

11TH EDITION

DECEMBER 10-13, 2024

HIV PERSISTENCE DURING THERAPY

Reservoirs & Eradication Strategies Workshop



Role of HIV-1 integration sites in clonal expansion of infected cells and maintenance of latency

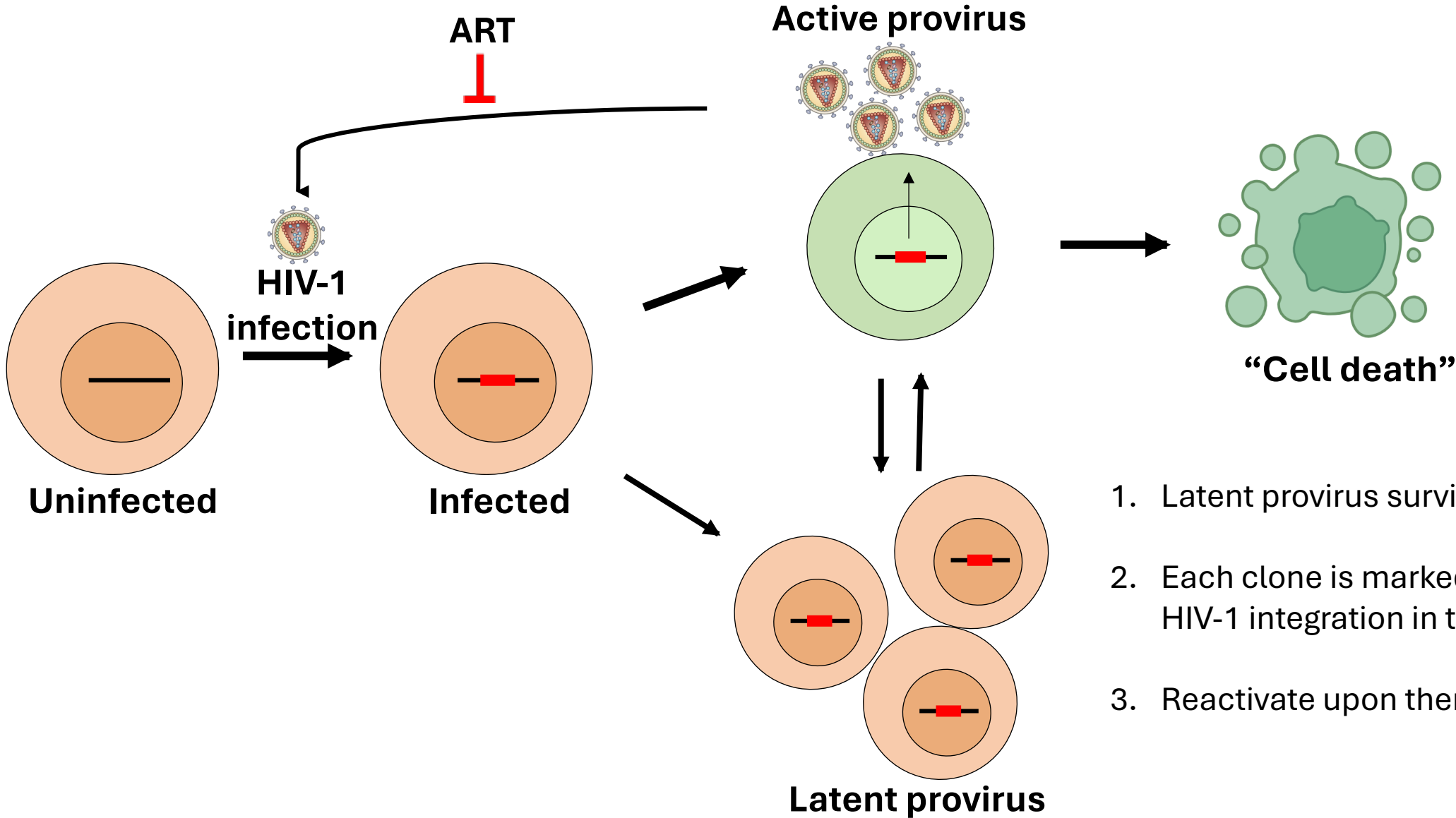
Virender Pal

Postdoctoral Associate

The Rockefeller University

www.hiv-persistence.com

Latent reservoir: a barrier to HIV-1 cure

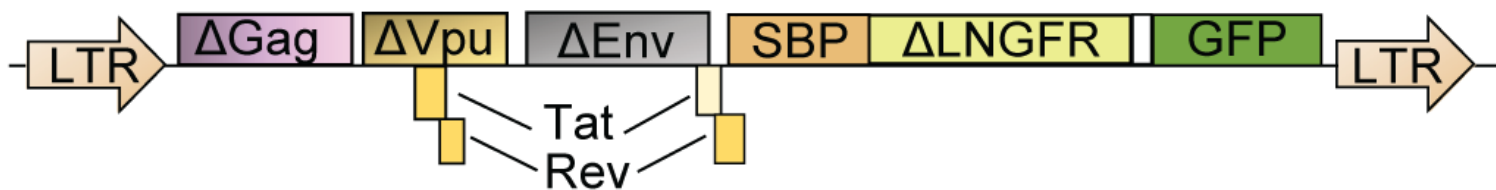


1. Latent provirus survive/clonally expand
2. Each clone is marked by unique site of HIV-1 integration in the host genome
3. Reactivate upon therapy interruption

HIV-1 dual reporter-based model to study clonal expansion and latency

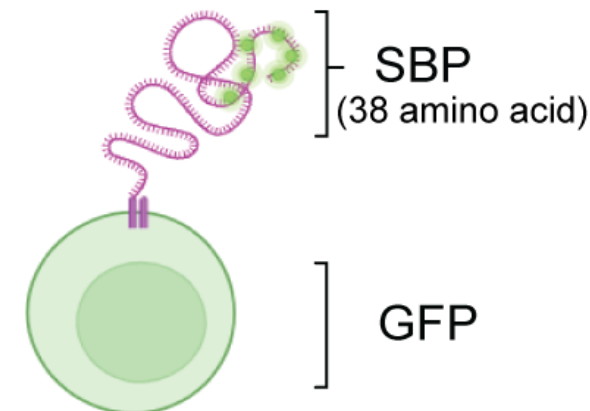
A.

