



Anti-PD-1 disrupts HIV latency in non-proliferating but not in proliferating T-cells

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N, Cameron PU and Lewin SR



Conflicts of interest

- Investigator initiated industry funded studies from
 - Viiv Healthcare
 - Gilead Sciences
 - Merck
 - Tetralogic
- Participation in educational activities or consultancies (paid to my institution) from
 - Viiv Healthcare
 - Gilead Sciences
 - Merck
 - Calimmune



Background



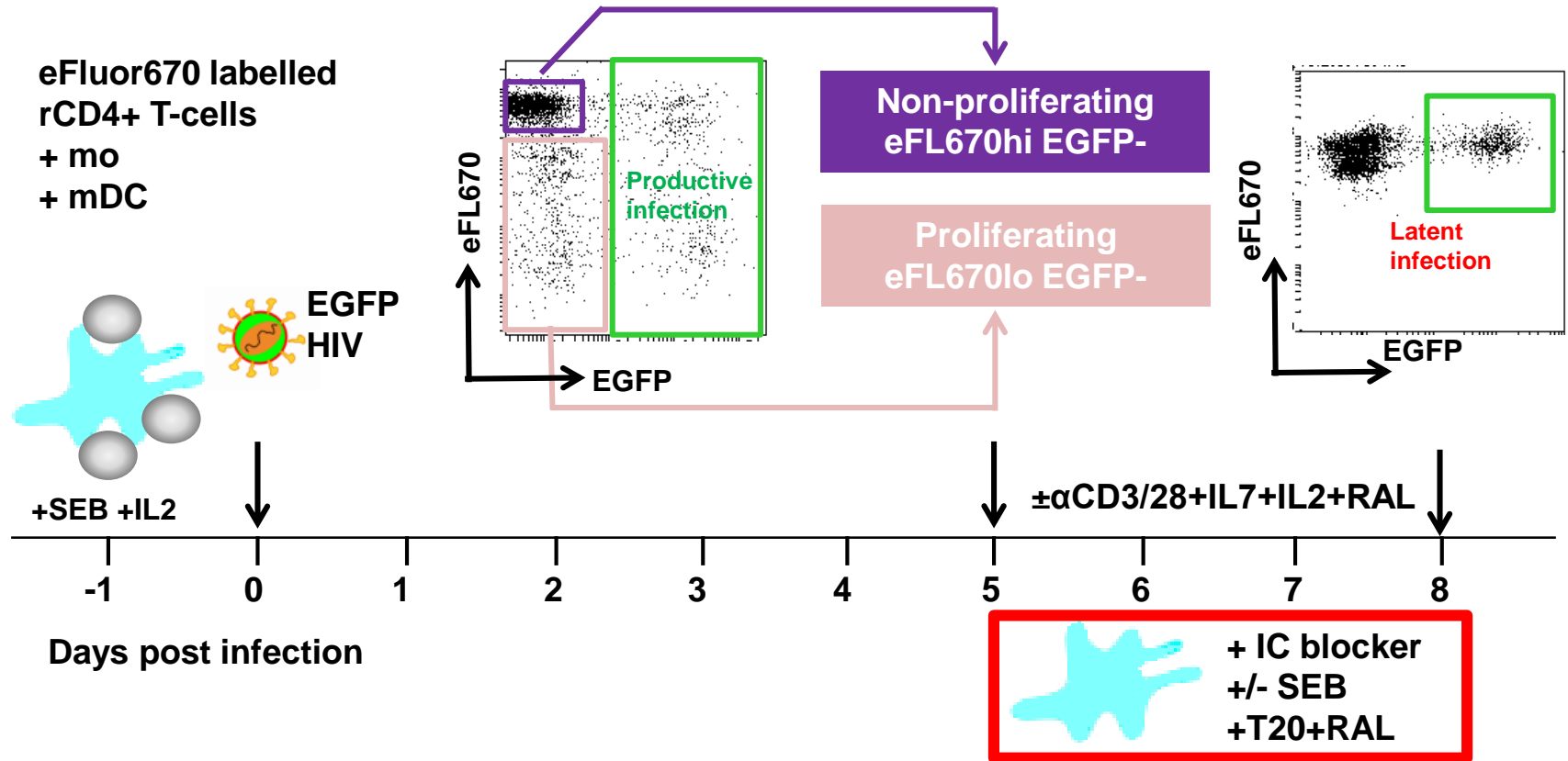
- In HIV-infected individuals on ART, HIV is enriched in PD-1^{hi} cells and cells that express multiple immune checkpoint markers ^{1,2}
- Anti-CTLA-4 (ipilimumab) increased cell associated unspliced HIV RNA in vivo, consistent with latency reversal ³
- The combination of anti-PD-1 and anti-CTLA-4 has enhanced potency in the management of metastatic melanoma ⁴

