

Small Molecule Disruption of Cellular Pathways Reveals Novel Host Targets for HIV Latency Reversal and Suppression

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Background

HIV Reservoir

Antiretroviral Therapy (ART) has shown to efficiently suppress proviral activity of HIV in people living with HIV (PLWH) but is ineffective in clearing the virus. Integrated HIV genome in resting CD4+ T cells generating the latent reservoir has led to persistence of the infection and continued barrier to finding a cure.

PI3K/AKT/mTOR Signalling Pathway

- Intracellular host signalling pathway that affects activity associated with cell growth, cell-cycle progression, proliferation, cell survival and apoptosis (1).
- HIV proteins such as Tat and Nef have shown to regulate this pathway depending on stage in replication and lifecycle to enhance cellular survival or apoptosis (2,3).
- Increased levels of HIV proteins present in the cell upon reactivation has shown to induce apoptosis and pyroptosis (4).

Can targeting the PI3K/AKT/mTOR signalling pathway alter levels of HIV transcription and induce apoptosis in latent HIV-infected CD4+ T cells?

Aims & Hypothesis

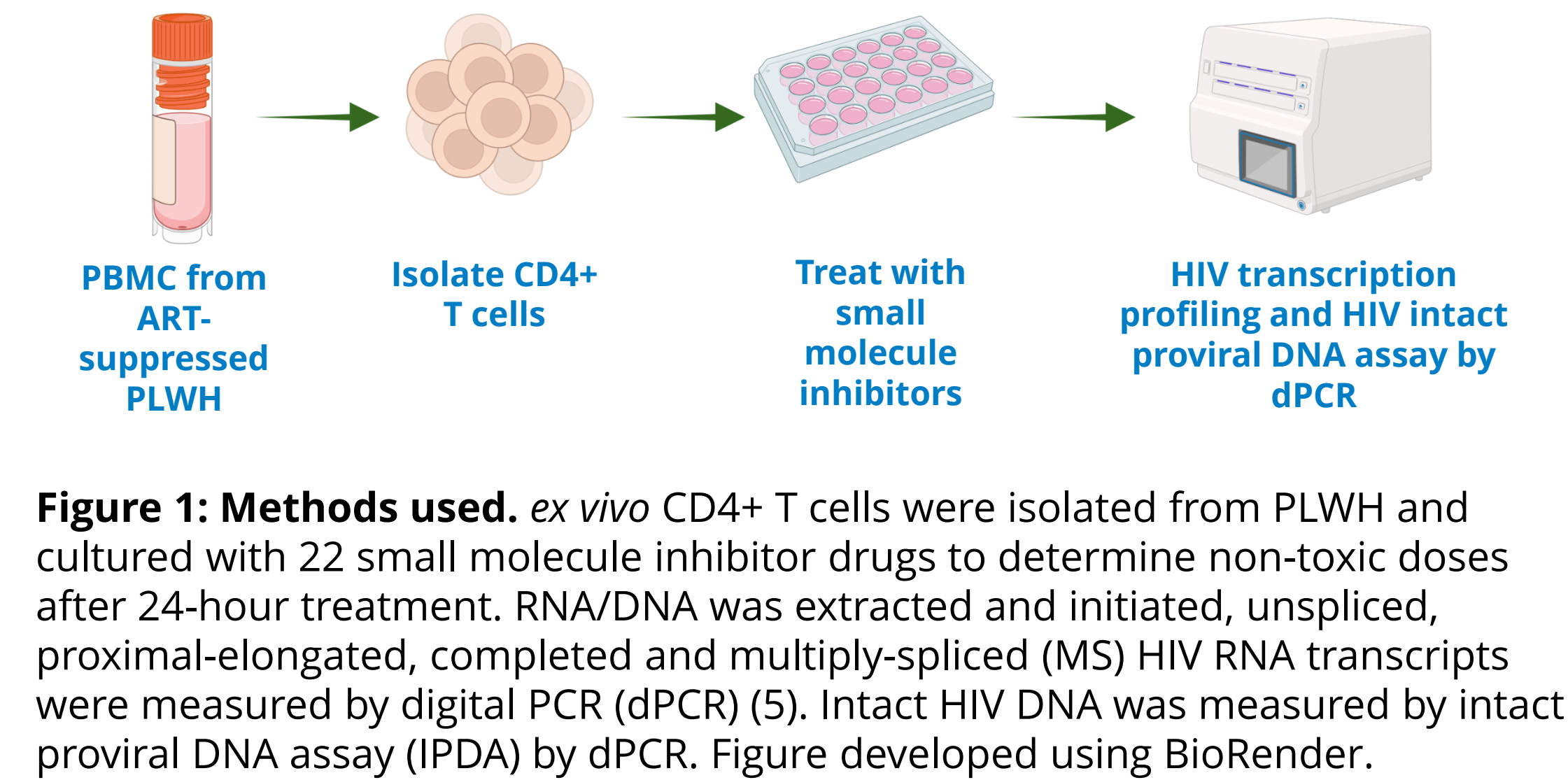
Hypothesis:

- Targeting host factors with small molecule inhibitors may reveal new cellular targets for cure strategies
- Targeting the PI3K signalling pathway will alter levels of HIV transcription in latent HIV-infected CD4+ T cells from PLWH and induce selective cell death.

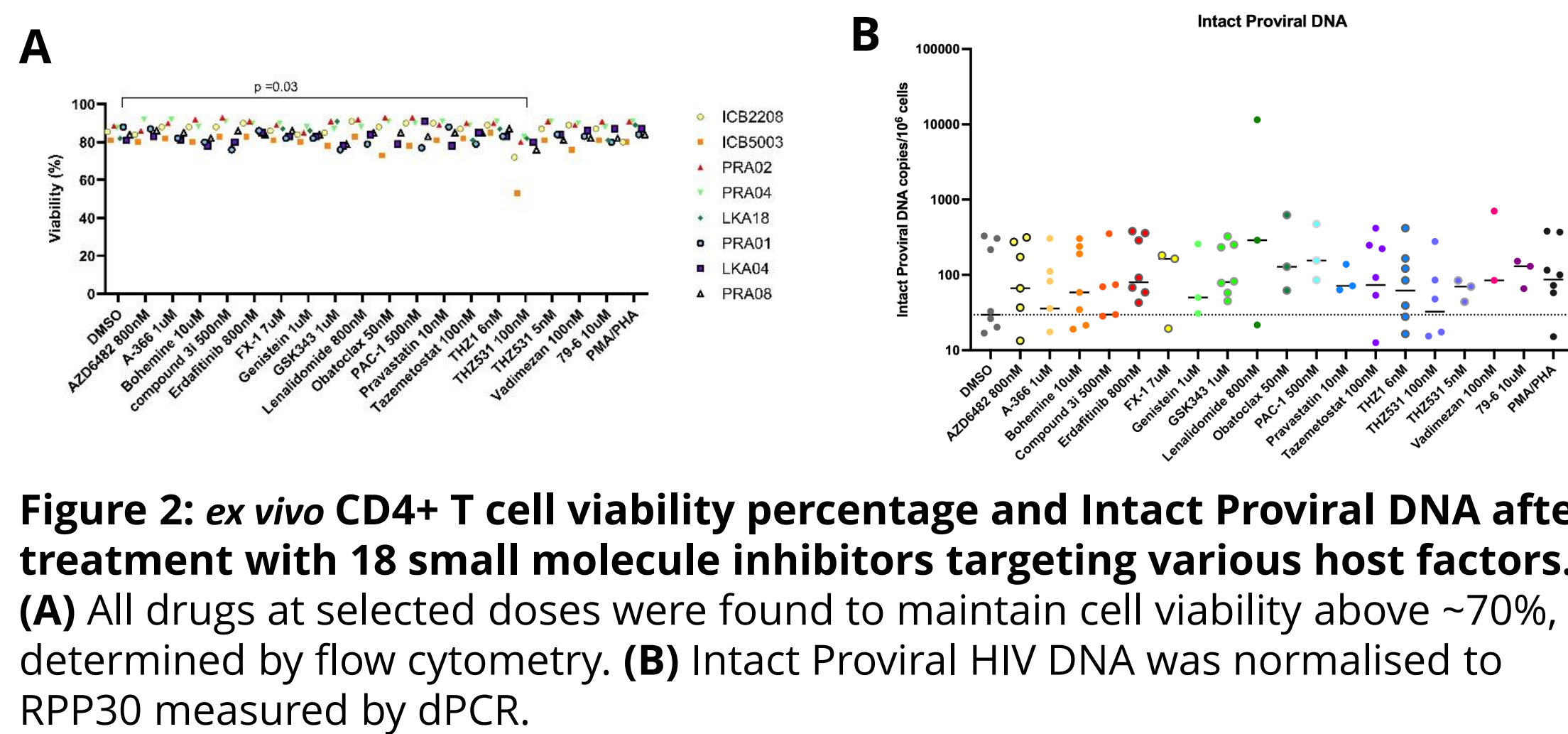
Aims:

1. Investigating small molecule inhibitors to identify factors associated with HIV transcription *ex vivo*.
2. Determining whether PI3K inhibition sensitizes infected cells to apoptosis.

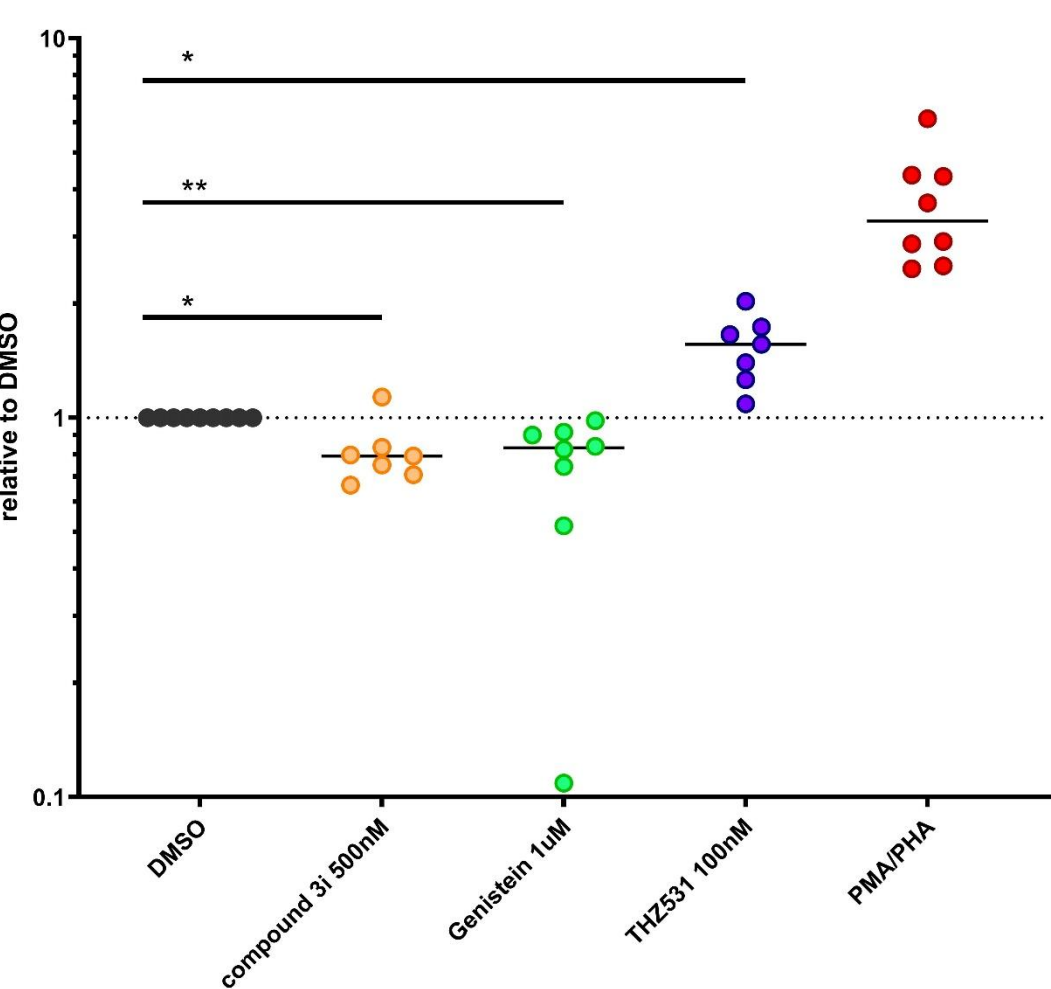
Methods



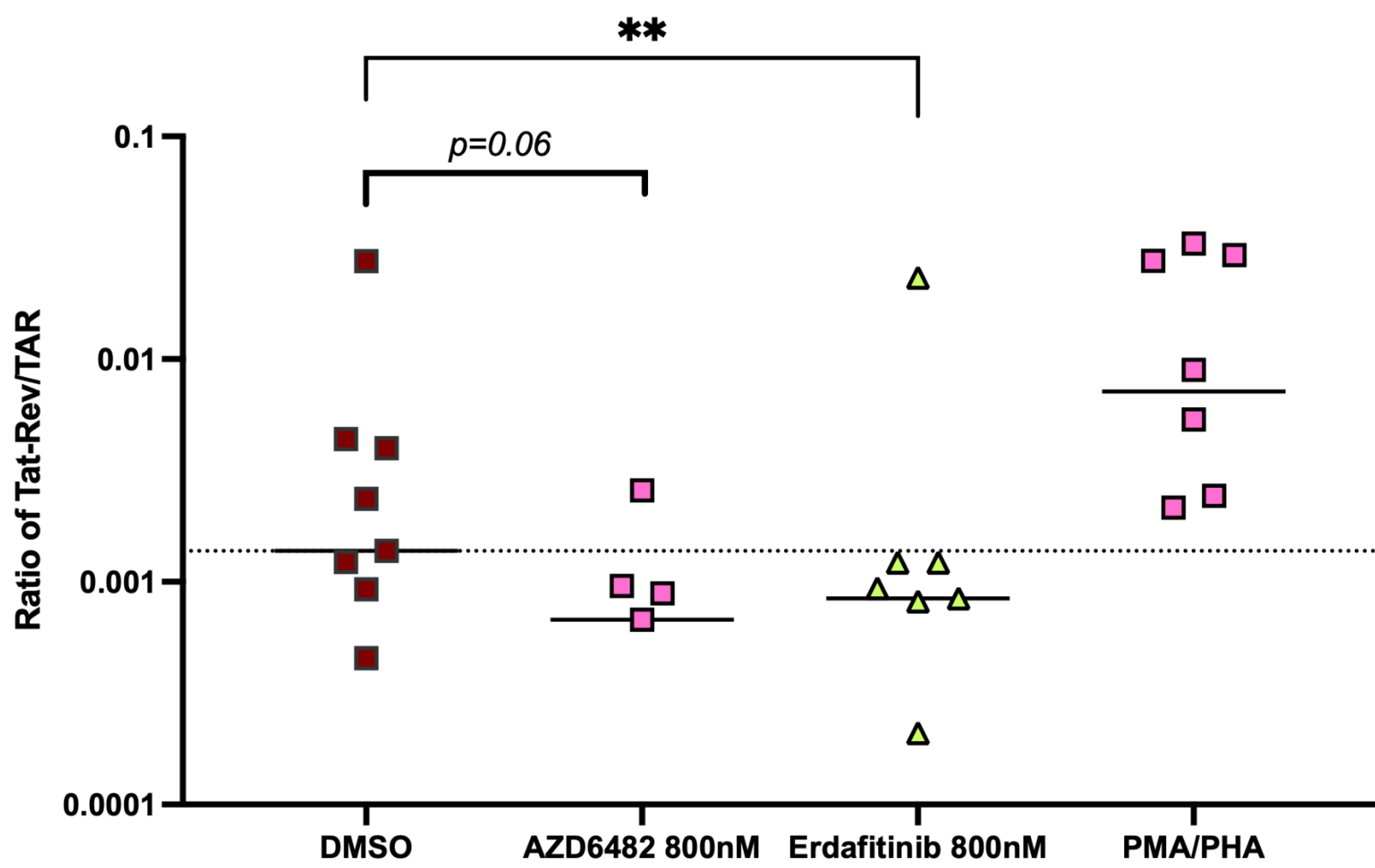