Dual tagged HIV-1 reporter



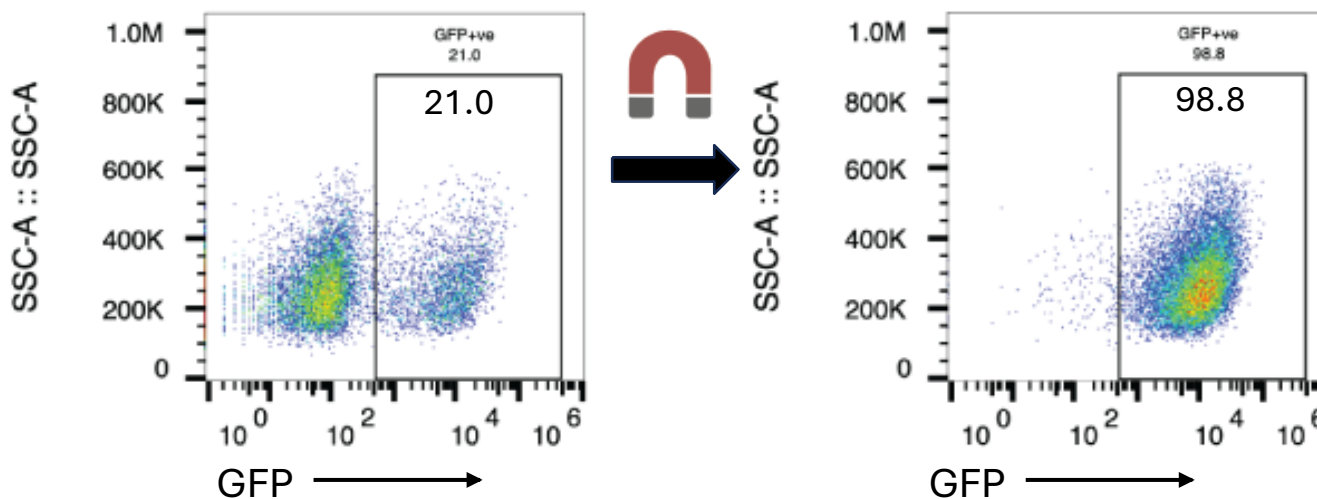
B.

Infected cell



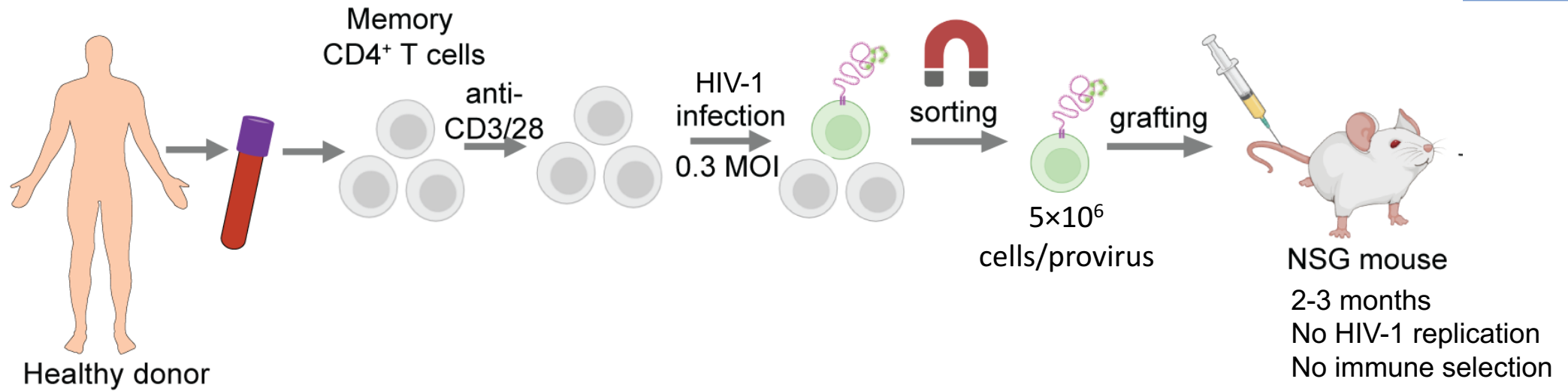
C.

Infected cell sorting

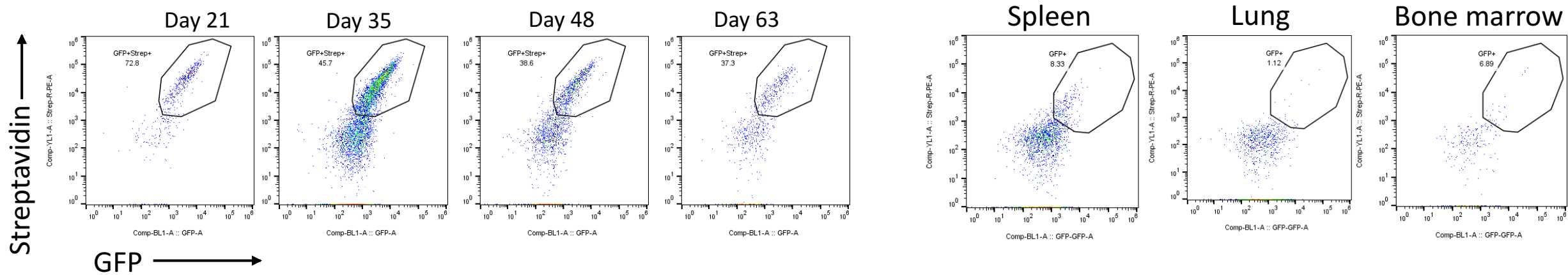


Acknowledged Frauke Muecksch

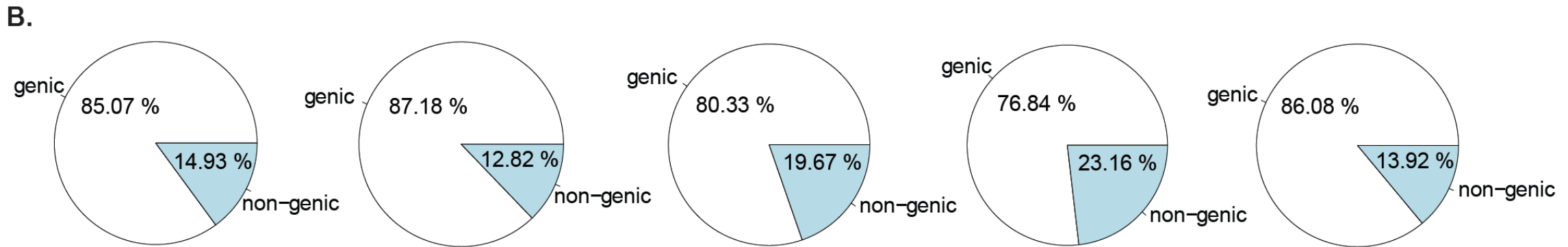
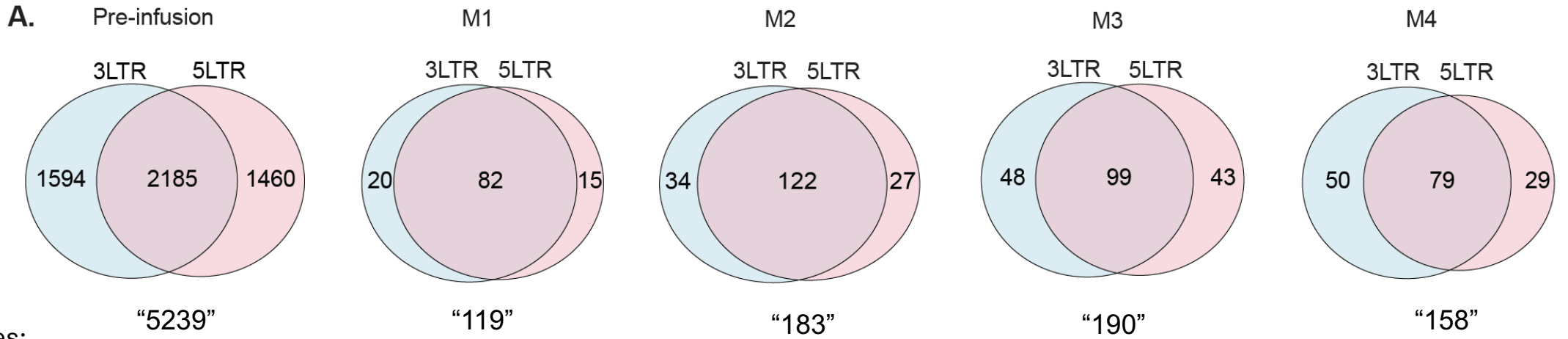
Engraftment of mice with memory CD4⁺ T-cells with single HIV-1 proviruses



