OREGON HEALTH & SCIENCE UNIVERSITY

VGTI VACCINE & GENE THERAPY INSTITUTE

B Cell Follicle Sanctuary Permits Persistent Productive SIV Infection in Elite Controllers: Implications for HIV Cure Research

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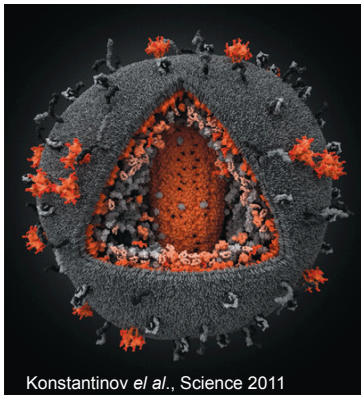
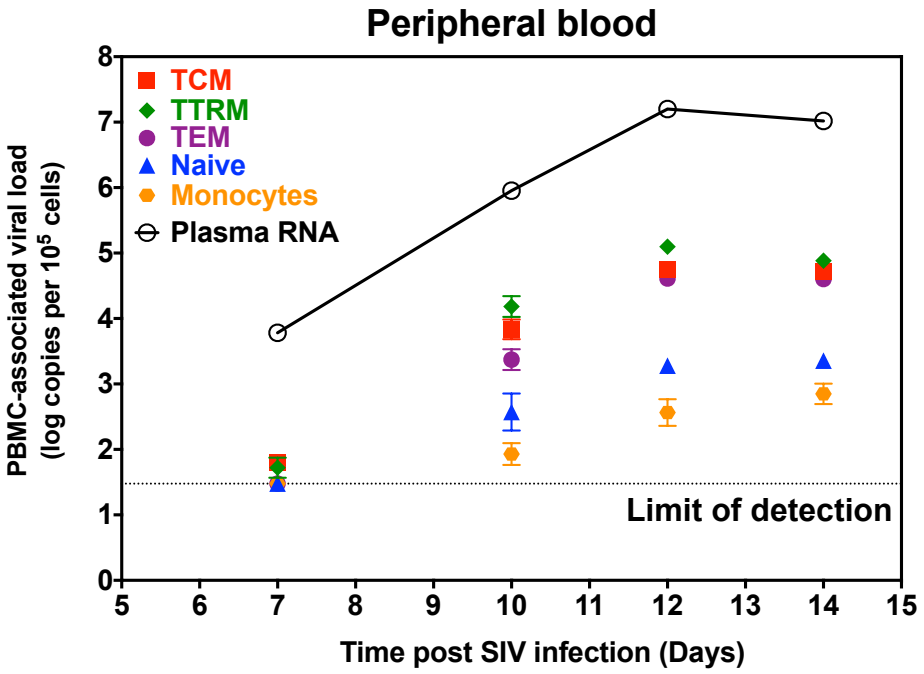
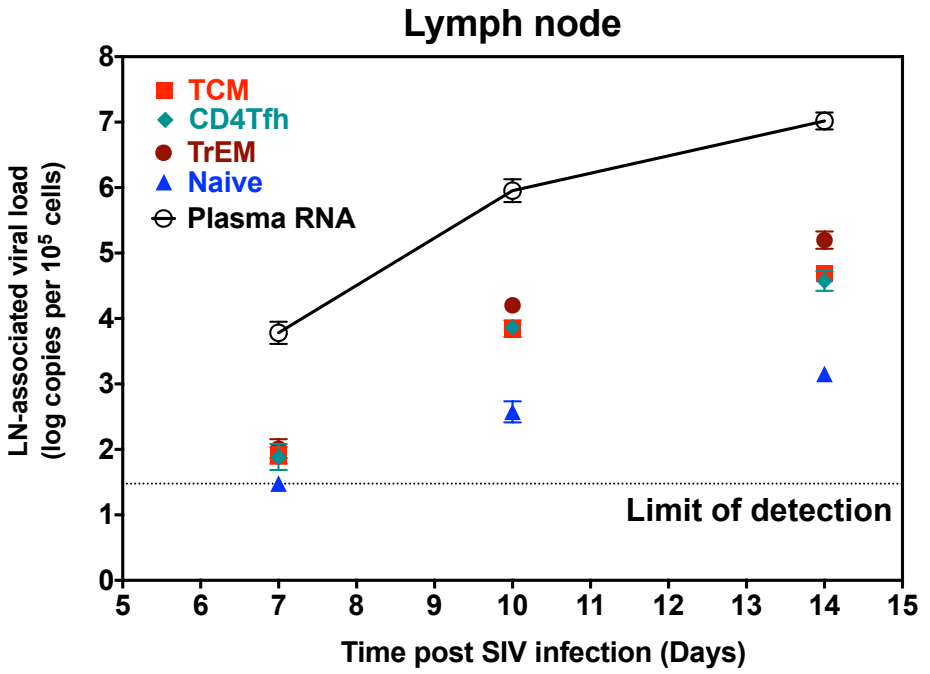


Konstantinov *el al*., Science 2011

The SIV reservoir is progressively seeded during early, acute SIV infection, preferentially in CD4+ memory T cells

Cell-associated SIV DNA in sorted lymphocyte subsets





TCM: CD4+ central memory
TTRM: CD4+ transitional memory
TEM: CD4+ effector memory
Tfh: CD4+ follicular helper T cells
TrEM: CD4+ transitional/effector memory

. . . Suggesting early cART initiation would result in a significantly diminished viral reservoir.

Indeed, early ART dramatically limits the peak and duration of viremia during acute SIV infection

The timing of ART initiation determines the level of cell-associated viral loads after 6 weeks of treatment

Delay in ART for one day during earliest stages (days 4 to 7) has durable effect

No virus detected in plasma, PBMC, or lymph node in monkeys treated on days 4/5 after several weeks of treatment

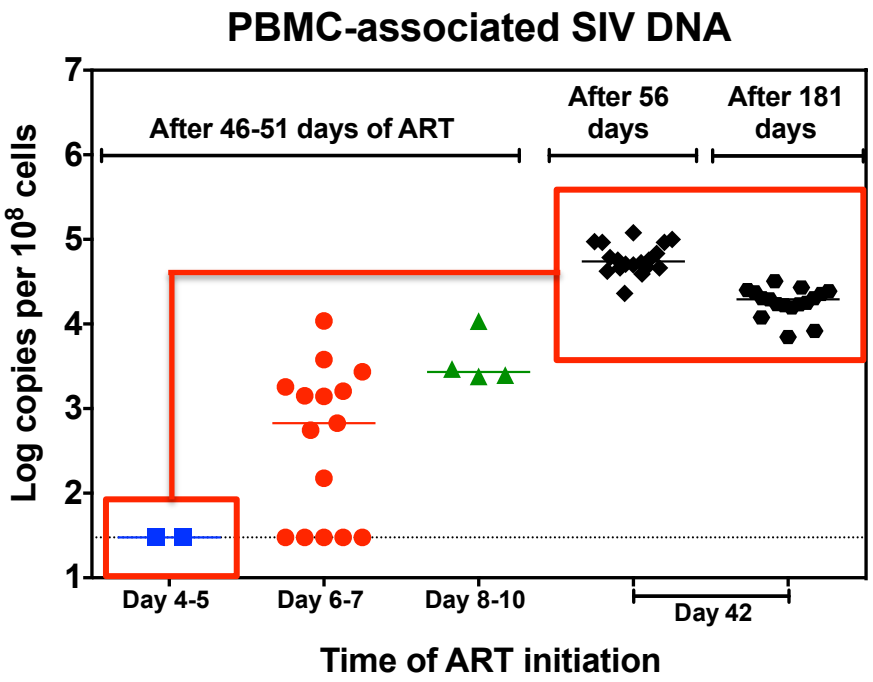
. . . profiles that are almost identical to that seen in earliest treated humans (Hatano/DARE)

However . . . the functional reservoir persists!

