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

Ong J[1], Tumpach C[1], Dunn E[1], Darmani F[1], Kim Y[1], Chang J[1], Wallace L[1], Rhodes A[1], McMahon J H[2], Yukl S A[3,4], Lewin SR[1,5], Roche M[1], Telwatte S[1]

[1] University of Melbourne/Peter Doherty Institute Department of Infectious Diseases,

[2]The Alfred Hospital and Monash University, Melbourne, Australia,

[3] Department of Medicine, University of California San Francisco (UCSF), San Francisco, California, United States

[4] Department of Medicine, San Francisco VA Medical Center, San Francisco, California, United States

[5] Monash University/Alfred Hospital, Department of Infectious Diseases

Background: Latently-infected CD4+ T cells are considered the main barrier to curing HIV-1. Current strategies under investigation for a functional cure include agents that activate or durably suppress HIV transcription in latently infected cells. Our preliminary data identified a range of host factors implicated in HIV transcription in primary cell models. We hypothesised that targeting these host factors with small molecule inhibitors may reveal new cellular targets for cure strategies.

Methods: We evaluated 17 small molecule drugs for their ability to modulate HIV transcription ex vivo in CD4+ T cells from people living with HIV (PWH). We determined non-toxic doses for each compound and treated CD4+ T cells from PWH for 24 hours before extracting RNA/DNA and measuring initiated, unspliced, proximal- and distal- elongated, completed and multiply-spliced (MS) HIV RNA by digital PCR. We measured HIV-1 DNA by the intact proviral DNA assay.

Results: In unstimulated CD4+ T cells, we observed differential activity on HIV expression across the inhibitors tested, though no drug reduced intact or total HIV DNA. We found two drugs capable of inducing small reductions in MS HIV RNA: the fibroblast growth factor receptor (FGFR) inhibitor erdafitinib (FC= 0.44, p=0.047, n=9) and the CDK7 inhibitor THZ1 (FC=0.80, p=0.03, n=9). Inhibition of PI3Kβ (a downstream enzyme activated by FGFR engagement) by AZD6482 also tended to decrease MS RNA (FC=0.34, p=0.06, n=8).

Conclusion: We identified several mechanistically diverse small molecules that perturb HIV-1 expression at one or more stages of transcription. Two inhibitors, erdafitinib and THZ1, inhibited HIV MS RNA in unstimulated CD4+ T cells from PWH. Given the role of FGFR engagement on PI3K pathway signalling and trending decrease in MS RNA with PI3Kβ inhibition, these data suggest that targeting PI3K pathway effectors could be a novel target for interventions aimed at perturbing HIV expression *in vivo*.

DISCLOSURE OF INTEREST STATEMENT: None

Acknowledgement of Funding: This work was supported by the National Institutes of Health (R01AI194343; [ST]), the Doherty Institute for Infection and Immunity Locarnini Fellowship in Virology [ST] and University of Melbourne Department of Infectious Diseases Research Support Package [ST].