Could combination immune check point blockade be used to reverse latency and enhance HIV-specific T-cell function as a strategy for cure?

1 Chomont, Nat Med 2010; 2 Fromentin, PLoS Path 2016; Wightman, AIDS 2014; Postow, N Engl J Med 2015



In vitro model for HIV latency

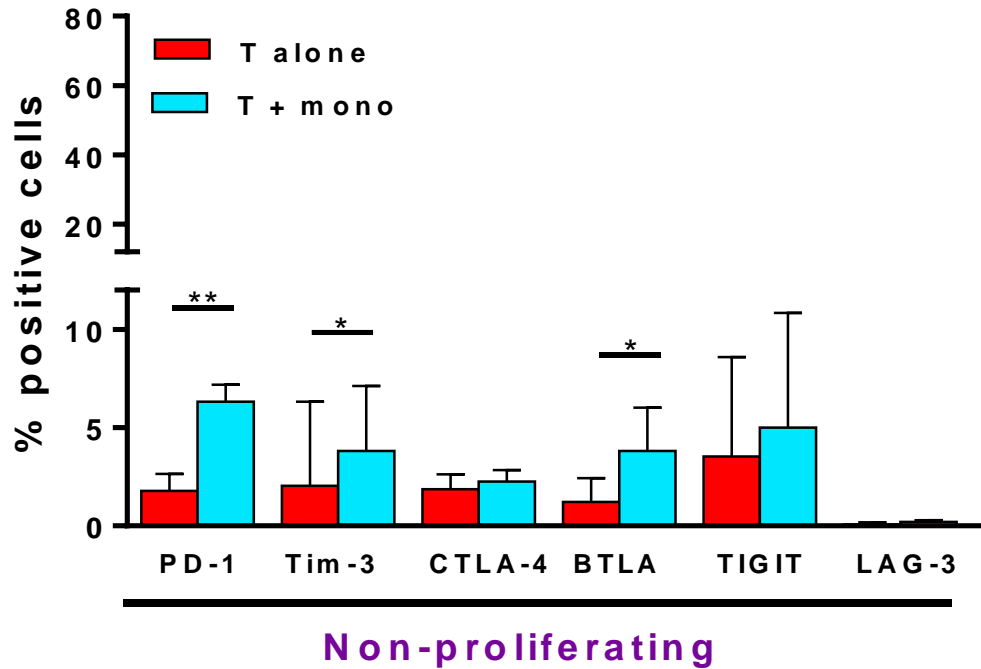


rCD4+ T-cells = resting CD4+ T-cells; SEB = Staphylococcal Enterotoxin B
mo=monocytes; mDC=myeloid DC
IC = immune checkpoint; RAL = raltegravir