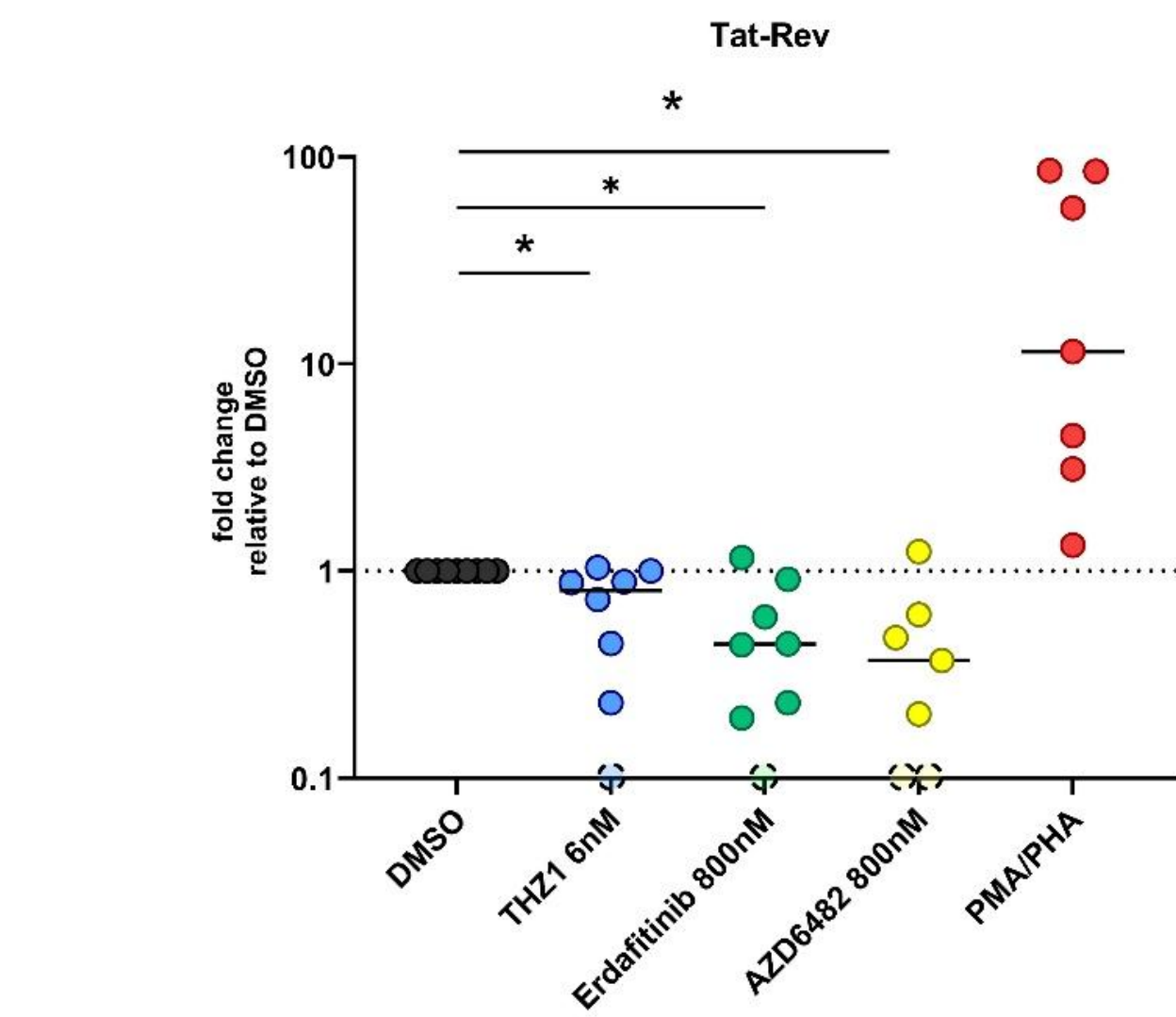
Results 1. Small molecule inhibition did not reduce HIV DNA levels in CD4+ T cells



