Th17 CELL MASTER TRANSCRIPTION FACTOR RORC2 REGULATES HIV GENE EXPRESSION AND LATENCY

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Introduction

BACKGROUND:

- **HIV-DNA reservoirs persist in CCR6+ CD4+ T-cells from colon and blood of ART-treated PLWH**

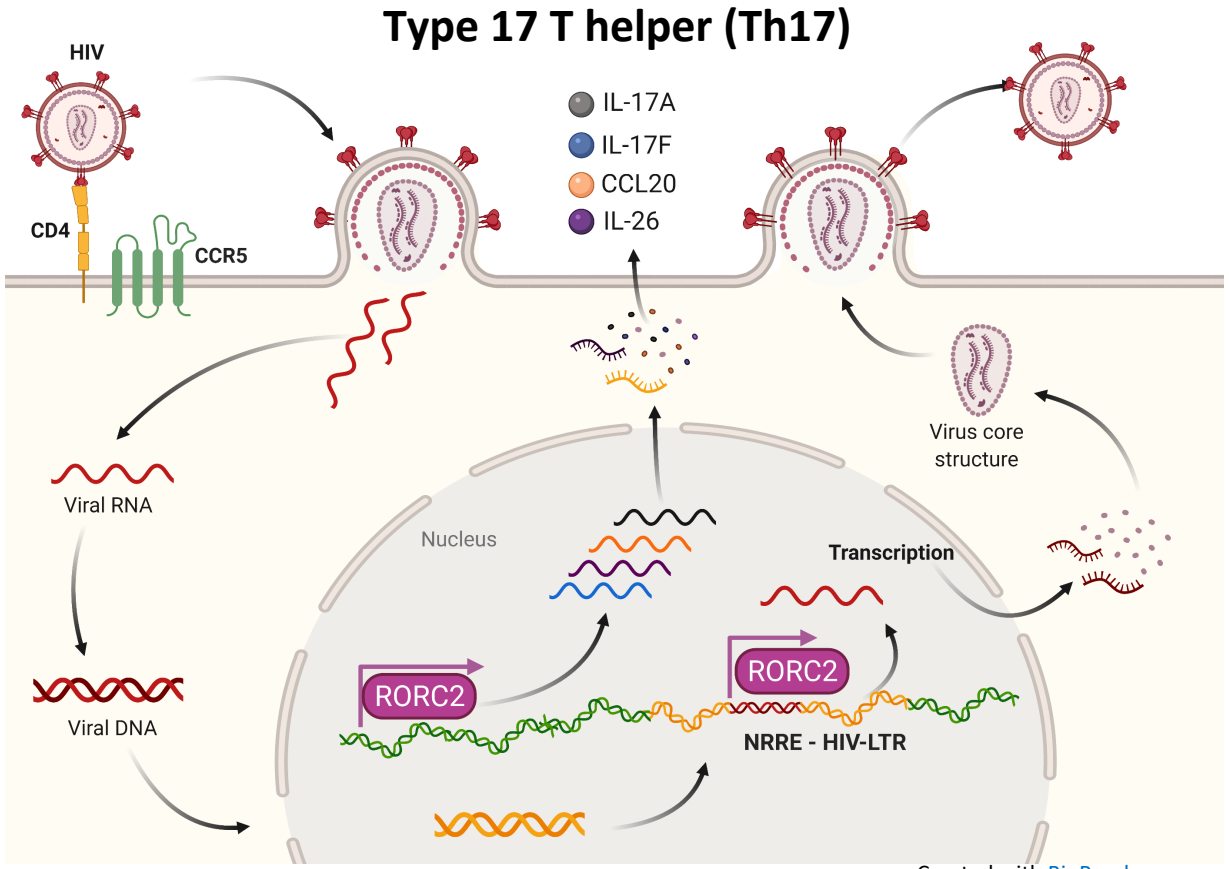
(*Gosselin/Wiche Salinas et al., AIDS, 2017; Anderson et al., JID, 2020)*

- **CCR6+ Th17 cells are enriched in HIV permissiveness factors and lack intrinsic antiviral mechanisms**

(*Cleret-Buhot et al., Retrovirology, 2013; Planas et al.,JCI insight 2017, Christensen-Quick et al., JVI 2016)*

