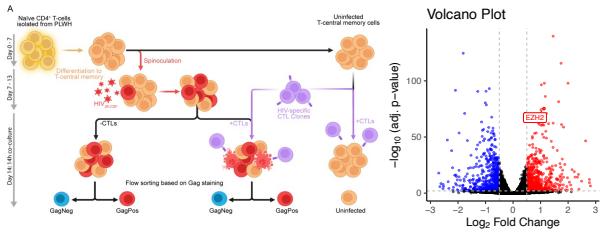
EZH2 inhibition mitigates HIV Immune evasion, reduces reservoir formation, and promotes skewing of CD8+ T cells towards less differentiated, exhausted phenotypes

#0533

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Overexpression of EZH2 in cells that survive CTL exposure

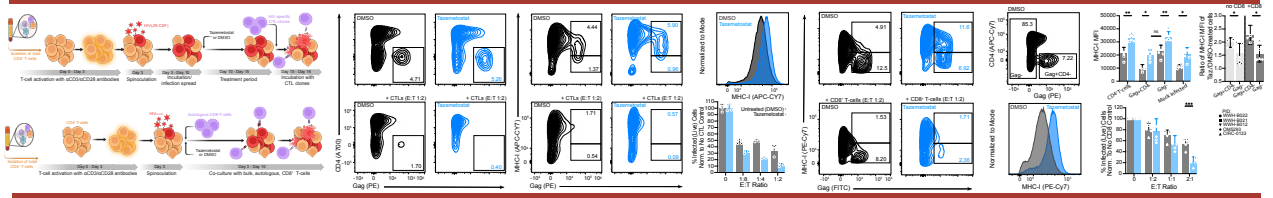


Transcriptional profiling of HIV-infected CD4+ T cells that survive co-culture with autologous CTLs show significant overexpression of EZH2

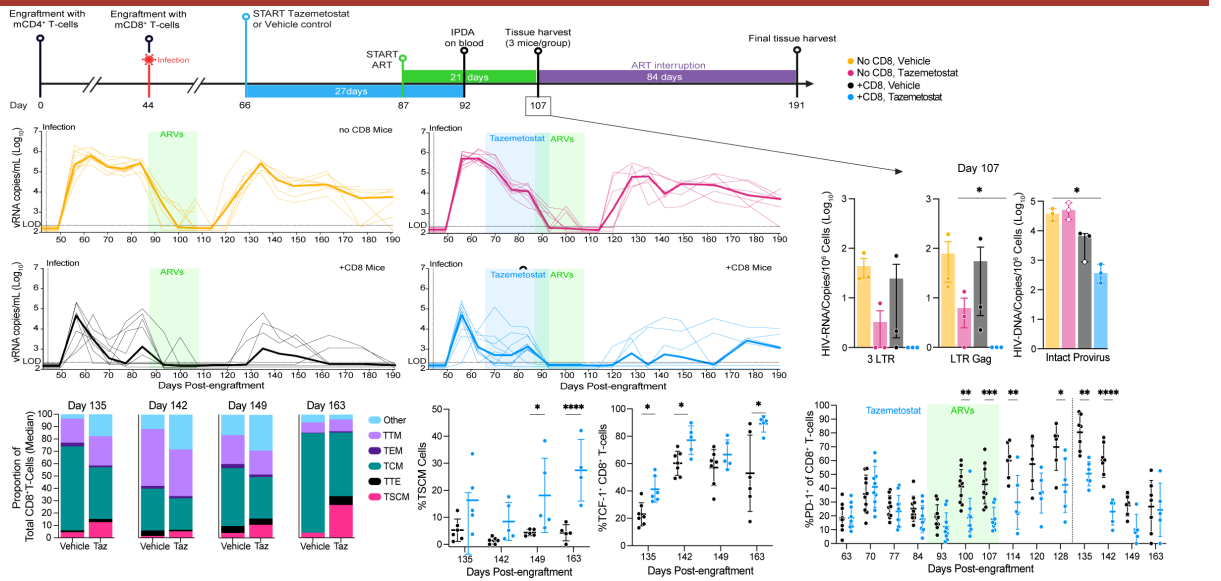
Overexpression of EZH2, the catalytic subunit of PRC2, is linked to immune evasion in cancer by suppressing MHC-I expression