Evans et al., Plos Path 2013; Kumar et al., Retrovirology 2016



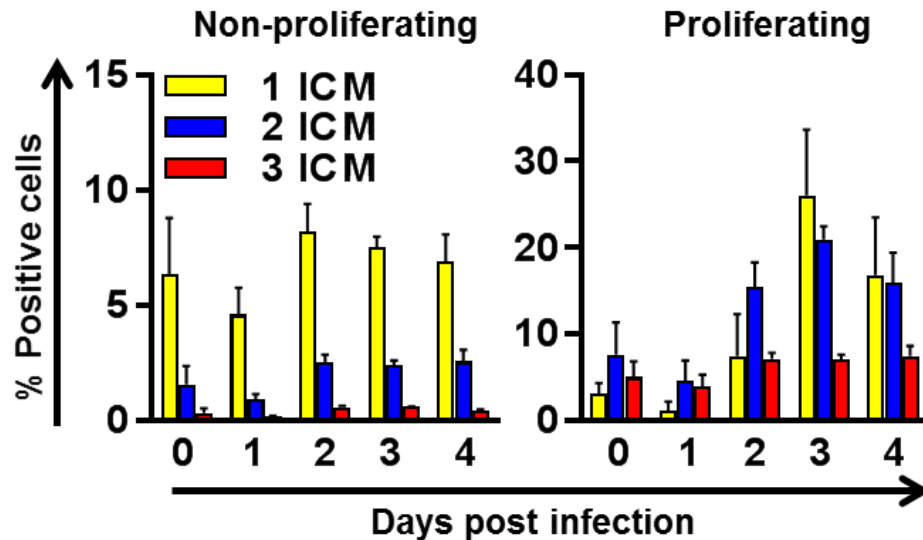
Immune checkpoint markers are expressed at high levels in proliferating T-cells following co-culture with monocytes



