The Circadian Clock Machinery Regulates HIV Transcription in CD4+ T cells

Christ-D. Ngassaki-Yoka[1,2], Debashree Chatterjee[1,2] , Tomas Wiche Salinas[1,2], Laurence Raymond Marchand[2], Yuwei Zhang[1,2], Nicolas Cermakian[3], Jean-Pierre Routy[4], Laura Solt[5], and Petronela Ancuta[1,2]

[1]Departement de Microbiologie, Infectiologie et Immunologie, Faculté de Médicine, Université de Montréal, Montréal, QC, Canada; [2]Centre de Recherche du CHUM, Montréal, QC, Canada; [3]Douglas Mental Health University Institute, McGill University, Montréal, QC, Canada; [4]McGill University Health Centre: Glen Site, Research Institute, Montréal, QC, Canada; [5]Department of Immunology and Microbiology, The Scripps Research Institute, Jupiter, Florida, USA

Abstract

Background: The Th17-polarized CD4+ T-cells are key HIV infection targets. Current ART targets different steps of the viral replication cycle but not the transcription, a process under the control of host-cell transcription factors. We previously reported a transcriptional signature associated with HIV permissiveness in Th17 cells, including the circadian clock components/regulators CLOCK, BMAL1 and REV-ERBα.

Hypothesis: We hypothesized that REV-ERBα regulates both RORγt-mediated effector functions and BMAL1-mediated HIV replication in Th17 cells.

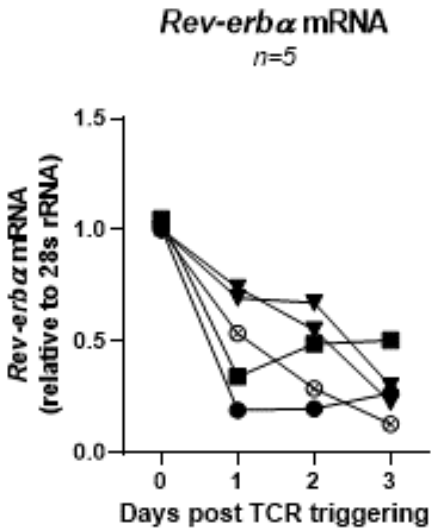
Methods: We used available REV-ERBα agonists (SR9009, SR9011). Memory CD4+ T-cells from uninfected individuals were stimulated via αCD3/αCD28 and exposed to HIV in vitro. A viral outgrowth assay (VOA) was performed with memory CD4+ T-cells of ART-treated PLWH activated via αCD3/αCD28. cytokines and HIV-p24 levels were measured by ELISA.

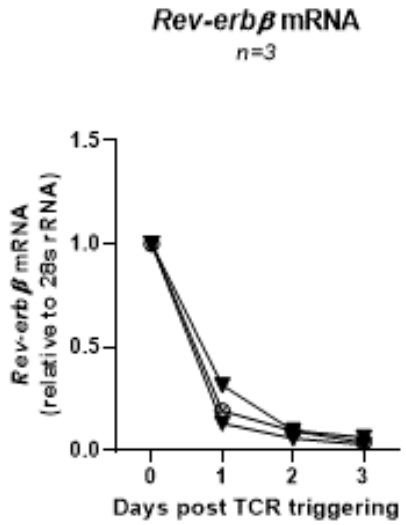
Results: REV-ERBα agonists potently reduced RORγt/BMAL1 mRNA expression and inhibited HIV replication *in vitro* and in VOA. The antiviral effect coincided with decreased IL-17A and IFNγ production. Studies are in progress to define molecular mechanism by which REV-ERBα interferes with HIV transcription.

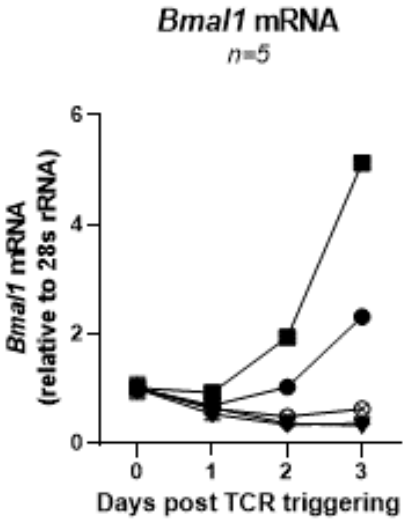
Conclusion: These results provide a strong rationale for further evaluating the possibility to therapeutically target REV-ERBα to block residual HIV transcription as a way to limit chronic immune activation and non-AIDS co-morbidities during ART.