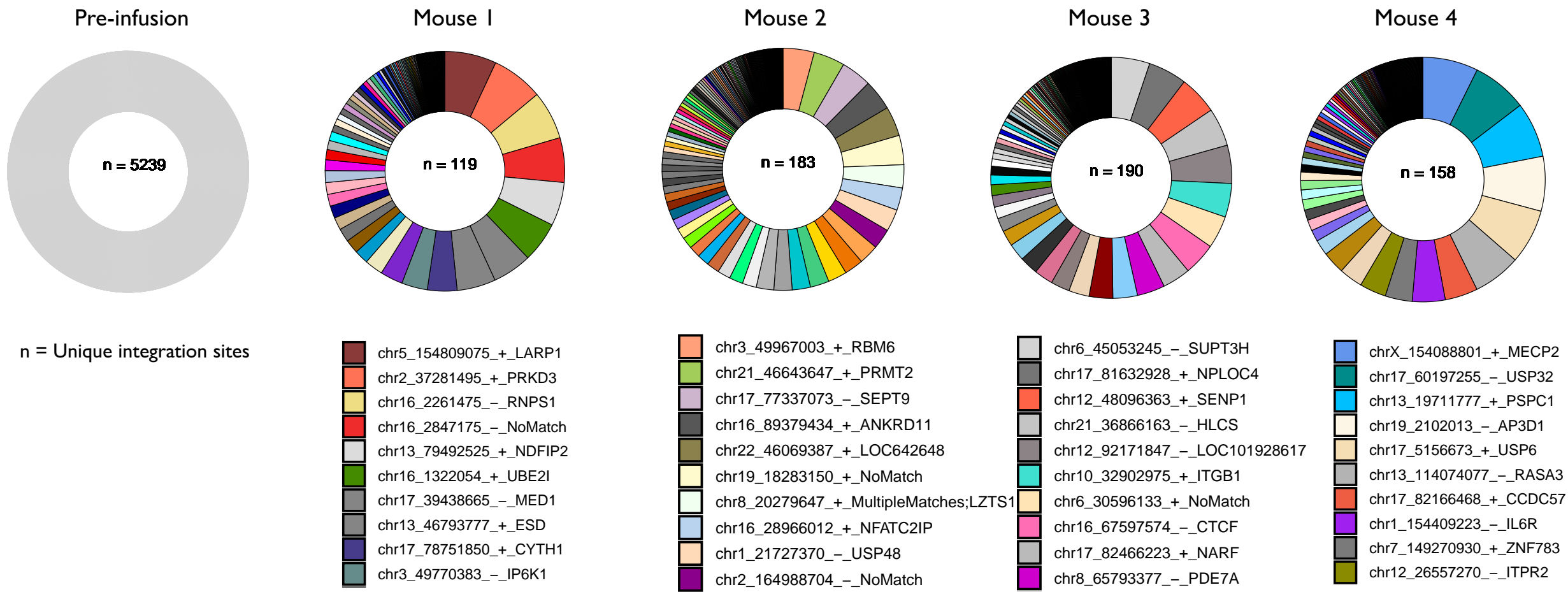
Peripheral blood



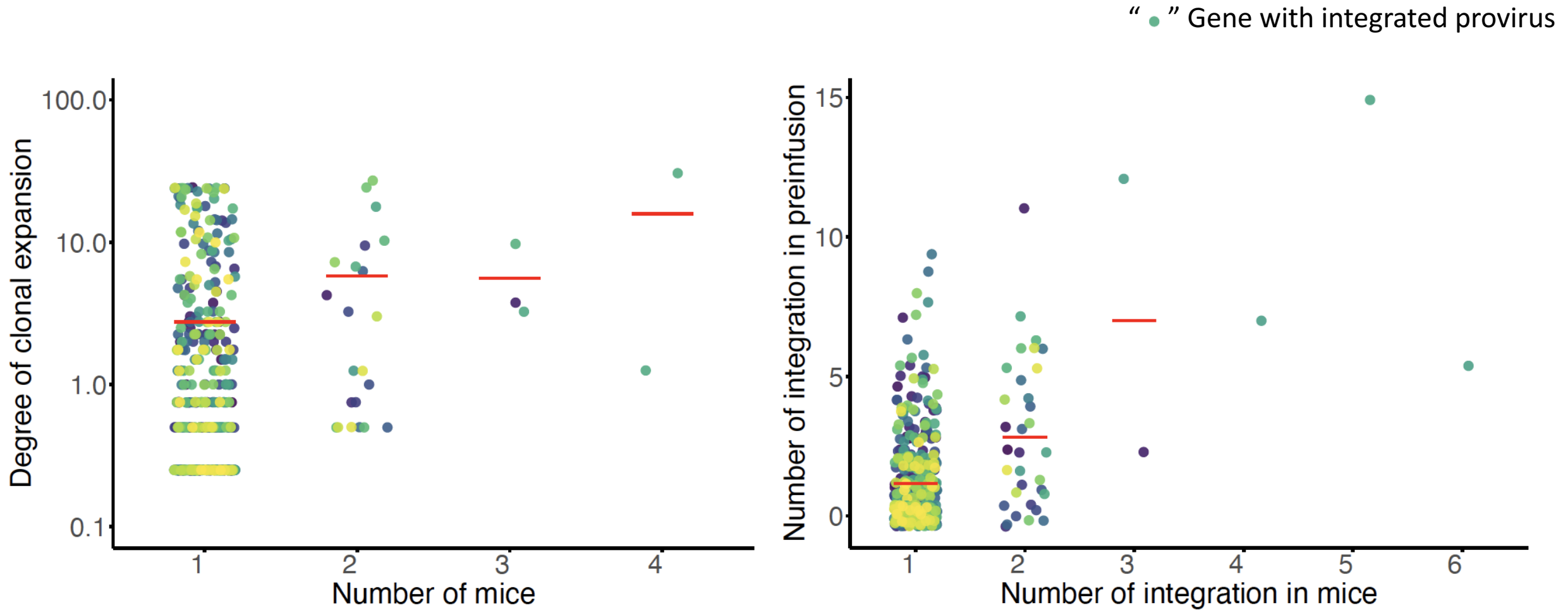
Number and distribution of HIV-1 integrations sites



