In vitro HIV infection reduces IL-17 expression by human Th17 cells

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I have no conflicts of interest

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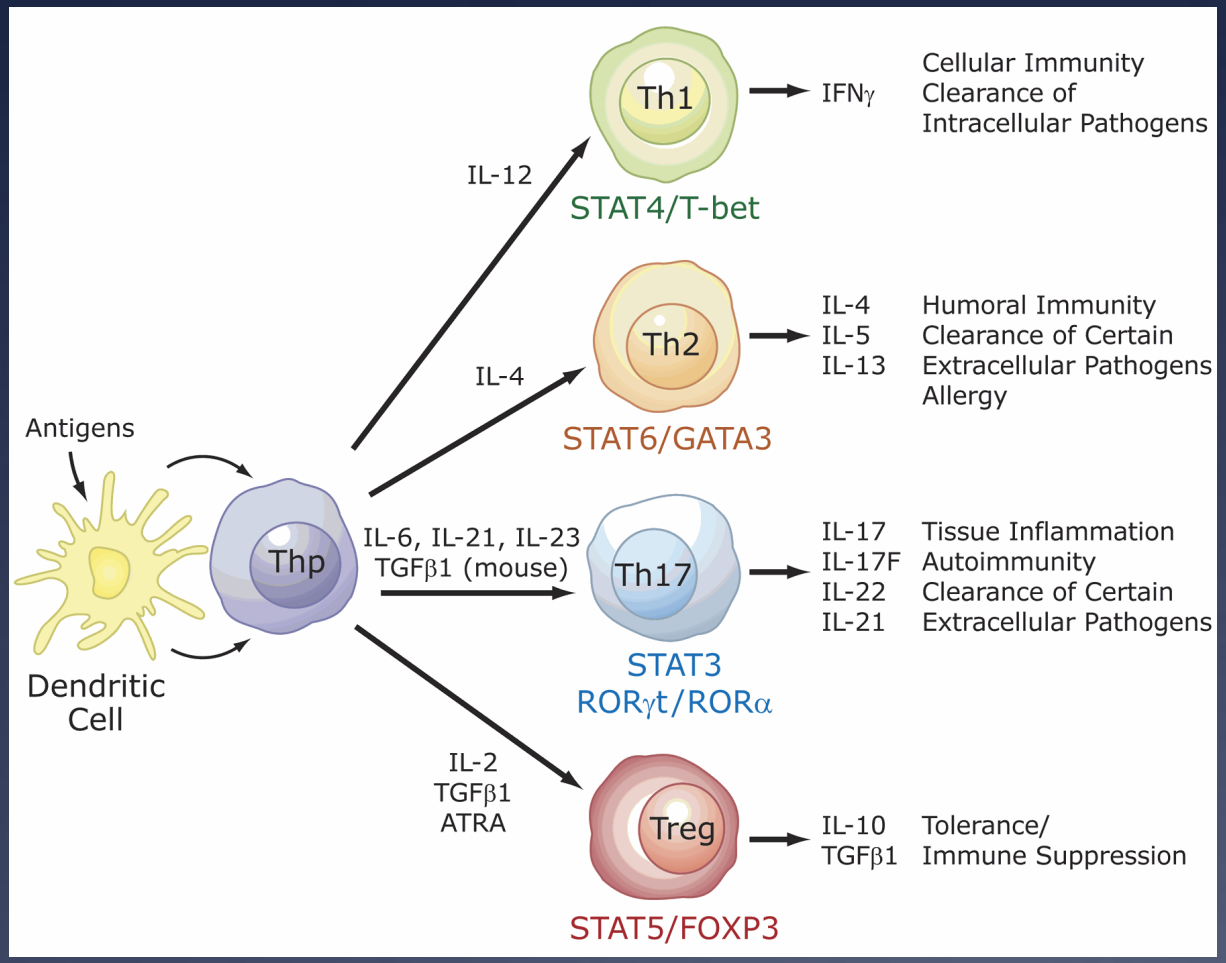
Th17 Cells



- IL-17:
  - Prod^{n} of IL-6, IL-1β, TNF-a, IL-8, MCP-1
  - Antimicrobial peptides
  - Wound healing
- Vital role in maintaining mucosal barrier integrity

Th17 cells and HIV

Differential Th17 CD4 T-cell depletion in pathogenic and nonpathogenic lentiviral infections

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Th17 cells, Job's syndrome and HIV: opportunities for bacterial and fungal infections

Joshua D. Milner[a], Netanya G. Sandler[b] and Daniel C. Douek[b]