- **Retinoic acid receptor-related orphan receptor 2 (RORC2): the master regulator of Th17 polarization**

(*Ivanov et al., Cell, 2006; Yang XO et al., Immunity, 2008)*



HYPOTHESIS:

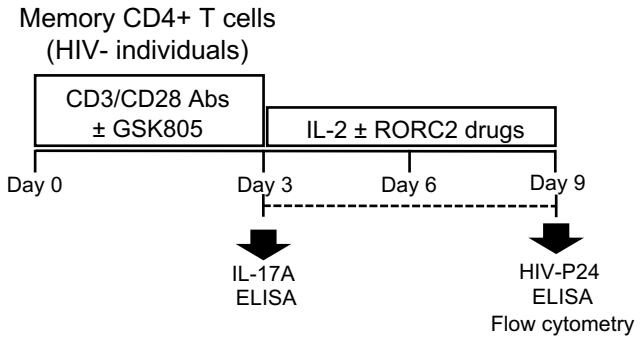
- **RORC2 mediates the permissiveness of Th17 cells to HIV infection and sustains viral reservoir reactivation from latency and viral outgrowth**

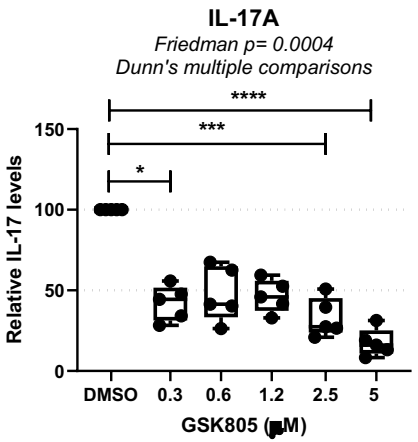
OBJECTIVE:

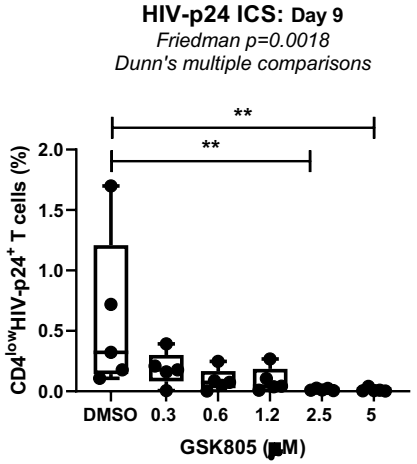
- **To define mechanisms by which RORC2 regulates HIV replication in CD4+ T cells**