***30 million LN cells; copy Eq. cell-associated SIV DNA/RNA transferred:**

Rh24458: 1 (one!) copy DNA; no detectable RNA
Rh27380: 4 (four!) copies DNA; no detectable RNA

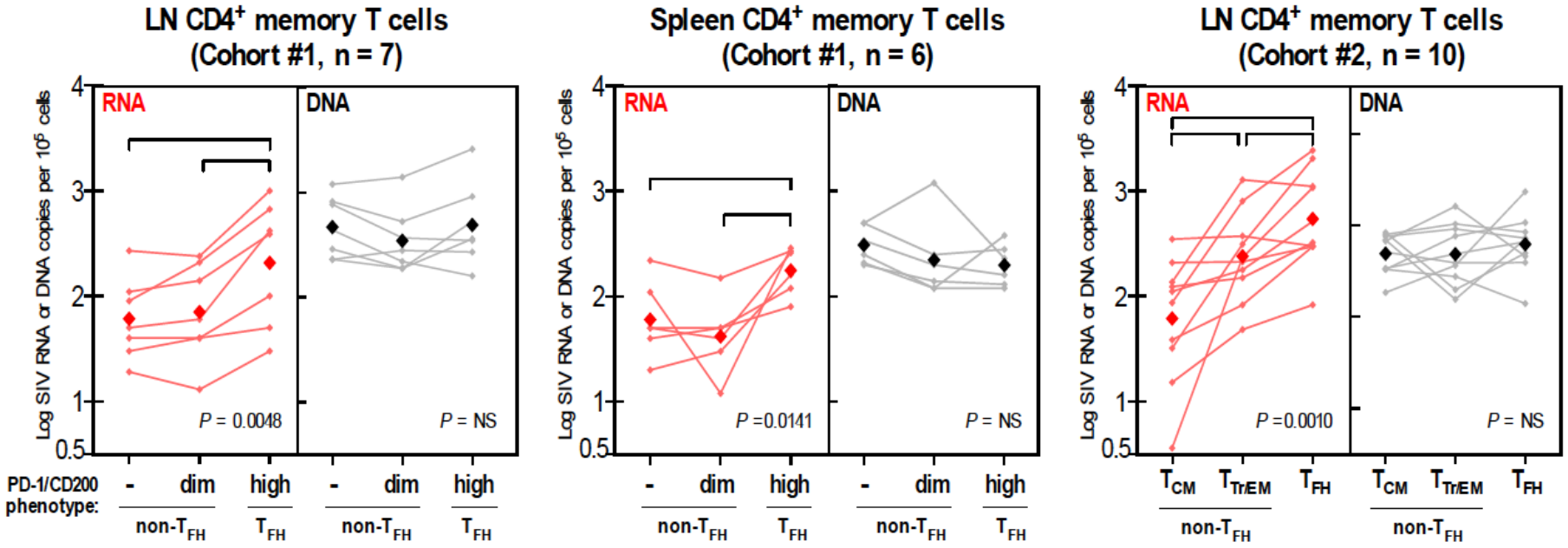
The reservoir is BIG and it may take only 1 cell with latent replication-competent virus to prevent cure!



An >3 log reduction in reservoir size had NO “clinical” impact!

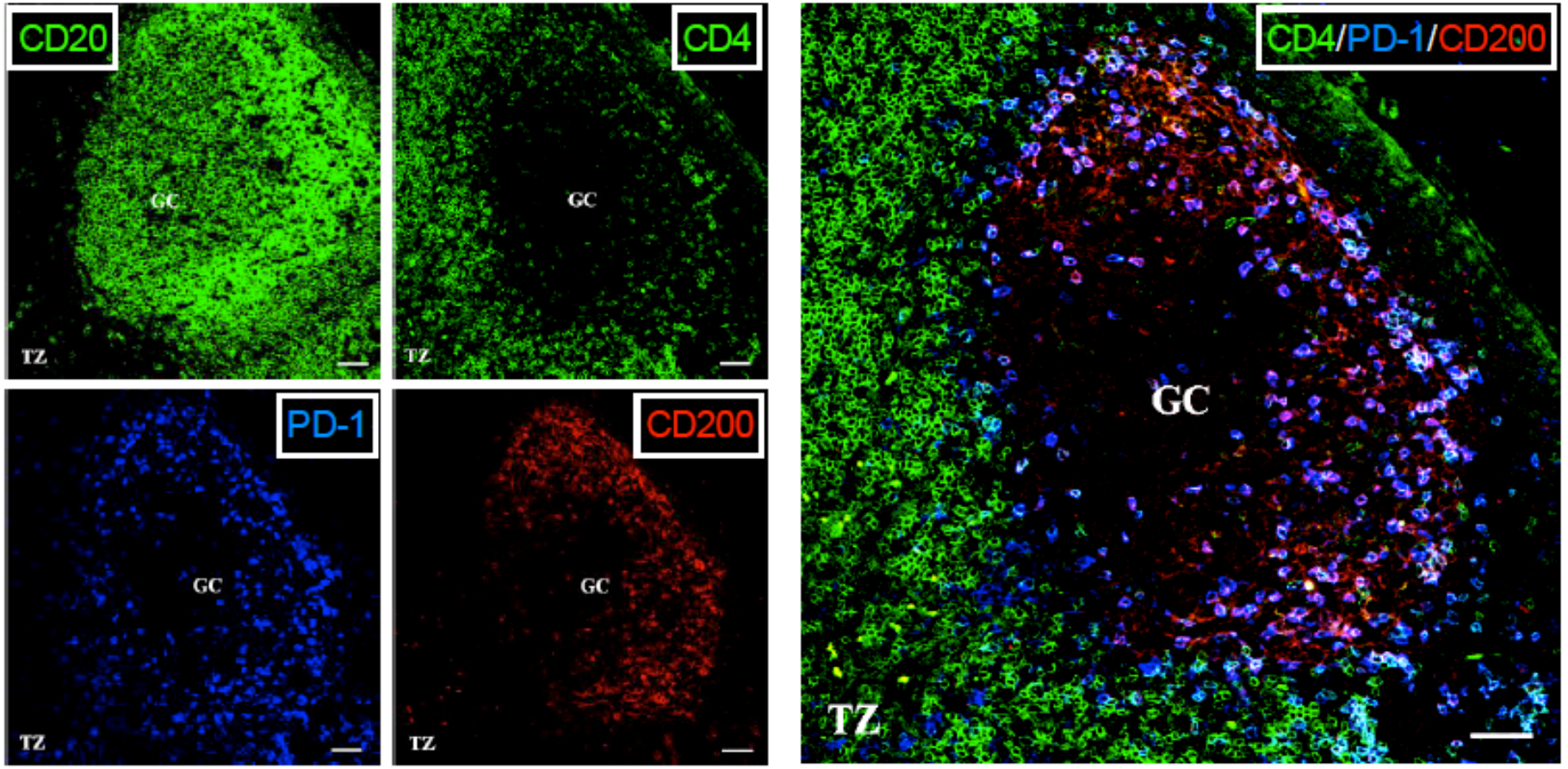
So what helps the virus persist?