Clonal expansion of HIV-1 infected cells in mice

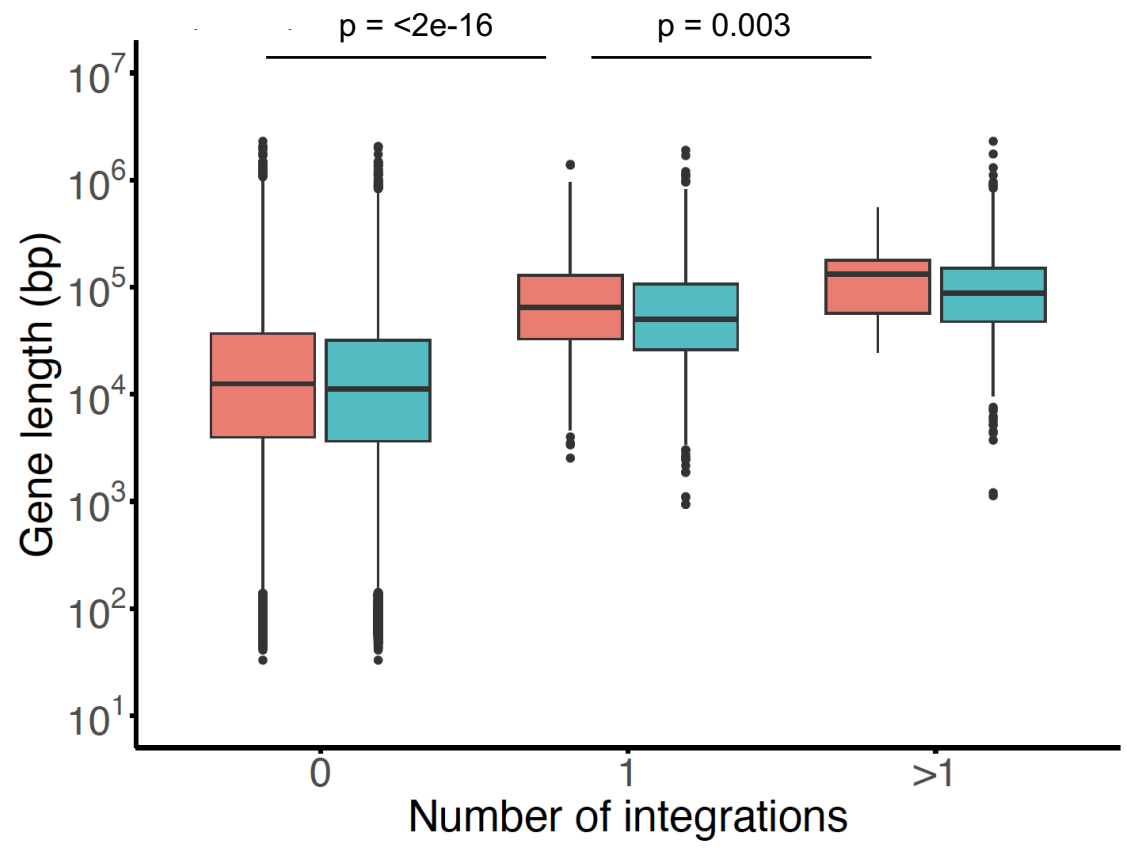


Does HIV-1 integration derive cell survival and expansion in mice?