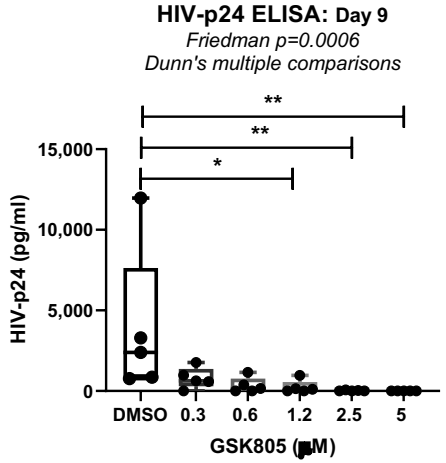
Results - 1

1. RORC Reverse Agonists Inhibit HIV-1 Infection in Primary CD4+ T Cells



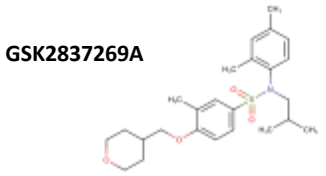


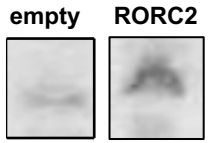


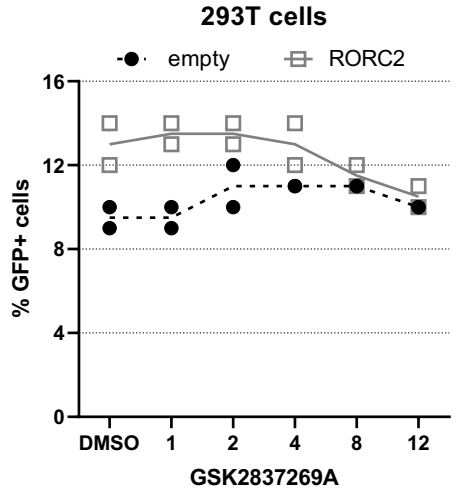


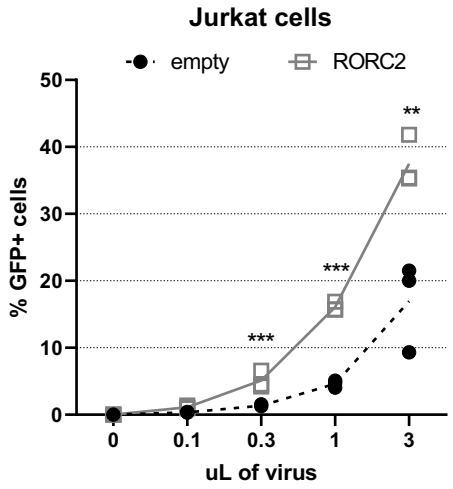
2. RORC2 is a Host Co-factor for HIV-1 Infection of CD4+ T Cells