In SIV+ monkeys on fully suppressive cART (pvl < 60 copies/ml), cell-associated SIV DNA is found at similar levels in both paracortical (non-T_{FH}) and follicular (T_{FH}) $CD4^+$ memory cells.



But median cell-associated SIV RNA levels are >5 fold higher in the small (~14%) $CD4^+$ T_{FH} subset

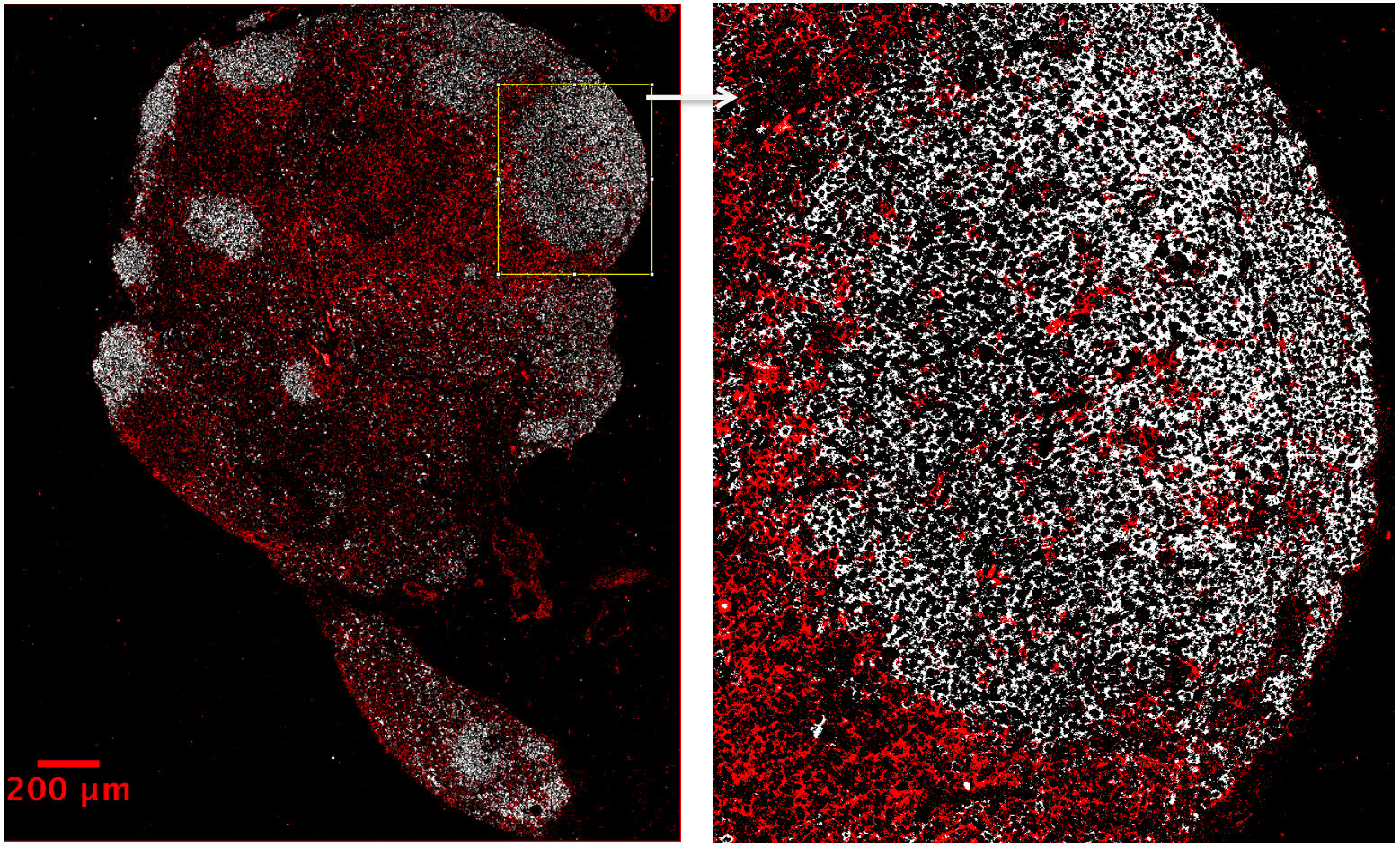
Localization of Follicular CD4+, PD-1+, CD200+ T_{FH} is restricted to B cell follicles



So why is this "bad" from a cure perspective

Most CD8$^+$ effector T cells lack the appropriate chemokine receptors for B cell follicle entry and therefore are largely excluded from B cell follicles

CD20 (white) and CD8$^+$ (red) staining of axillary lymph node



nature medicine

B cell follicle sanctuary permits persistent productive simian immunodeficiency virus infection in elite controllers