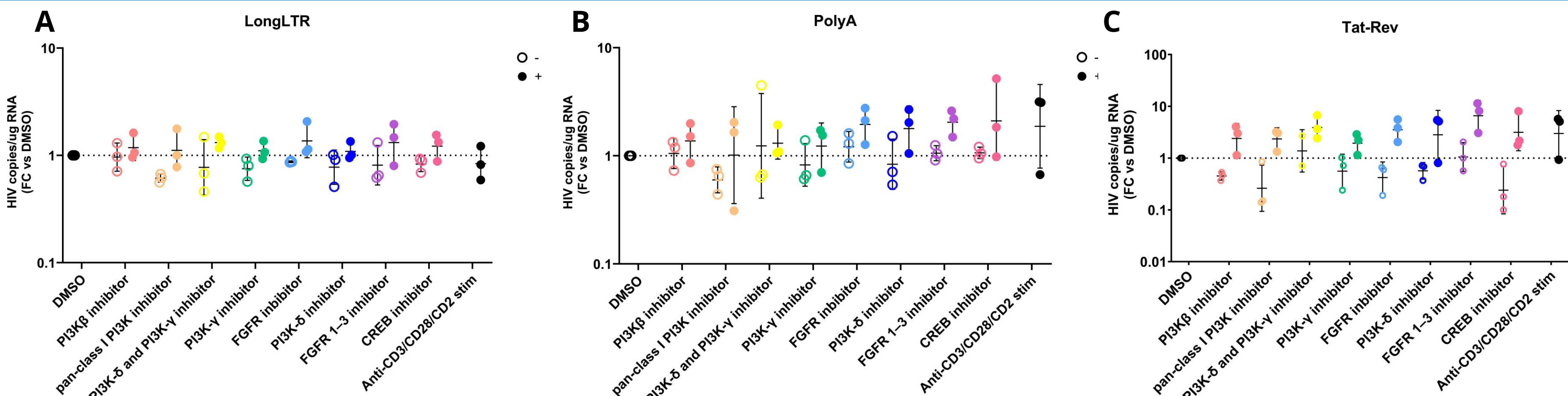
2. Small molecule inhibition modulated HIV transcription



3. Small molecule inhibition induced reductions to MS HIV RNA



4. Selective PI3K-targeting showed variable responses to HIV RNA transcripts



- Eganelisib elicited a reduction in stimulation-induced Tat-Rev RNA across three donors.
- In the presence of anti-CD3/CD28/CD2, selected inhibitors lowered the magnitude of reactivation.

Conclusions

We identified several mechanistically diverse small molecules that perturb HIV-1 expression at one or more stages of transcription, multiple inhibitors targeting elements of the PI3K pathway. Notably, THZ1, Erdafitinib, and Eganelisib were found to reduced multiply-spliced HIV RNA transcripts indicating a potential reduction to productive infection.

Future directions: We aim to determine levels of intact proviral HIV DNA post small molecule inhibitor treatment and assess for early apoptotic markers to identify induction of targeted apoptosis in HIV-infected CD4+ T cells.

Acknowledgments

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