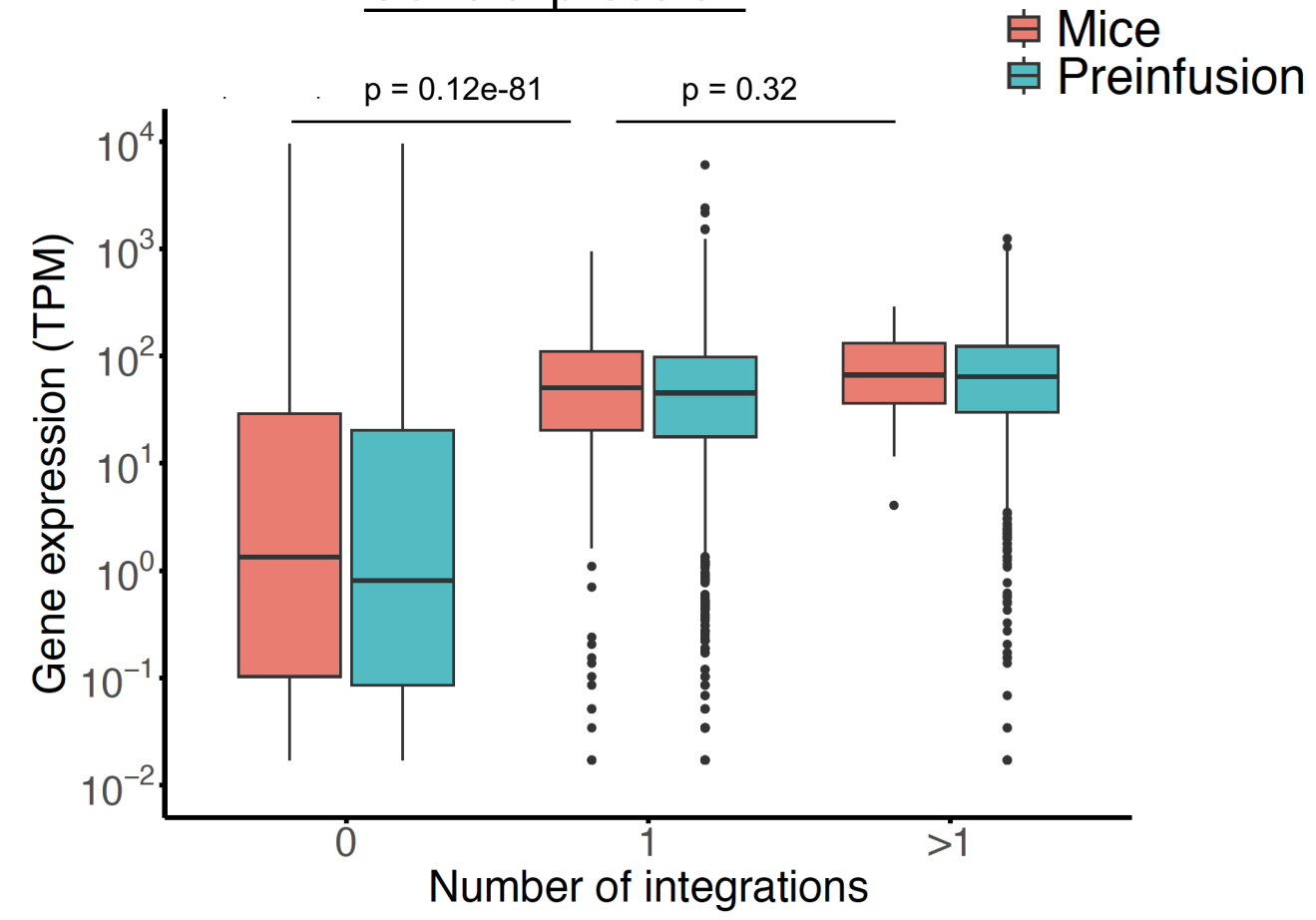


Gene length and expression levels predicts HIV-1 integrations

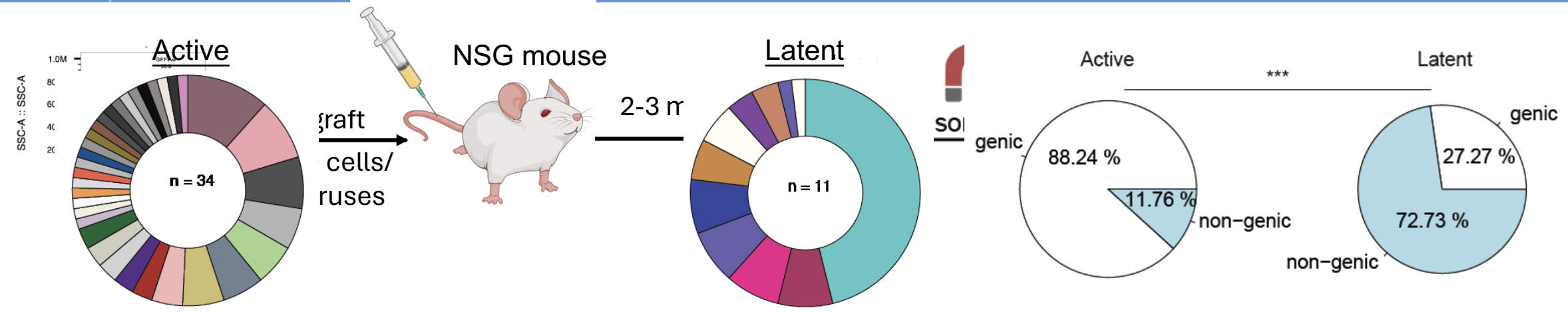
Gene length



Gene expression



Integration sites of active and latent proviruses



- chr1_225984862+_SDE2
- chr2_24501693-_NCOA1
- chr16_196016-_LUC7L
- chr3_90576297-_non-genic
- chr17_78420328+_PGS1
- chr12_70317216+_CNOT2
- chr1_155531283+_ASH1L
- chr6_28244789+_ZKSCAN4
- chr2_121762102-_TSN
- chr19_49560513+_NOSIP
- chr19_52930075-_ZNF816-ZNF321P
- chr12_62315082+_USP15
- chr10_91950418+_BTAF1
- chrX_81224216-_SH3BGRL
- chrX_97150435-_DIAPH2
- chr9_136475913+_SEC16A
- chr8_411428+_FBXO25

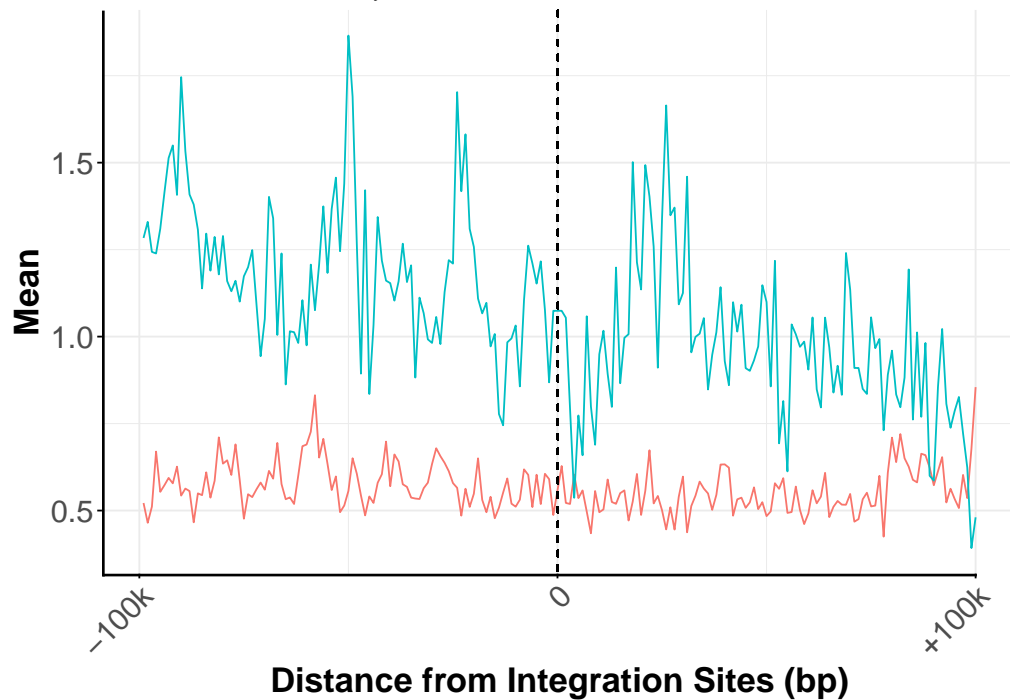
- chr7_99412857-_BUD31
- chr6_35637698-_FKBP5
- chr6_63646904+_PHF3
- chr4_137102355+_LOC105377441
- chr3_177551435+_LINC00578
- chr3_17402193+_TBC1D5
- chr3_149602896-_WWTR1
- chr2_KI270893v1_alt_136946+_LOC728323
- chr19_2214715+_DOT1L
- chr16_68090273+_NFATC3
- chr16_246393+_FAM234A
- chr15_99399616+_LOC105371018;LOC105371017
- chr14_74371798-_non-genic
- chr11_64774526-_SF1
- chr11_15961653-_non-genic
- chr1_153862834-_GATAD2B
- chr3_91166033+_non-genic