Tazemetostat, an FDA-approved EZH2 inhibitor, has not yet been studied for its potential in HIV treatment

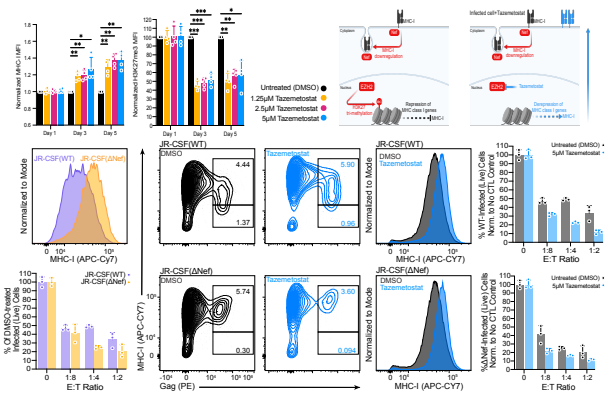
Tazemetostat enhances CTL-mediated elimination of HIV-infected cells in vitro counterbalancing Nef-mediated downregulation of MHC-I



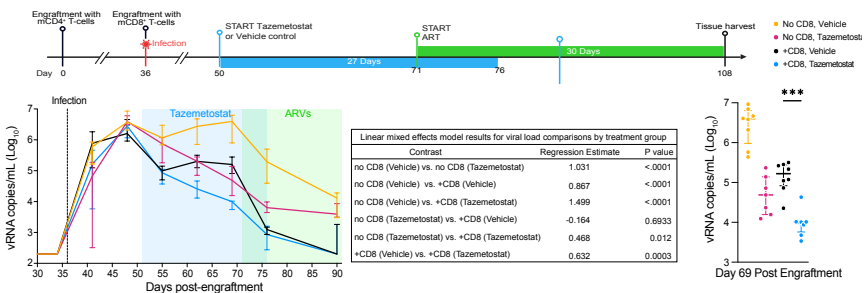
Tazemetostat enables CD8-mediated reductions in HIV reservoir seeding and skews CD8+ T cells to a more stem-like less exhausted profile



Tazemetostat increases surface MHC-I on CD4+ T-cells & counteracts Nef-mediated downregulation of MHC-I



Tazemetostat enhances CD8+ T-cell mediated control of HIV viremia in vivo



Linear mixed effects model results for viral load comparisons by treatment group

Contrast	Regression Estimate	P value
no CD8 (Vehicle) vs. no CD8 (Tazemetostat)	1.031	<.0001
no CD8 (Vehicle) vs. +CD8 (Vehicle)	0.867	<.0001
no CD8 (Vehicle) vs. +CD8 (Tazemetostat)	1.499	<.0001
no CD8 (Tazemetostat) vs. +CD8 (Vehicle)	-0.164	0.6933
no CD8 (Tazemetostat) vs. +CD8 (Tazemetostat)	0.468	0.012
+CD8 (Vehicle) vs. +CD8 (Tazemetostat)	0.632	0.0003

Conclusions

- *EZH2* is overexpressed in HIV-infected CD4+ T-cells that survive CTL co-culture.
- Inhibiting EZH2 by tazemetostat increases MHC-I expression on HIV-infected CD4+ T-cells, enhances their elimination by CTLs, and augments suppression of viral replication in vitro, in part by counterbalancing MHC-I-Nef-mediated MHC-I downregulation.
- In a participant-derived xenograft (PDX) mouse model, tazemetostat increases MHC-I expression enabling CTLs to reduce viral reservoir seeding and resulting in sustained skewing of CD8+ T-cells to less differentiated and less exhausted phenotypes.

Plain language summary

- We identified the expression of EZH2 as a mechanism by which infected cells can resist elimination by CTLs.
- Using the FDA approved tazemetostat, we observe a reduction in HIV reservoir formation and improvement in CD8+ T-cell phenotypes in vivo.
- These results warrant continued assessment of tazemetostat in NHP models and clinical evaluation in PLWH to achieve a functional cure for HIV.

Acknowledgements

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