Oral Abstract Session 4

OA4-1

The immune checkpoint blockers PD-1, LAG-3 and TIGIT are biomarkers of HIV infected cells during ART and identify distinct cellular reservoirs

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Background: The persistence of HIV in a small pool of long-lived latently infected resting CD4+ T cells is a major barrier to viral eradication. Identifying cellular markers that are preferentially expressed at the surface of latently infected cells may lead to novel therapeutic strategies to cure HIV infection. We have previously shown that HIV primarily persists in central (TCM), transitional (TTM) and effector memory (TEM) CD4+ T cells and that the levels of expression of the immune checkpoint blockers (ICBs) PD-1, LAG-3 and TIGIT are associated with HIV persistence during ART. We hypothesize that these markers identify memory CD4+ T cells highly enriched in latent HIV by continuously promoting HIV latency in infected CD4+ T cells.

Methods: 20 subjects on ART for >3 years with HIV viral load < 50 cop./mL and with CD4 count >350 cells/μL enrolled in the study. We measured integrated HIV DNA in sorted memory CD4+ T cell subsets expressing PD-1, LAG-3, TIGIT or co-expressing the 3 receptors. Wilcoxon test was performed to compare the frequencies of cells harboring integrated HIV DNA in the ICBs expressing cells with their negative counterpart.

Results: PD-1 identified TCM and TTM cells enriched for integrated HIV DNA (p=0.019, p=0.004 respectively). Latently infected TEM cells tended to express TIGIT (p=0.078), but did not differ from uninfected cells in PD-1 expression. LAG-3 identified latently infected memory CD4+ T cells independently of their differentiation fate (p=0.002 for the combined memory subsets). Importantly, CD4+ T cells co-expressing PD-1, LAG-3 and TIGIT were highly enriched for integrated HIV DNA when compared to unsorted CD4+ T cells (4-10 fold increase).

Conclusions: Our data demonstrate that PD-1, LAG-3 and TIGIT identify cells carrying integrated HIV DNA in virally suppressed subjects. Our results further suggest that PD-1, LAG-3 and TIGIT specifically contribute to viral persistence during ART in distinct memory CD4+ T cell subsets. Novel curative strategies interfering with ICBs pathway may be differentially beneficial to ART treated subjects depending on the localization of their HIV reservoir.

2014 â€œTowards an HIV Cureâ€ symposium Melbourne The Immune Checkpoints PD-1, LAG-3 and TIGIT are Biomarkers of HIV Infected Cells During ART and Identify Distinct Cellular Reservoirs Remi Fromentin, Wendy Bakeman, Mariam B Lawani, Gabriela Khoury, Elizabeth Sinclair, Frederick M. Hecht, Steven G. Deeks, Sharon R. Lewin, Jean-Pierre Routy, Rafick P. Sékaly, Nicolas Chomont Biomarkers of latently infected.Â PD-1-LAG-3 identifies TCM and TTM CD4 T cells enriched in integrated HIV DNA A B LAG-3 expression in CD4 T cell subsets TCM TTM 1000 100 10000 Integrated HIV DNA (cop/106 cells) Integrated HIV DNA (cop/106 cells) 20 p=0.156 10000 10000 40 TEM p=0.047 p=0.031 60 Integrated HIV DNA.