* p < 0.05, ** p < 0.01



Proliferating T-cells co-express multiple immune checkpoint markers



1 ICM
2 ICM
3 ICM

Non-proliferating



7.42%
2.36%
0.53%
89.69%

Proliferating

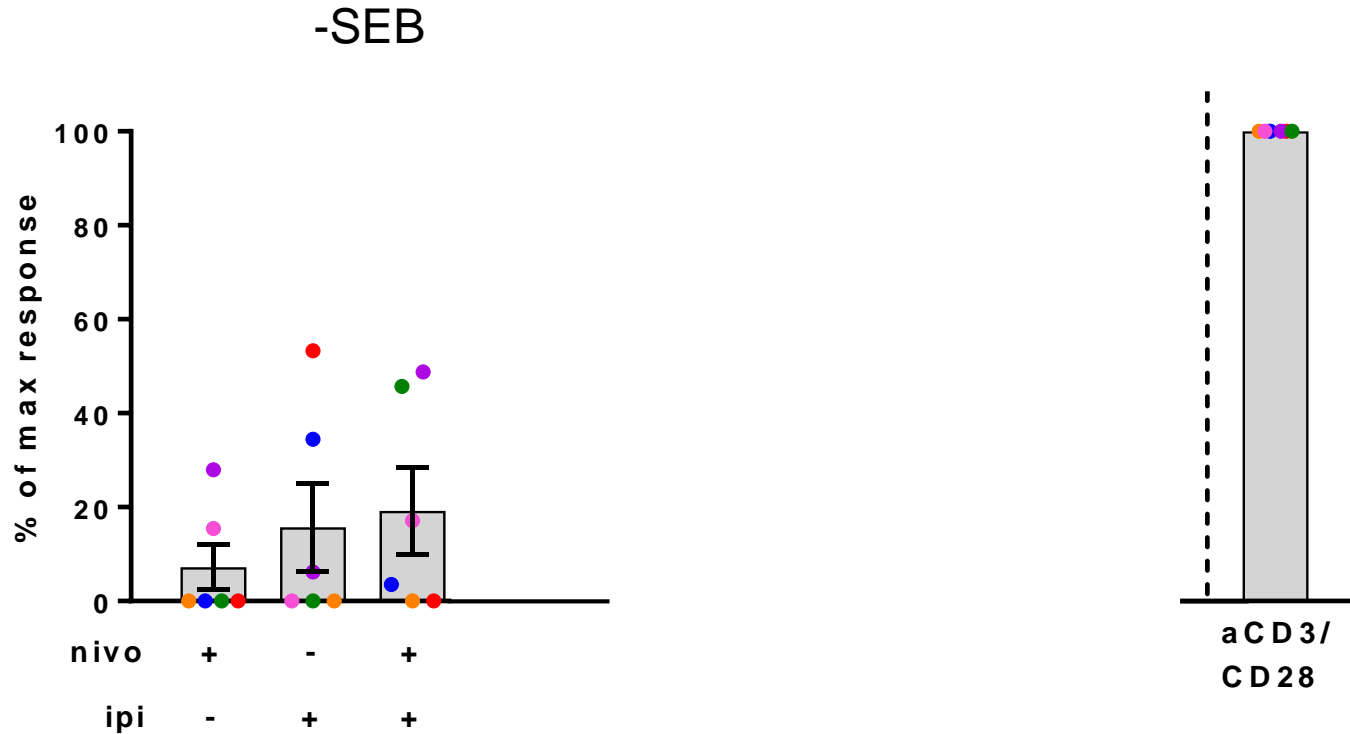


10.21%
18.88%
8.60%
62.31%

ICM = PD1+Tim3+TIGIT



Latency reversal in non-proliferating cells is possible in the presence of SEB or with multiple IC blockers