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PROGRESSOR

PVL > 85,000

SEMI-CONTROLLER

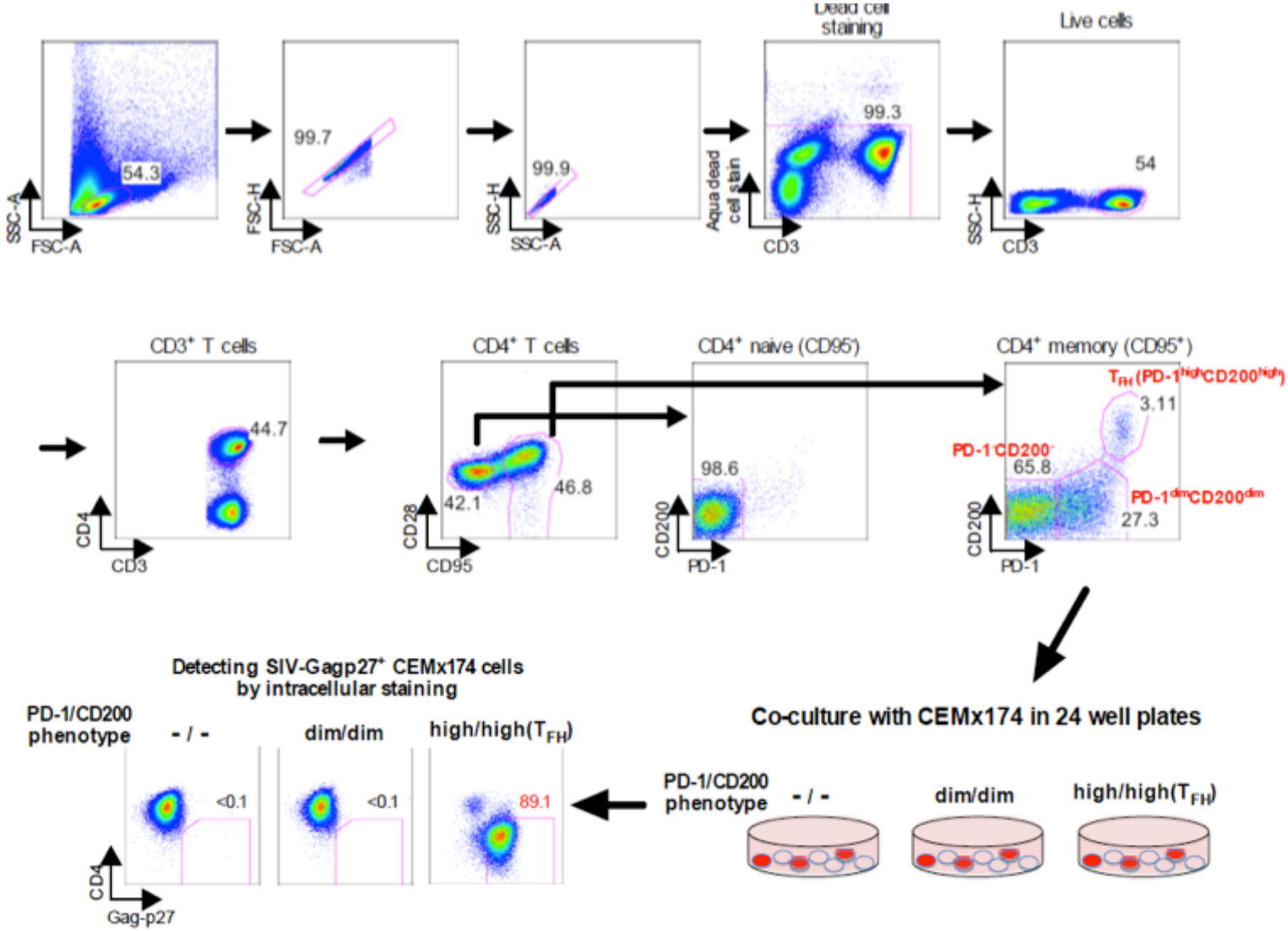
1,900< PVL< 35,000

ELITE CONTROLLER

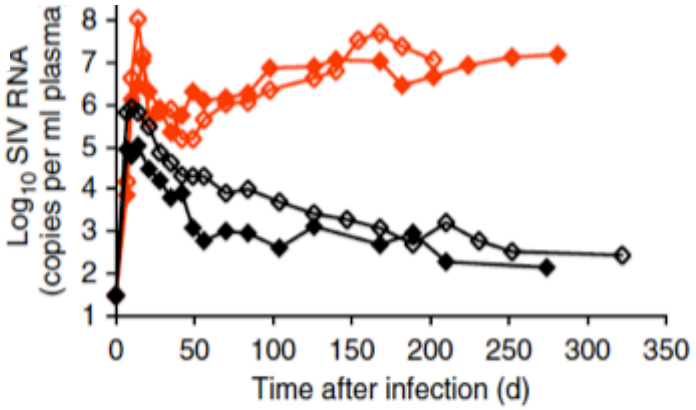
PVL< 600

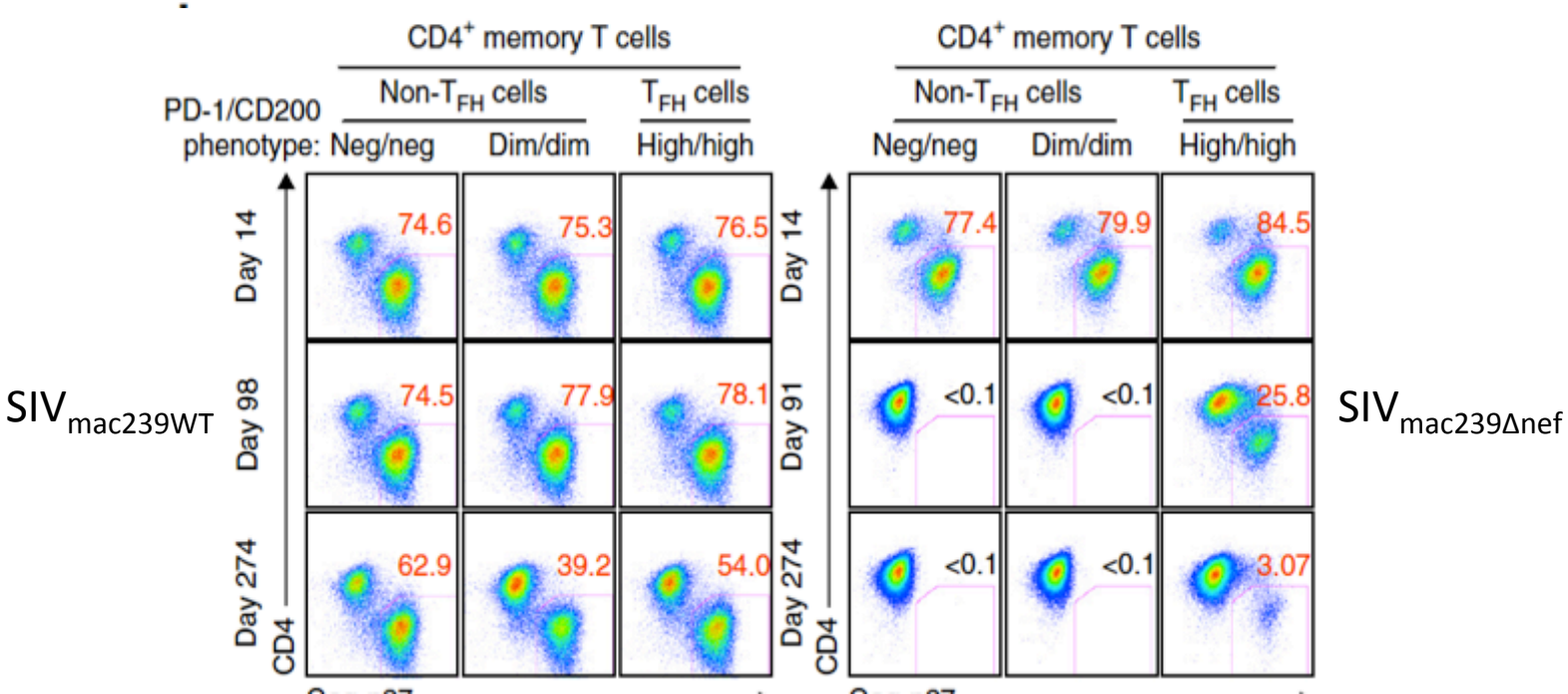
Hypothesis: Host/Immune control of WT virus results in progressive restriction of virus to B cell follicle CD4+ T_{FH}

Coculture Assay for Replication Competent LN/Spleen CD4+ Memory T cell Subsets



Immune control of LAV Associated with Progressive Restriction of Virus to PD-1+, CD200+, CD4+ GC T_{FH}

