1 monoclonal antibody Pembrolizumab can efficiently reverse HIV-1 latency *in vitro* and may therefore represent an ideal LRA

Acknowledgments

Prof. Giuseppe Pantaleo
Service of Immunology and Allergy
CHUV, Lausanne

Dr. Riddhima Banga
Olivia Munoz

Dr. Francesco Procopio
Dr. Alessandra Noto
Dr. Khalid Ohmiti
Dr. Craig Fenwick

Service of Infectious Diseases
Dr. Matthias Cavassini
Deolinda Alves

Service of Vascular Surgery
Prof. Jean-Marc Corpataux

Institute of Pathology
Prof. Laurence De Leval
Dr. Caterina Rebechini

Study Participants



FONDS NATIONAL SUISSE
SCHWEIZERISCHER NATIONALFONDS
FONDO NAZIONALE SVIZZERO
SWISS NATIONAL SCIENCE FOUNDATION

Foundation MACHAON
Geneva