A. RORC2 overexpression in Jurkat Cells

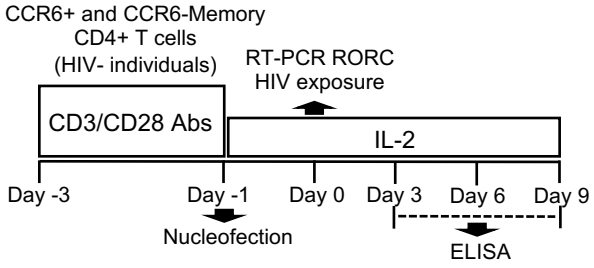


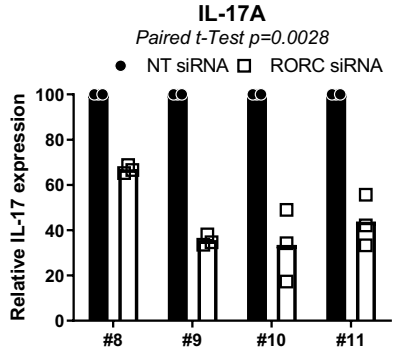


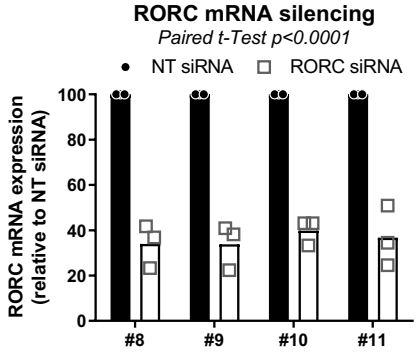


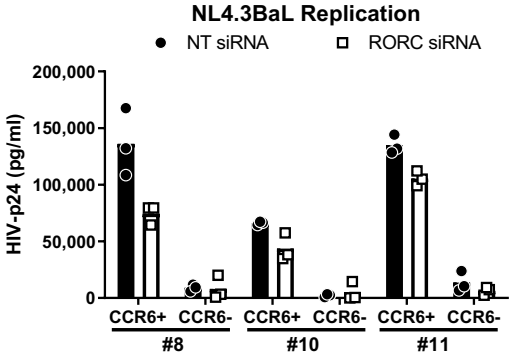


B. RORC2 silencing in primary CD4+ T cells



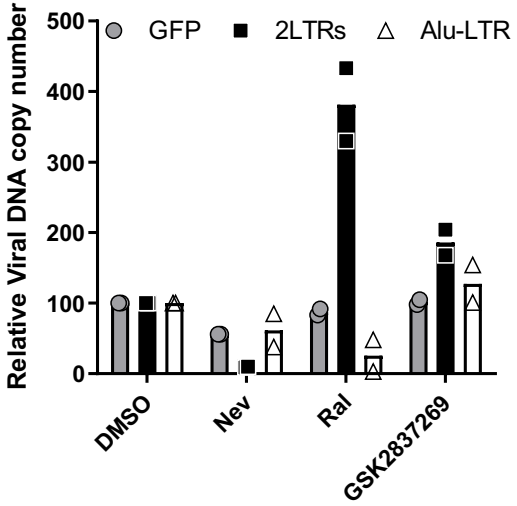


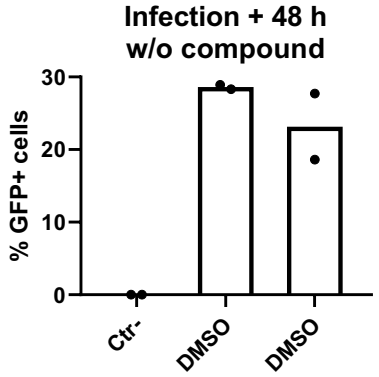