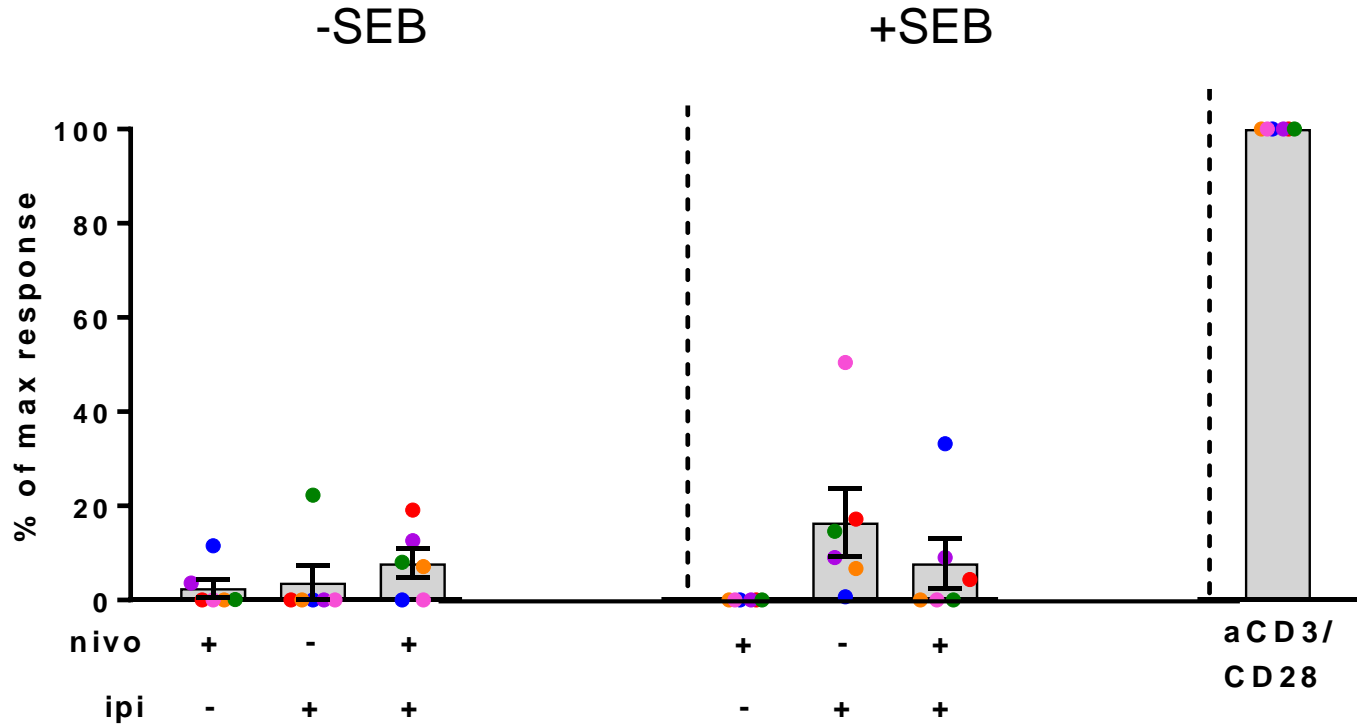


* $p < 0.05$, ** $p < 0.01$, student t test, ICB compared to isotype ctrl

N = 6, black lines are mean values \pm SEM



Proliferating cells: latency reversal is only possible with multiple IC blockers



* p<0.05, ** p<0.01, student t test, ICB compared to isotype ctrl

N = 6, black lines are mean values ± SEM

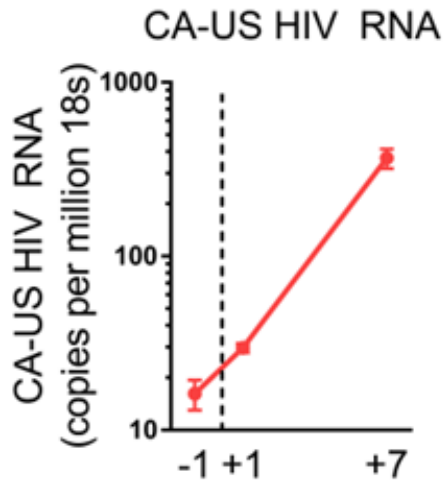
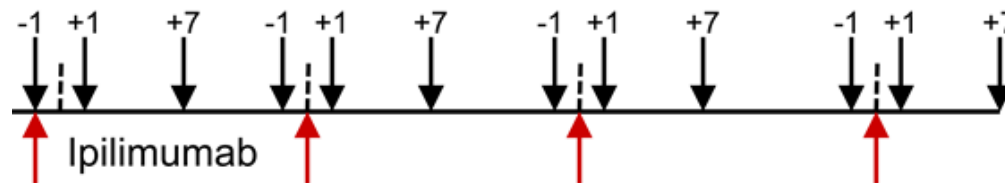


Anti-PD-1 (nivolumab) reverses HIV latency in vivo



Metastatic melanoma
HIV RNA < 20
CD4= 620 cells/ul
On ART for 8 years

cART





Summary

- Anti-PD-1 can reverse latency in vivo and in vitro but the effects differed in **proliferating** and **non-proliferating** latently infected cells
- In vitro, latency reversal with anti-PD-1 was only seen with the addition of
 - T-cell activation (SEB) or
 - Combination immune checkpoint blockade
- Co-expression of IC markers, especially on **proliferating** latently infected cells, may limit the potency of using anti-PD-1 alone for latency reversal
- Anti-PD-1 alone and in **combination with other ICBs**, should be further explored in clinical trials as a strategy to reverse latency



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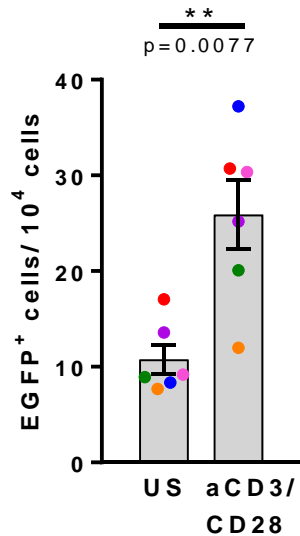
Bristol Myers Squibb

Alan Korman





Non-proliferating cells: latency reversal is possible with anti-PD1 in the presence of SEB



US = unstimulated;

* p<0.05, ** p<0.01, student t test

N = 6, black lines are mean values ± SEM