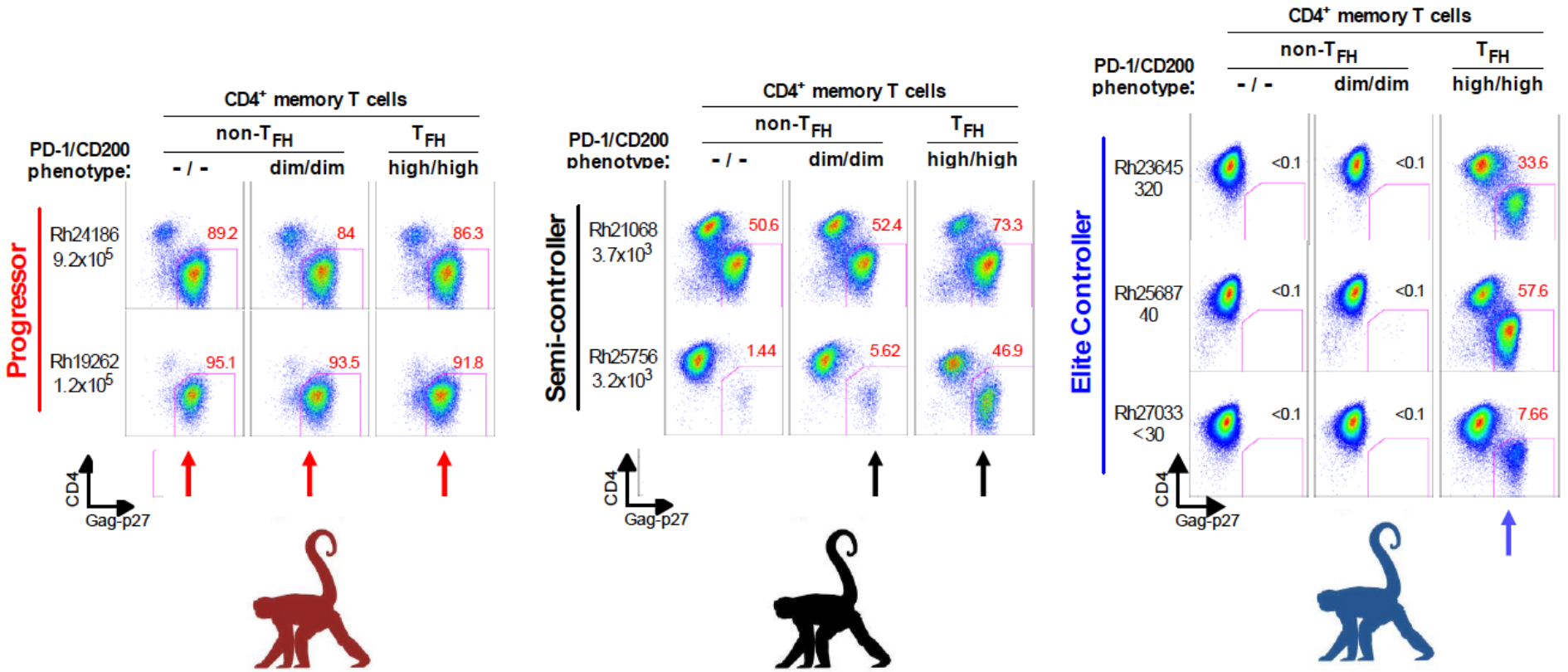




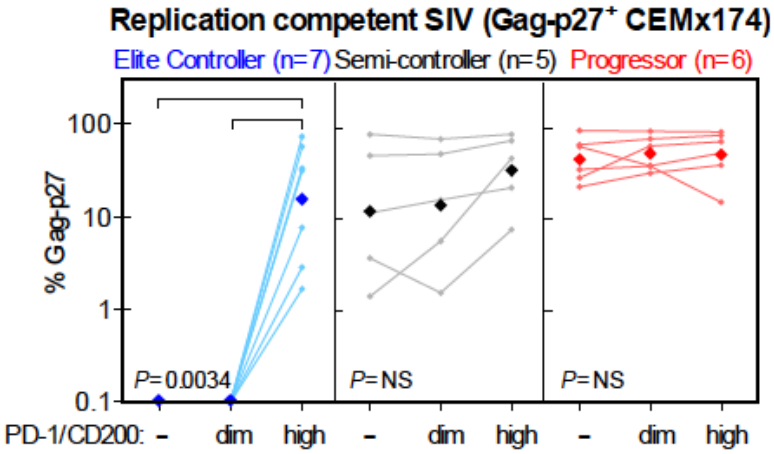
SIVmac239WT

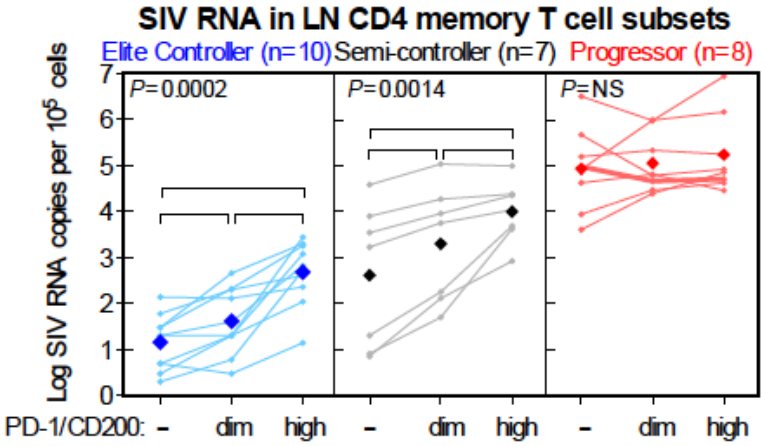
SIVmac239Δnef

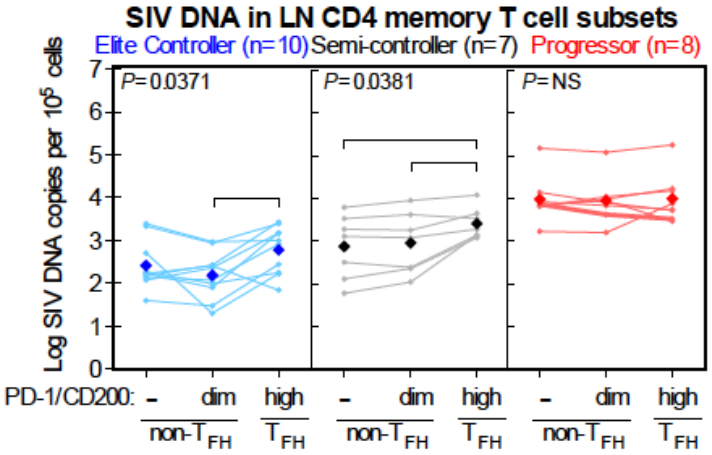
Productive SIV infection becomes increasing restricted to intrafollicular CD4+ T cells (T_{FH}) with higher levels of immune (CD8+ T cell-mediated) control.