- chr19_52930075-_ZNF816-ZNF321P
- chrUn_KI270589v1_14673+_non-genic
- chr9_64958404-_non-genic
- chr11_50769638+_non-genic
- chr10_91950418+_BTAF1
- chr21_10757680+_non-genic
- chr10_39161877-_non-genic
- chr9_40825156-_non-genic
- chr12_34427409+_non-genic
- chr6_26176240+_non-genic
- chr2_160288416+_RBMS1

Epigenetic feature associated with latent and active proviruses

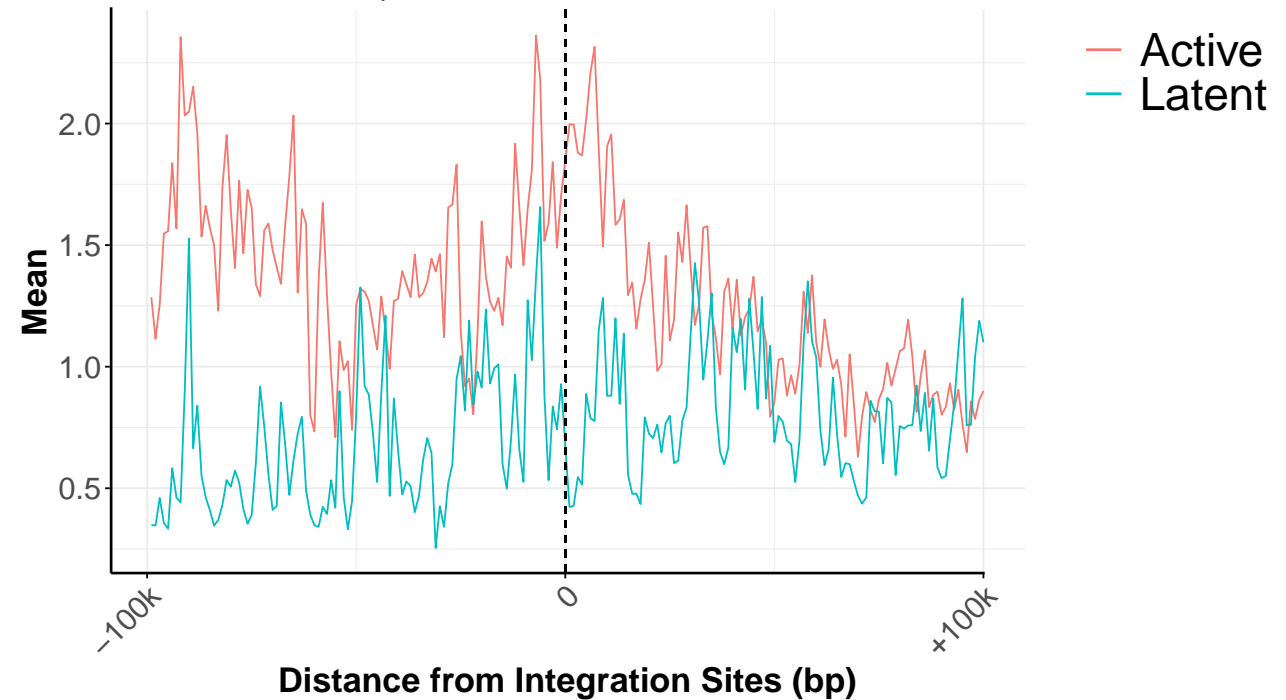
Repressive mark (enhancer element)

H3K9me3



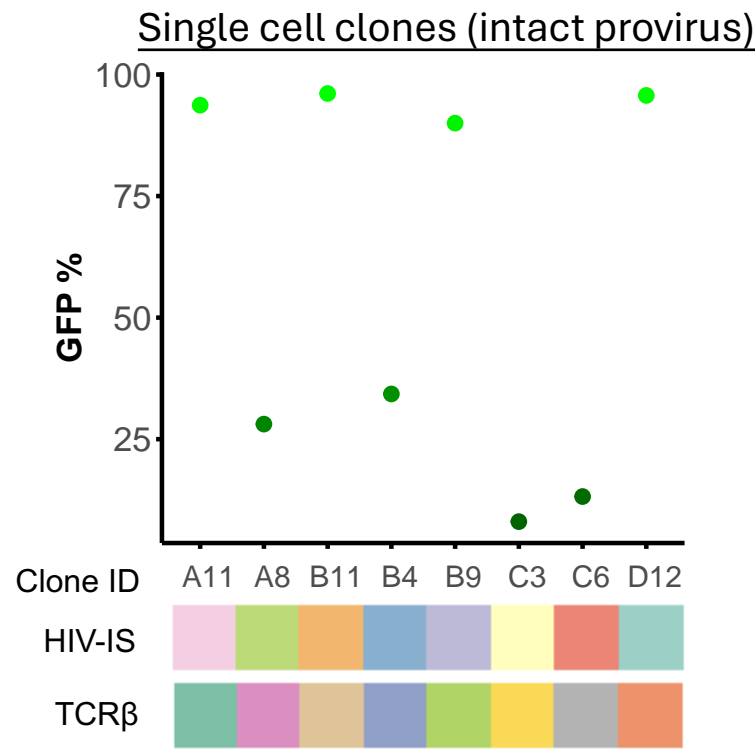
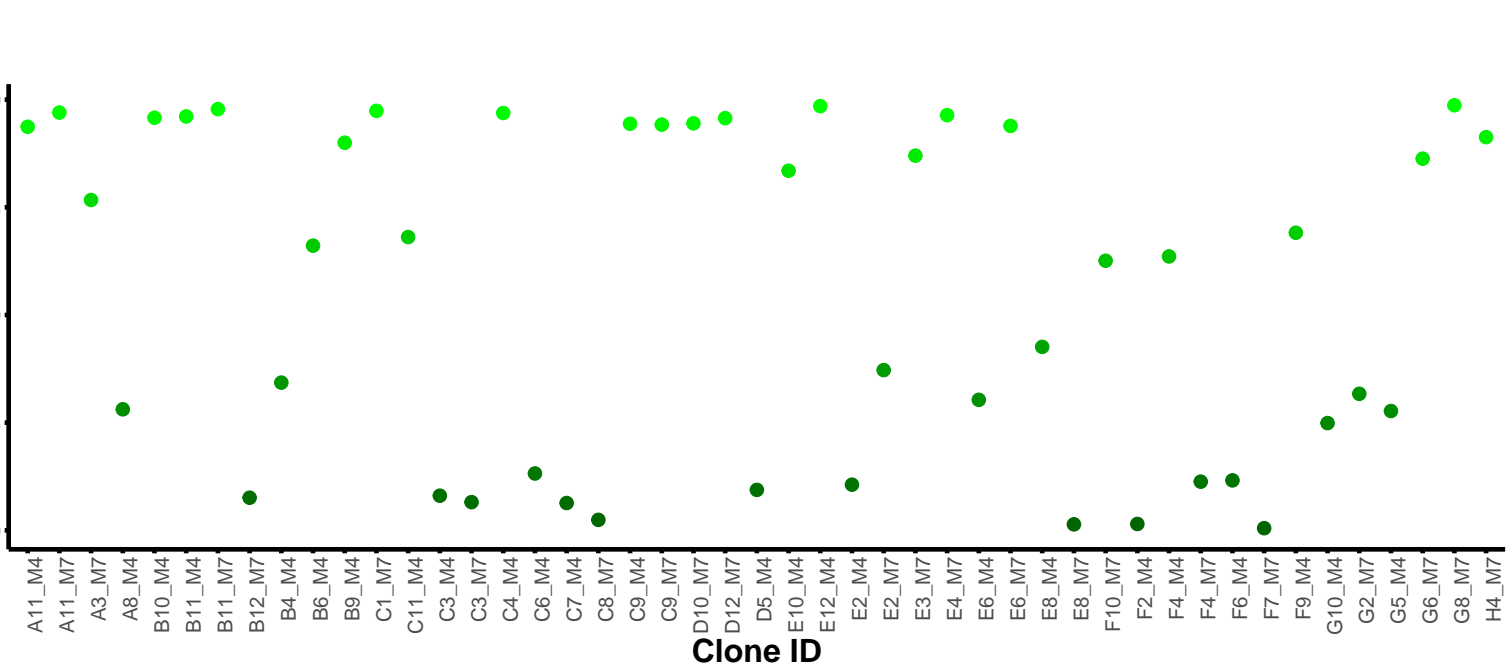
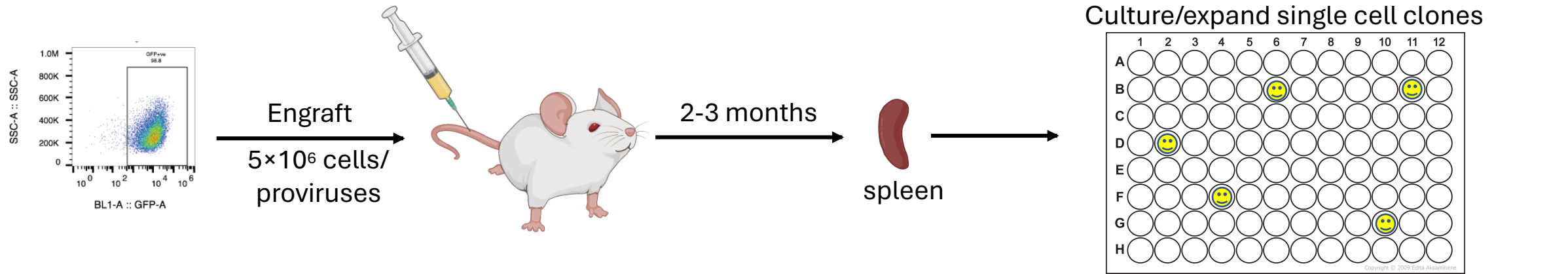
Activation mark (enhancer element)