Results

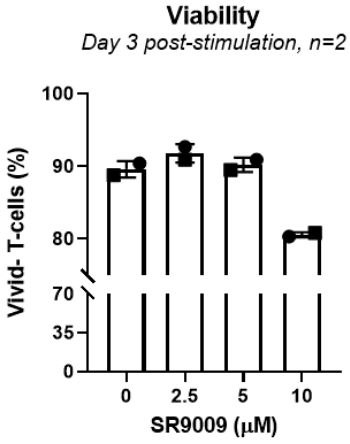
Kinetics of REV-ERBα, REV-ERBβ and BMAL1 mRNA expression upon stimulation of memory CD4+ T-cells *via* CD3/CD28

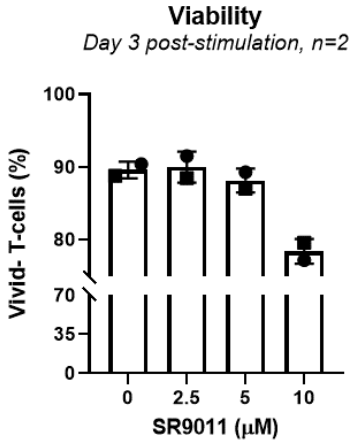


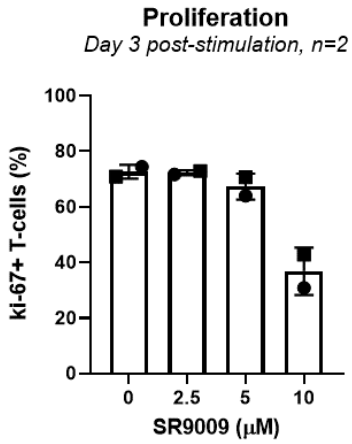


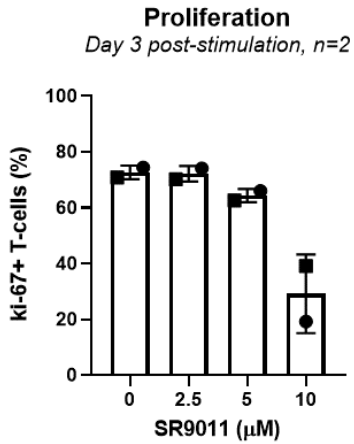


Screening for optimal SR9009 and SR9011 concentrations: Effect on cell viability and proliferation



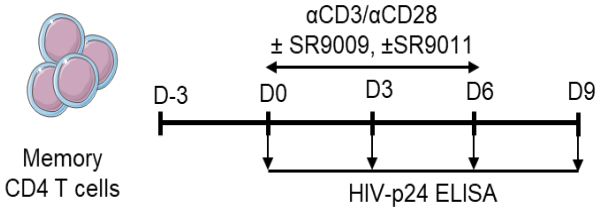


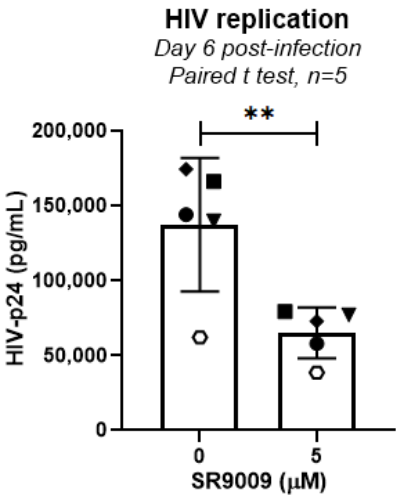


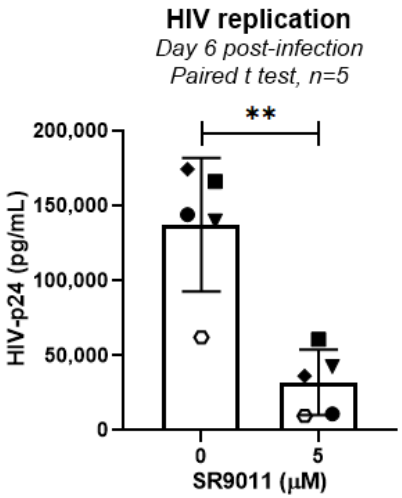


Results

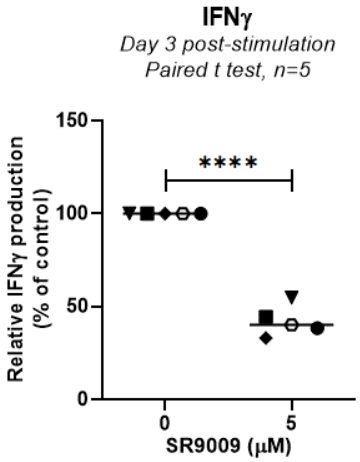
SR9009 and SR9011 inhibit HIV replication in memory CD4+ T-cells