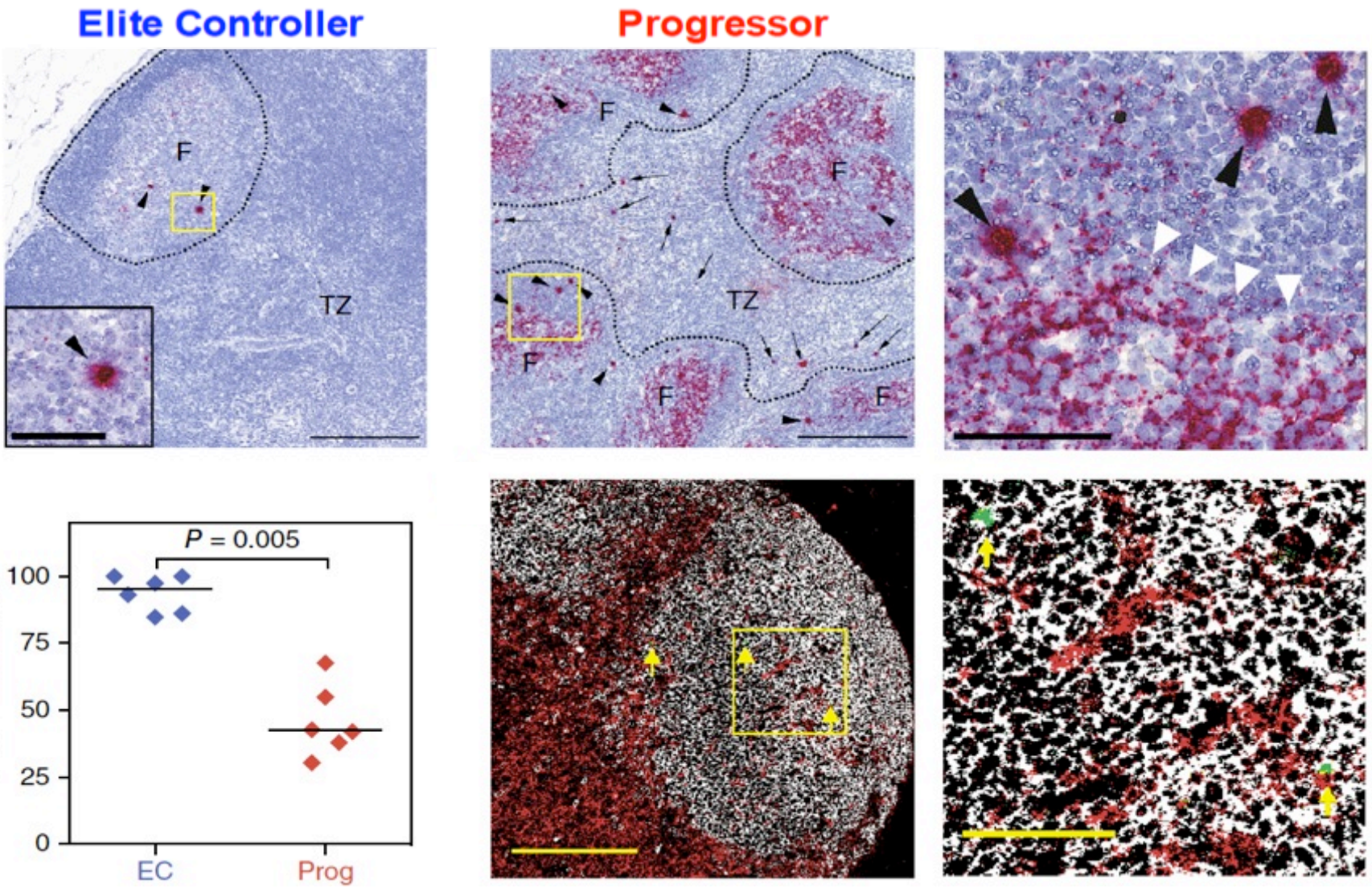
Immune control of SIV is Associated with Restriction of Virus (Replication competent, vRNA, vDNA) to PD-1+, CD200+, CD4+ T_{FH}



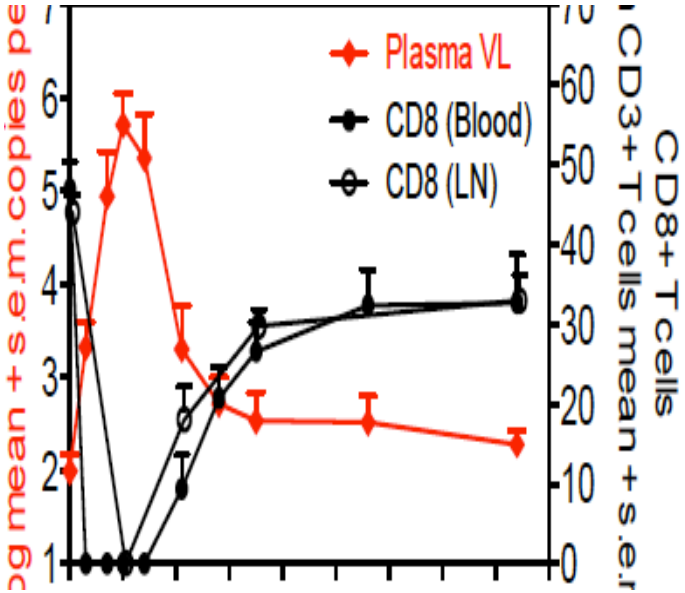


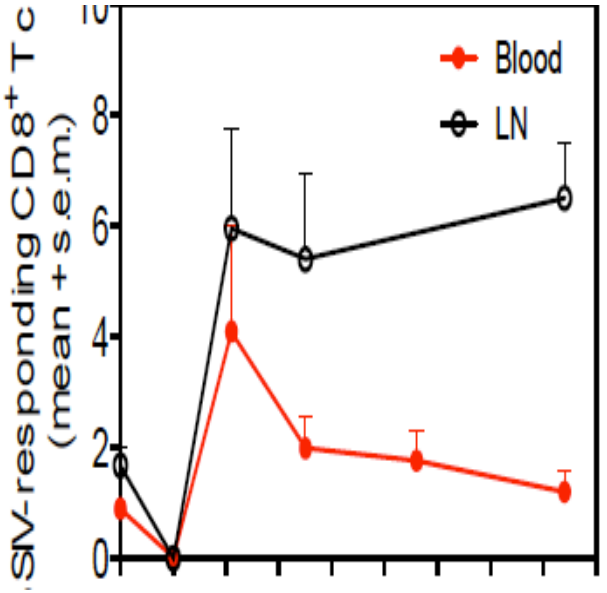


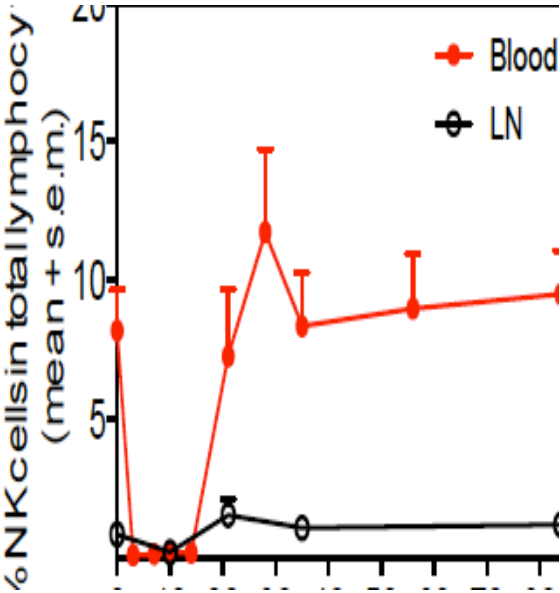
Anatomical Restriction of Virus to GC with Immune Control