H3K4me1

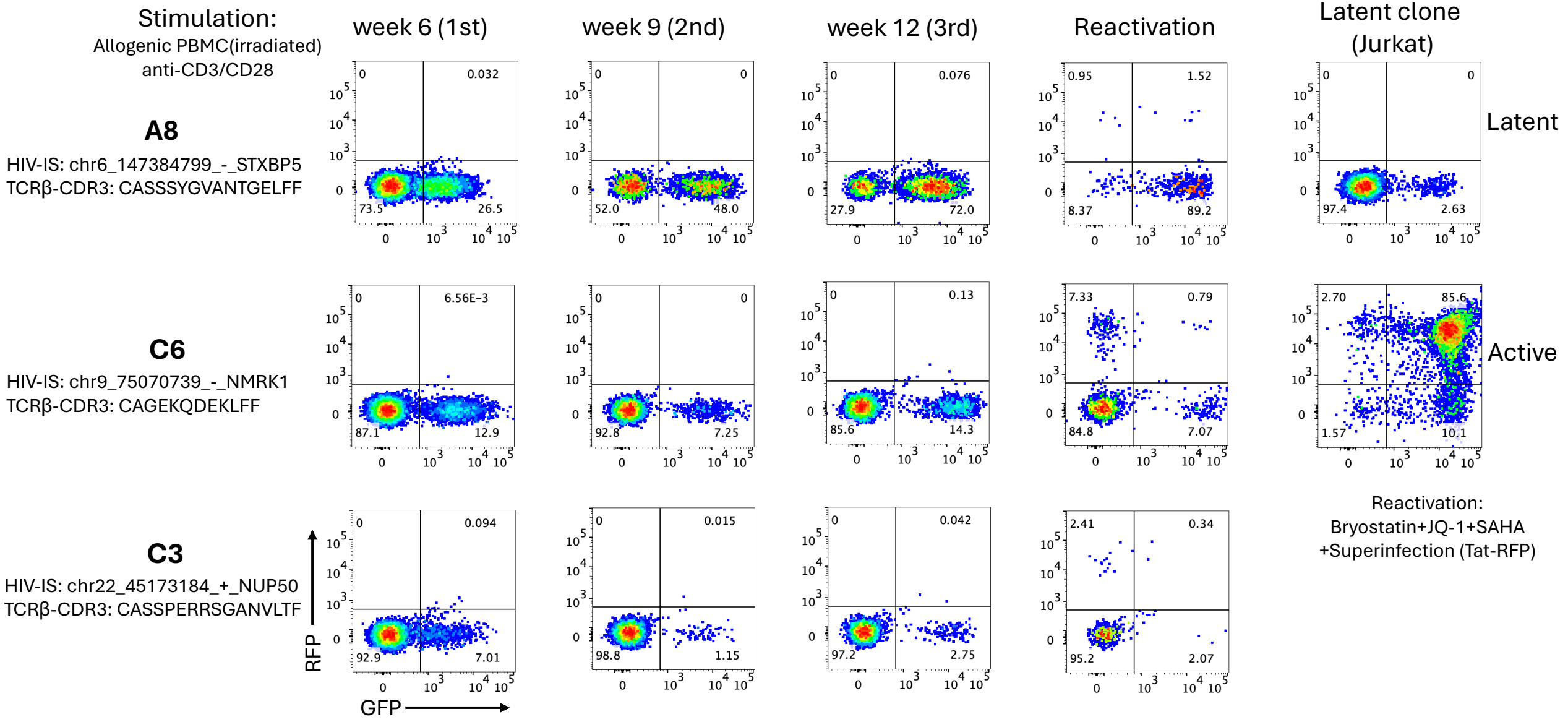


ENCODE project ChIP-seq dataset for primary memory CD4⁺ T cells

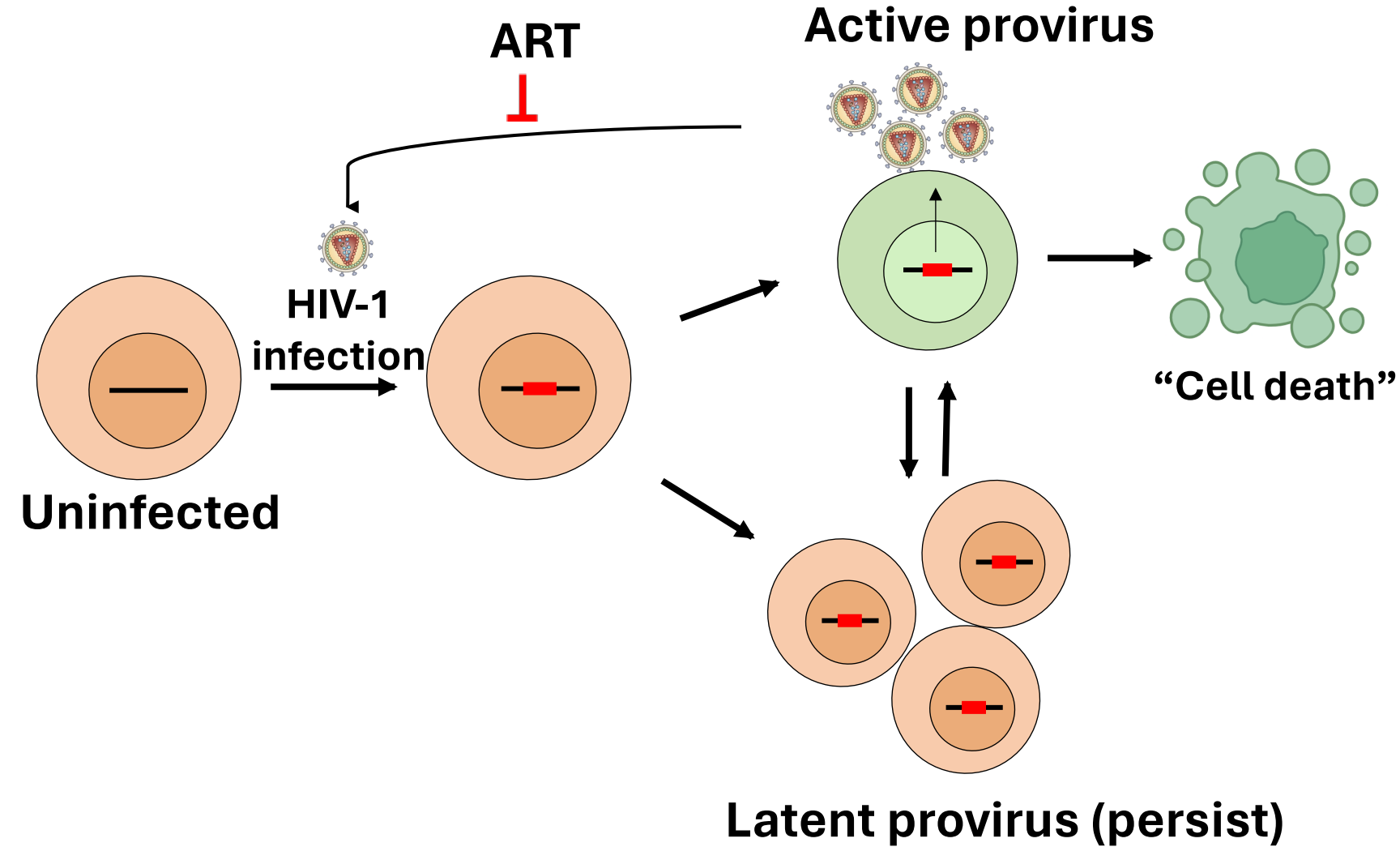
Memory CD4+ T-cell clones (mice) harboring single provirus



HIV-1 latent clones proviral transcriptional status and lack of response to LRA



Summary



1. HIV-1 integration does not drive cell survival/clonal expansion
2. Integration site is a key determinant of latency decision