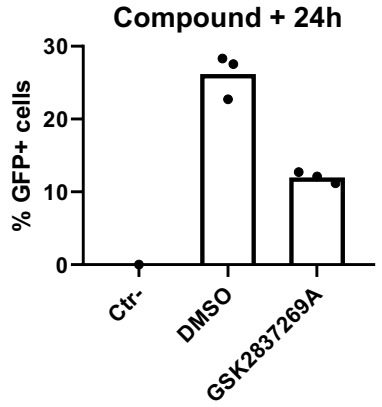


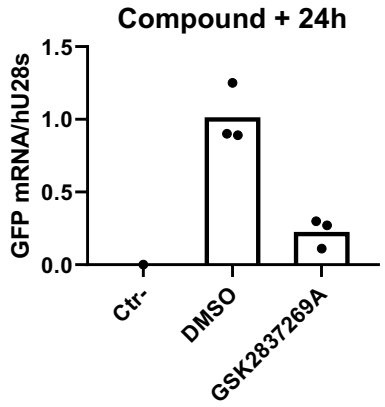
Results - 2

3. RORC2 Promotes HIV-1 Gene Expression

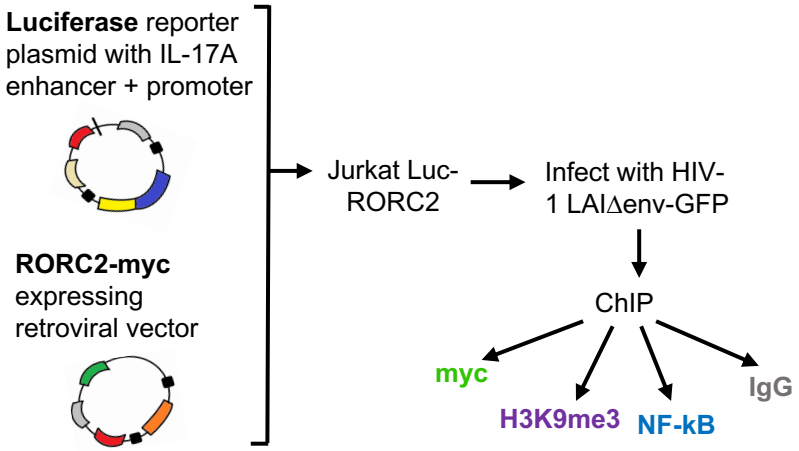


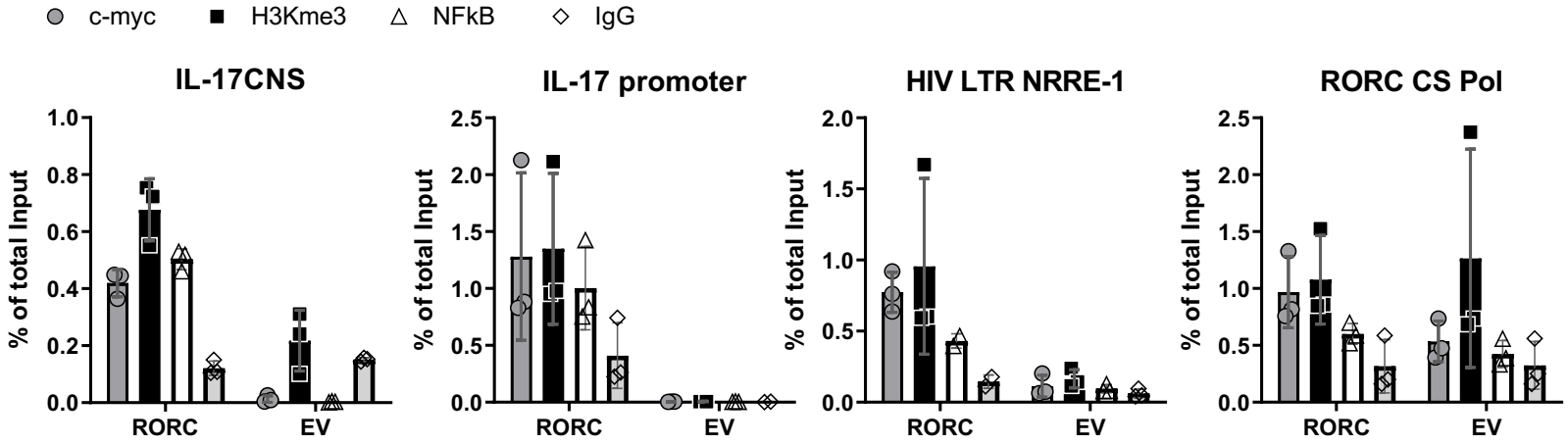






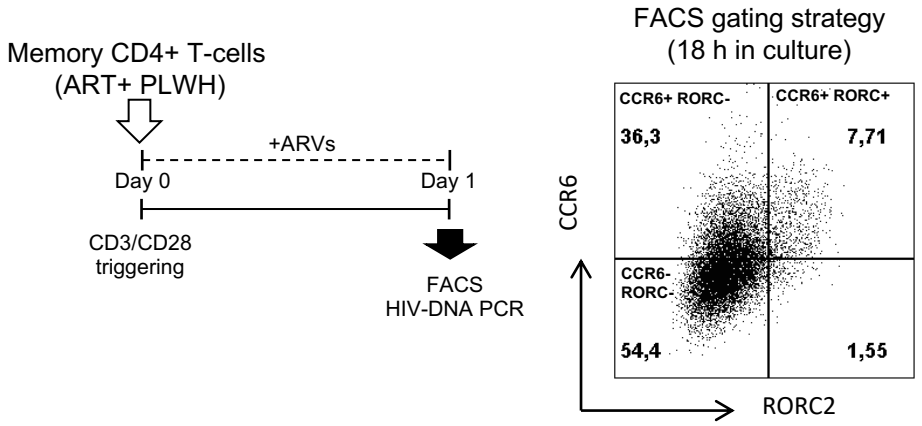
4. RORC2 Binds to the HIV-1 LTR (RORC2-myc ChIP)