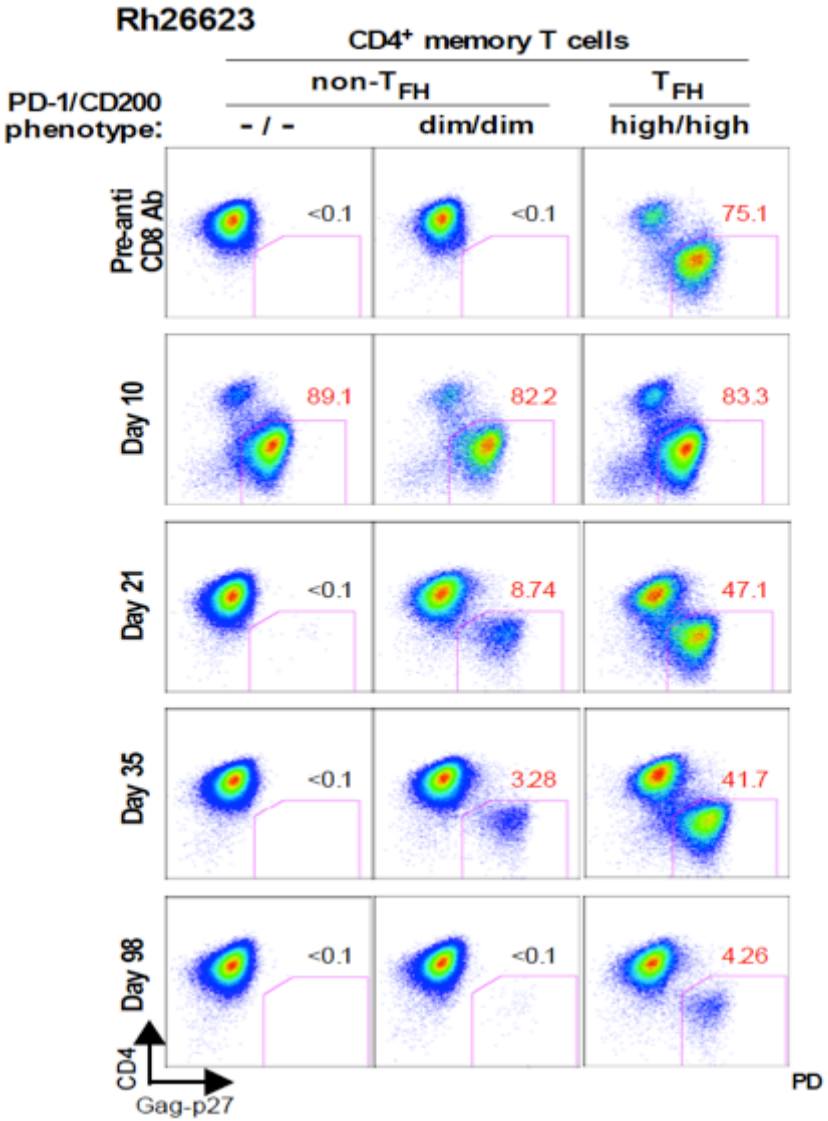
Depletion of CD8+ T cells and NK cells with Anti-CD8 mAb