3. Conventional LRA do not reactivate latent proviruses in memory CD4+ T-cells clones

Acknowledgements

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Collaborators

Heidelberg University, Germany

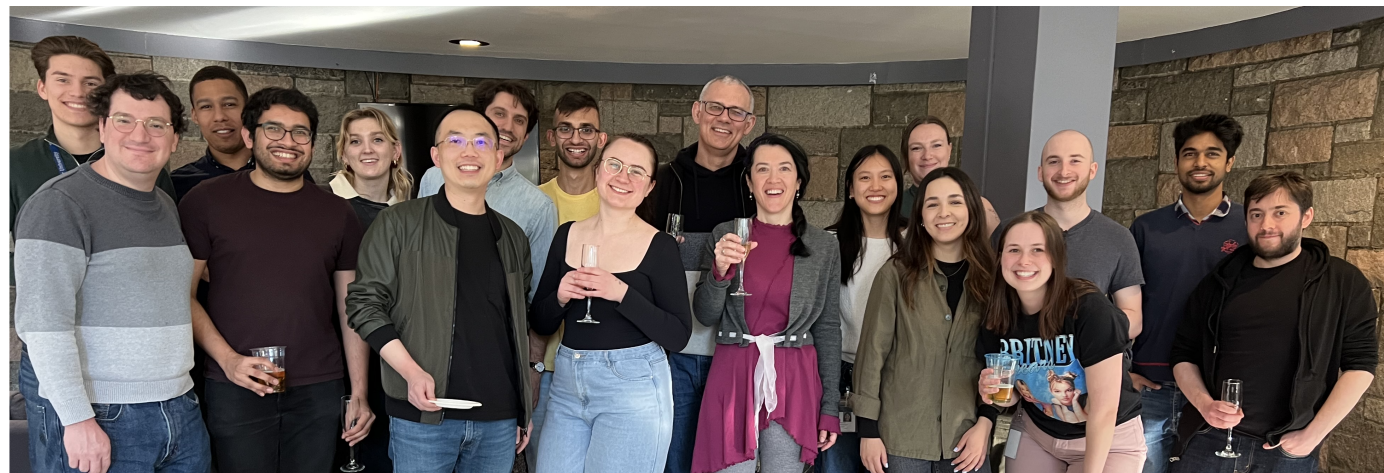
Frauke Muecksch

Weill Cornell Medicine, NY

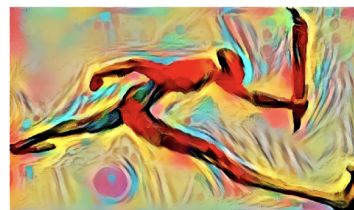
Brad Jones Guinevere Lee

Ali Danesh

Thinh Huynh



Research Enterprise to Advance a Cure for HIV



SCIENCE FOR THE BENEFIT OF HUMANITY