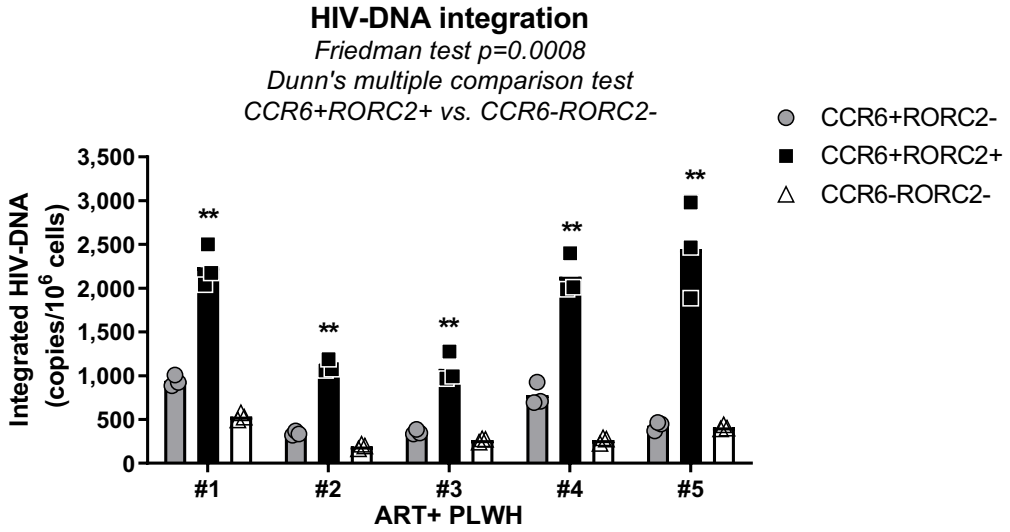




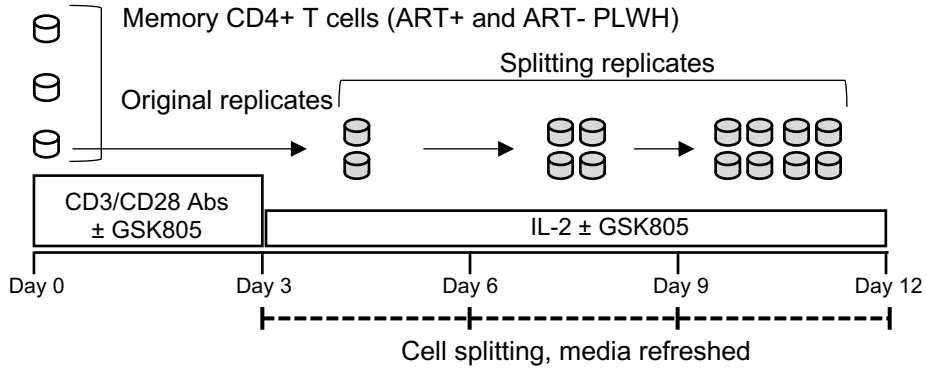
Results - 3

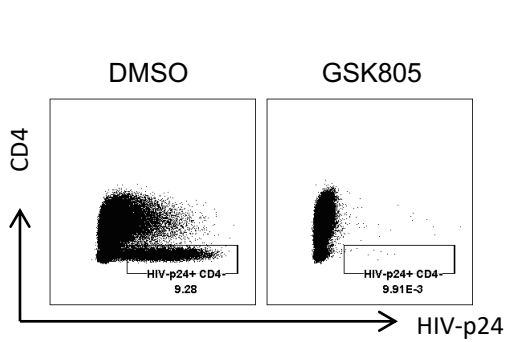
5. CD4+ T Cells Expressing a CCR6+RORC2+ Th17 Phenotype Are Enriched In Integrated HIV-DNA In ART-Treated PLWH

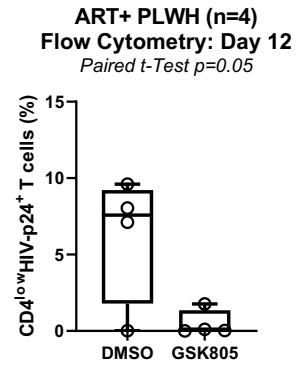


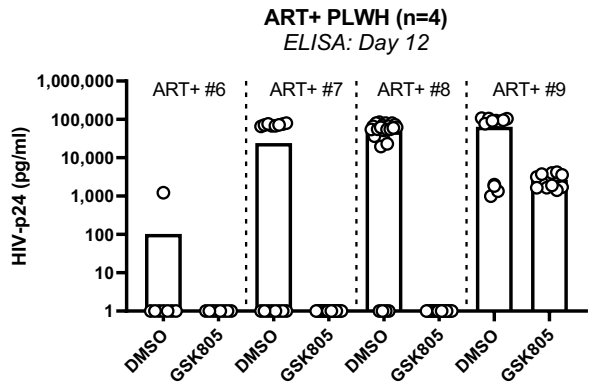


6. RORC Antagonism Inhibits HIV-1 Outgrowth in CD4+ T Cells of ART-Treated and Untreated PLWH









Conclusions

- **The Th17 cell master transcription factor RORC2 is critical host co-factor for HIV-1 replication**
- **RORC2 reverse agonists inhibited HIV-1 replication in primary CD4+ T cells in a dose-dependent manner**
- **RORC2 silencing inhibited HIV-1 infection in bulk memory and sorted CCR6+ CD4+ T cells**
- **RORC2 promoted HIV-1 gene expression**
- **Chromatin immune precipitation (ChIP) revealed that RORC2 binds to the HIV-1 promoter**
- **RORC2 reverse agonists potently reduced HIV-1 outgrowth in CD4+ T cells of ART-treated and untreated PLWH**
- **Altogether, these results provide a new explanation why Th17 cells are highly susceptible to HIV-1 infection and point to RORC2 as a novel cell-specific target for HIV-1 therapy.**

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