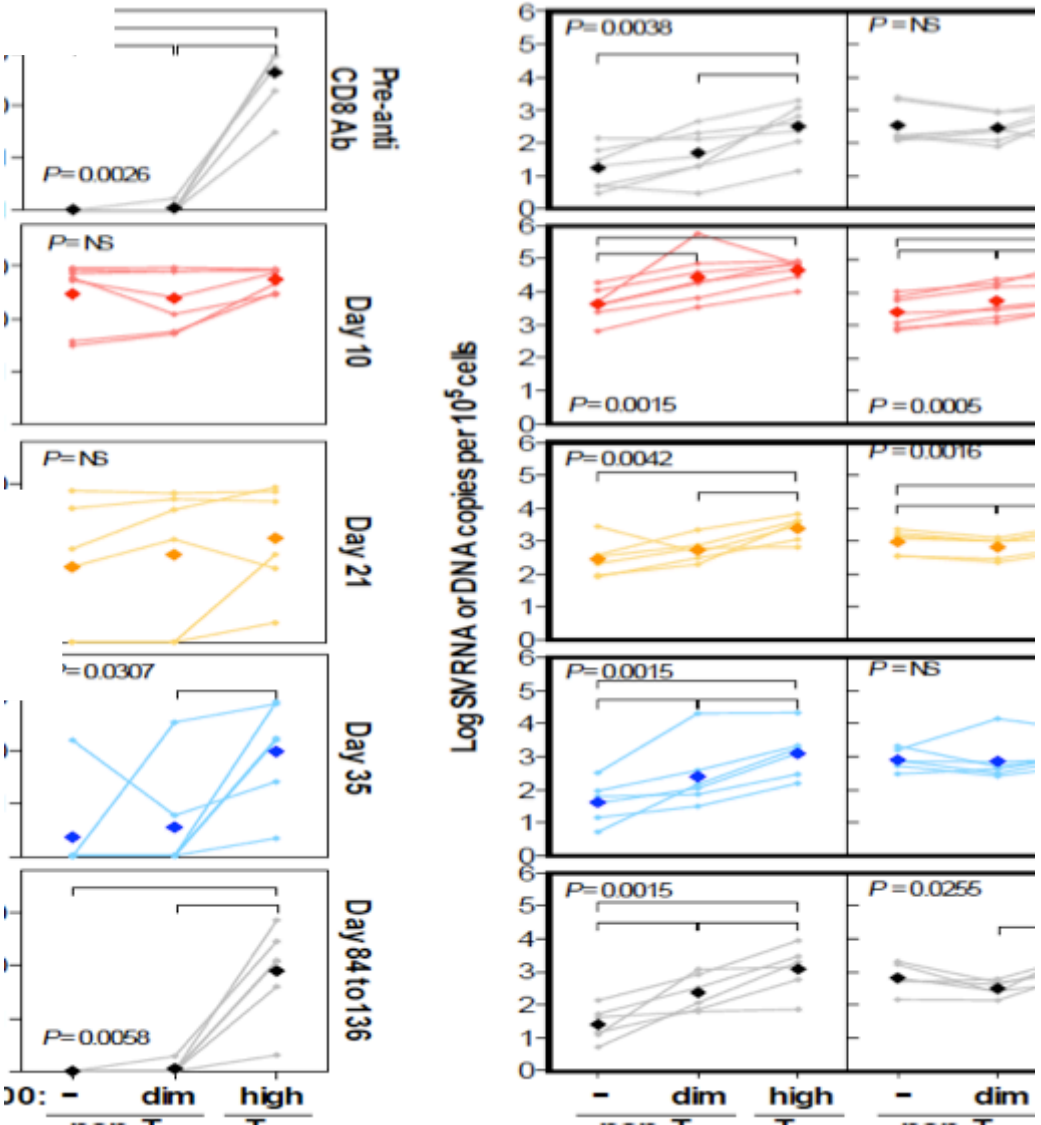




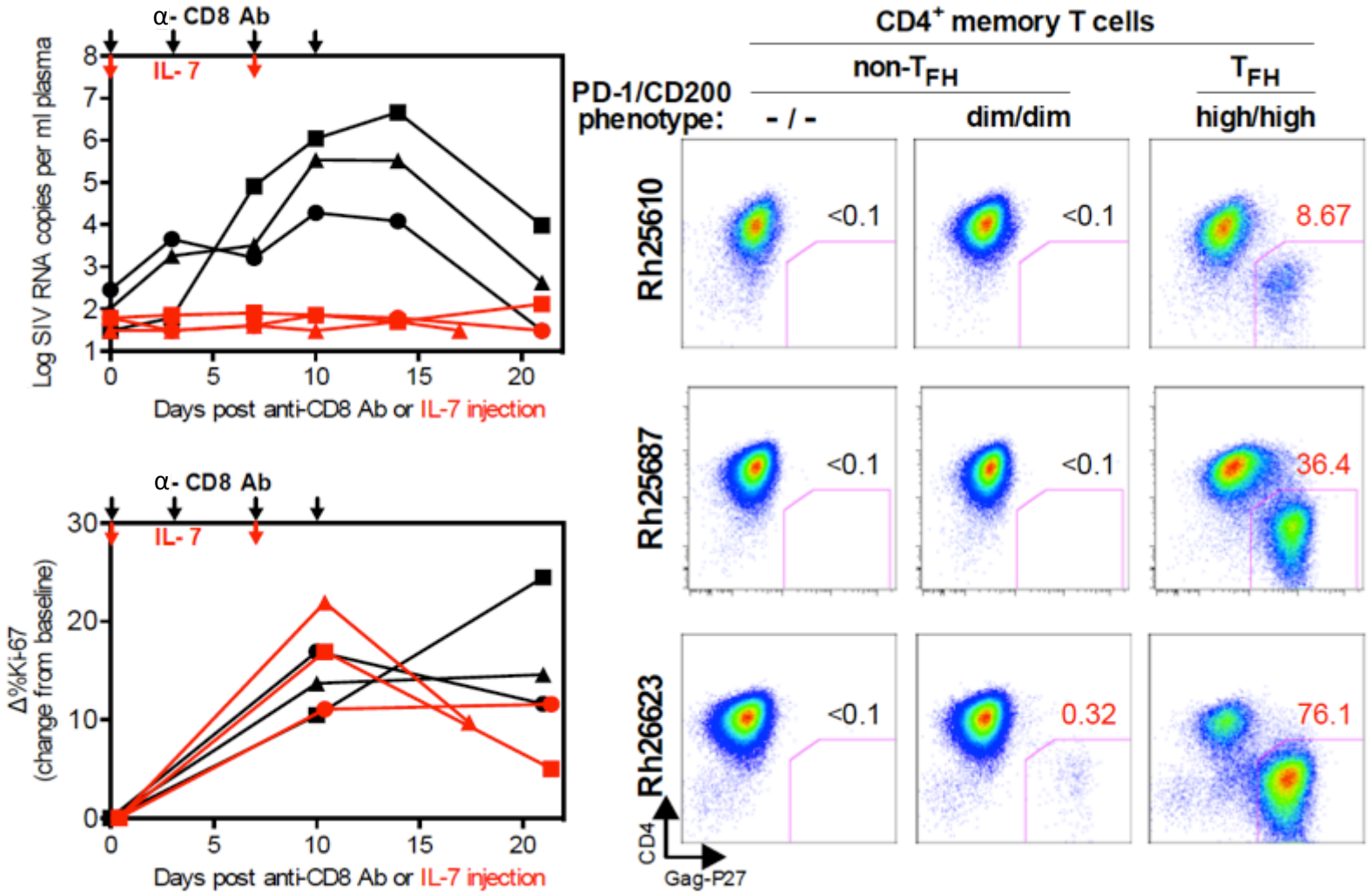
Transient CD8-Depletion Associated with Transient Expansion of Virus Beyond CD4+, PD-1+, CD200+ T_{FH}



Transient CD8-Depletion Associated with Transient Expansion of Virus Expression Beyond CD4+, PD-1+, CD200+ T_{FH}



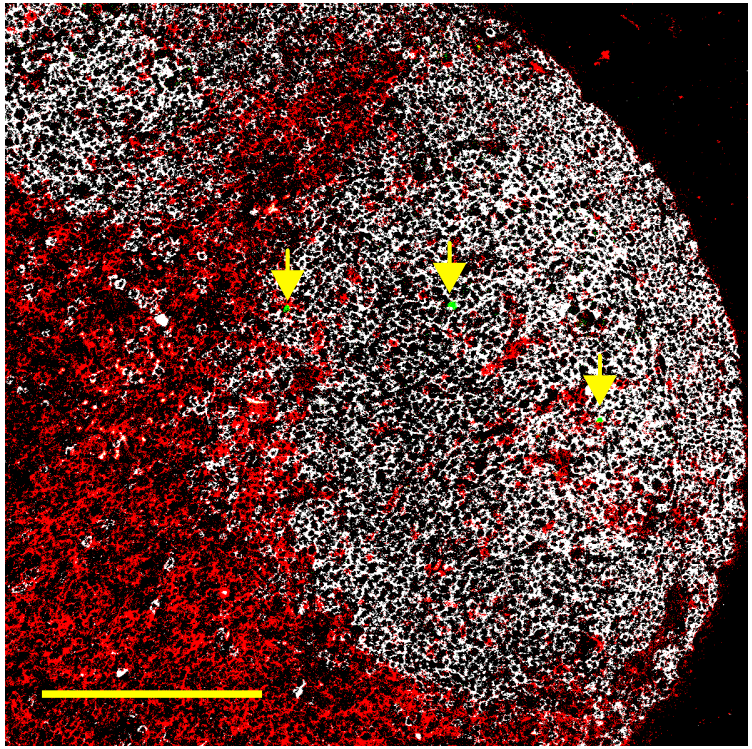
Virus Expansion with Transient CD8-Depletion is Due to Loss of CD8+ T Cell Control Not Proliferative Responses



Summary

- Under conditions of host restriction (EC, cART), virus is progressively restricted to B cell follicle CD4+ T_{FH}.
- Failure to clear likely due to lack of efficient trafficking of antiviral CD8+ T cells to follicles.
- Suggests B cell follicles are a source for residual viral replication, maintenance of immune responses; potential source of residual immune activation, viral evolution/escape.
- Barrier to complete viral clearance/cure.

As B cell follicles exclude most CD8+ T cells, compromising anti-viral effector responses therein, it creates a sanctuary for productive SIV infection of intrafollicular CD4+ T_{FH}



The finding that in monkeys with cART-suppressed infection, that residual SIV replication and/or reactivation preferentially occurs within this sanctuary suggest that efforts to use CD8+ T cell responses to purge reservoirs after latency induction will be hampered, if not completely stymied, by this SANCTUARY!

Two on-going studies will ask whether, and to what extent, RhCMV/ SIV vectors will be able to clear or control cART-suppressed SIV infections when used as a therapeutic vaccine.

cART cessation planned for mid-2015

Delaney AIDS Research Enterprise
DARE
to find a cure

GILEAD
Advancing Therapeutics.
Improving Lives.

BILL & MEL
GATES

"I believe HIV cure is achievable, but not with a single 'Magic Bullet' modality (even CMV vectors). Rather, cure will require a multi-modal therapeutic approach to 1) stop viral spread, 2) induce latent virus reactivation, 3) surmount 'sanctuaries', and 4) kill (likely all) viral Ag+ cells, which must be based on a fundamental understanding of virology and immunobiology of cART-suppressed infections"… **Louis J. Picker, M.D.**

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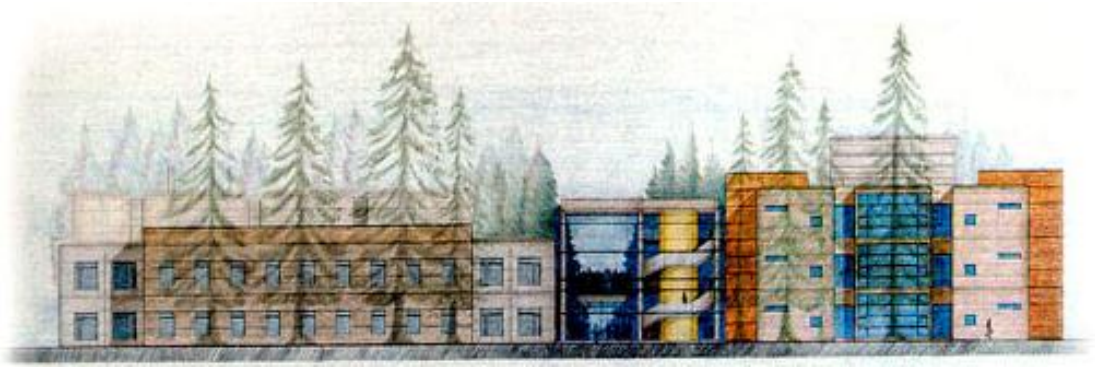

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