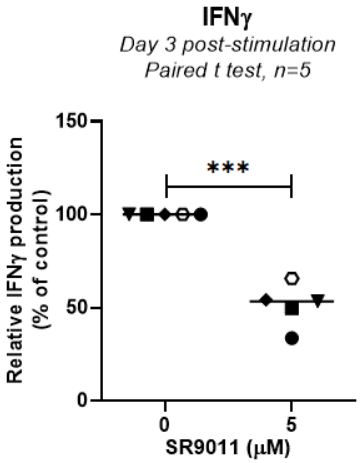


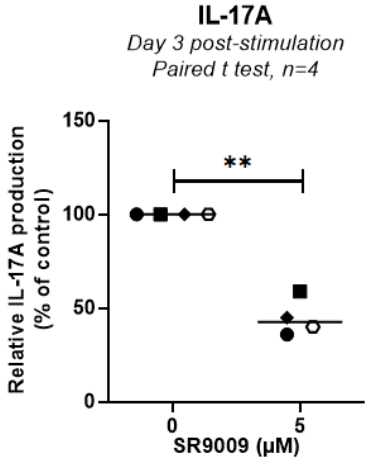


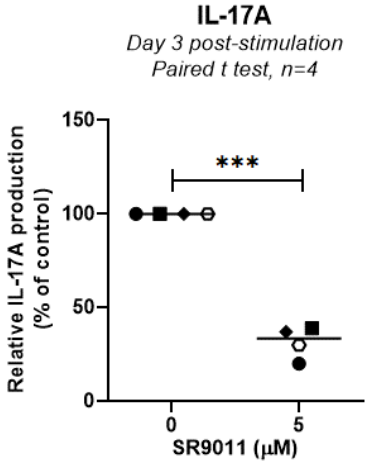


SR9009 and SR9011 inhibit IFNγ and IL-17A production



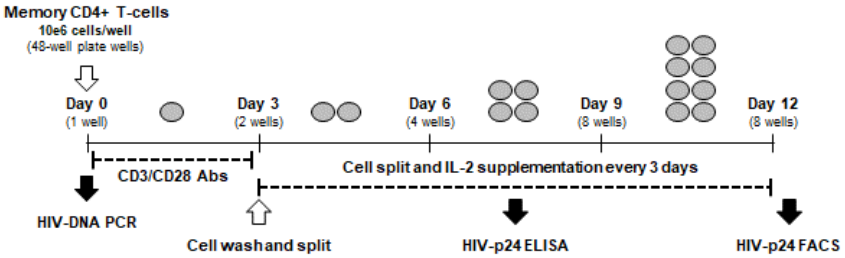


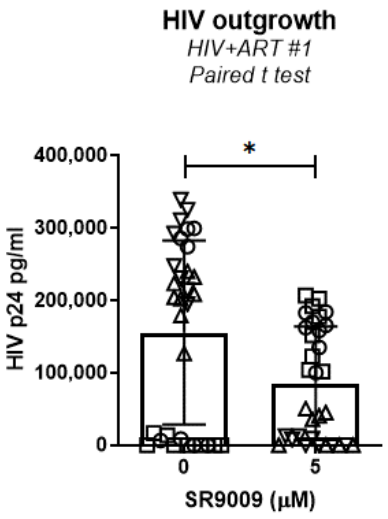


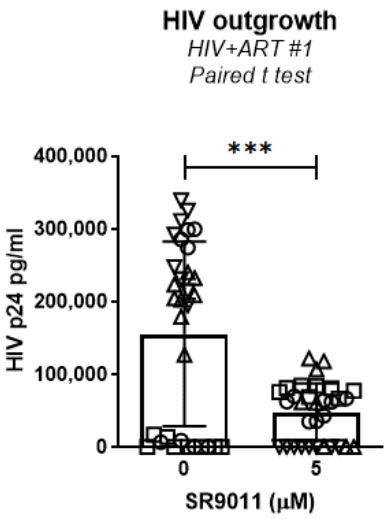


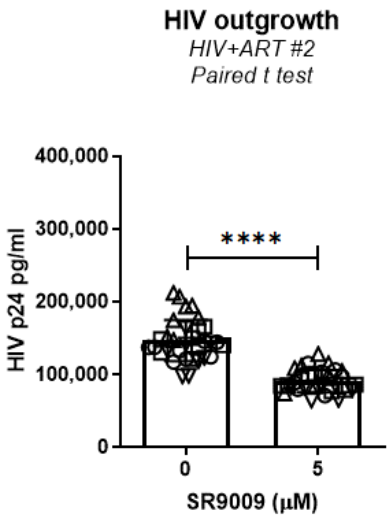
Results

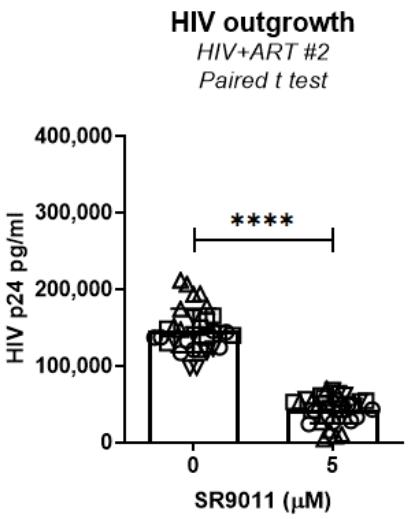
Effects of SR9009 and SR9011 on HIV reactivation: viral outgrowth assay on T-cells from ART-treated PLWH











♦ Acknowledgements

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