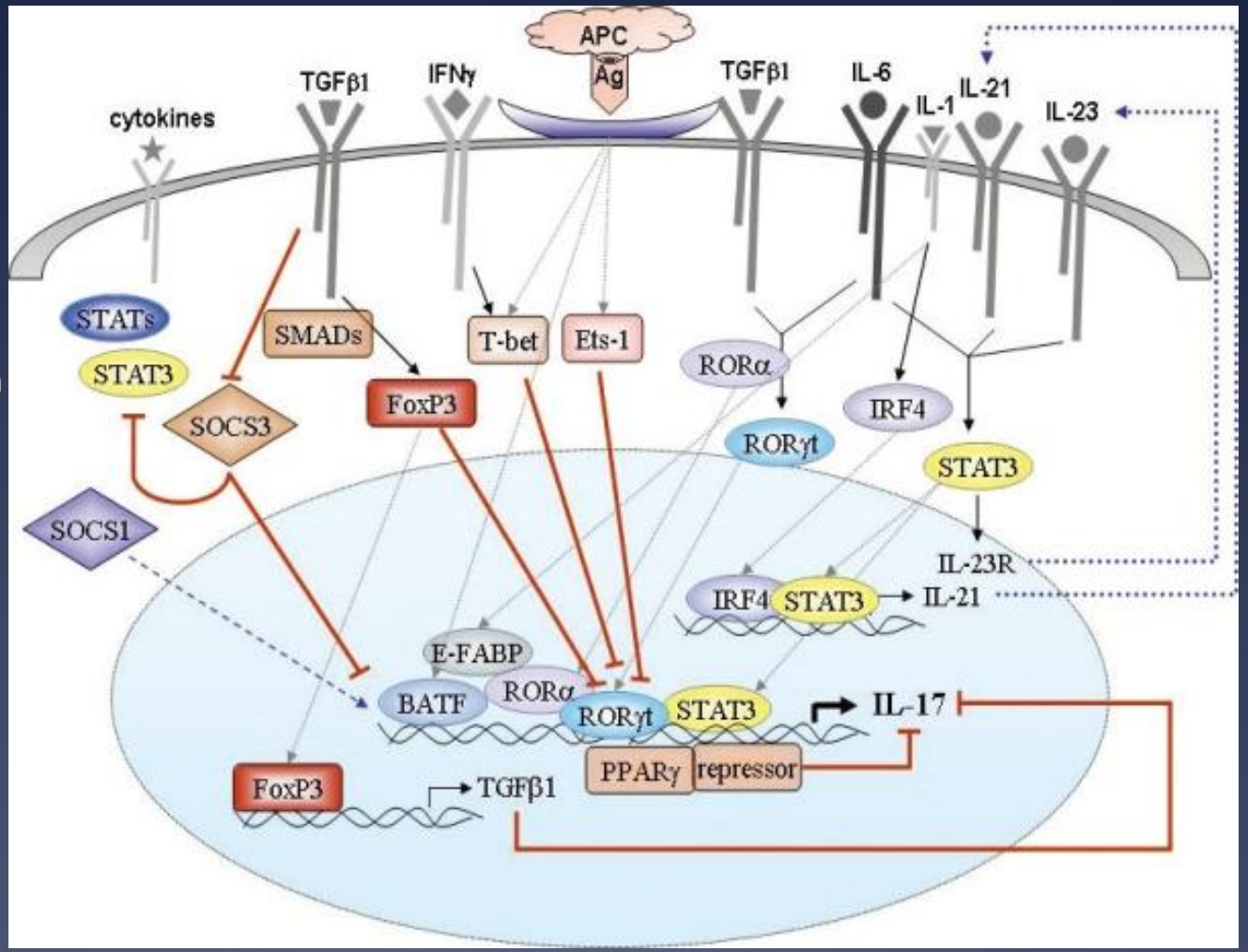
Sigmoid Th17 populations, the HIV latent reservoir, and microbial translocation in men on long-term antiretroviral therapy

Duncan Chege[a,*], Prameet M. Sheth[a,*], Taylor Kain[a], Connie J. Kim[a], Colin Kovacs[c], Mona Loutfy[a,c,d], Roberta Halpenny[d,e,f], Gabor Kandel[e], Tae-Wook Chun[g], Mario Ostrowski[a,b,e], Rupert Kaul[a,b,f], the Toronto Mucosal Immunology Group

- Th17 cells depleted in early in HIV infection
- Loss correlates to increased microbial translation
- Deficit persists despite HAART

IL-23 signalling in Th17 precursors

- Jak2, Tyk2 →
  - Stat3, RORa/γt
- Outcomes →
  - IL-17/21/22 prod^{n}
  - ⇧IL-23R
- Th17 cells are plastic!



IL-23, HIV, and Th17 cells

The interleukin 23 receptor is essential for the terminal differentiation of interleukin 17–producing effector T helper cells *in vivo*

Mandy J McGeachy[1], Yi Chen[1], Cristina M Tato[1], Arian Laurence[2], Barbara Joyce-Shaikh[1], Wendy M Blumenschein[1], Terrill K McClanahan[1], John J O'Shea[2] & Daniel J Cua[1]

Anti-retroviral therapy fails to restore the severe Th-17: Tc-17 imbalance observed in peripheral blood during simian immunodeficiency virus infection

M. Kader[1], S. Bixler[1], M. Piatak[2], J. Lifson[2] & J.J. Mattapallil[1]

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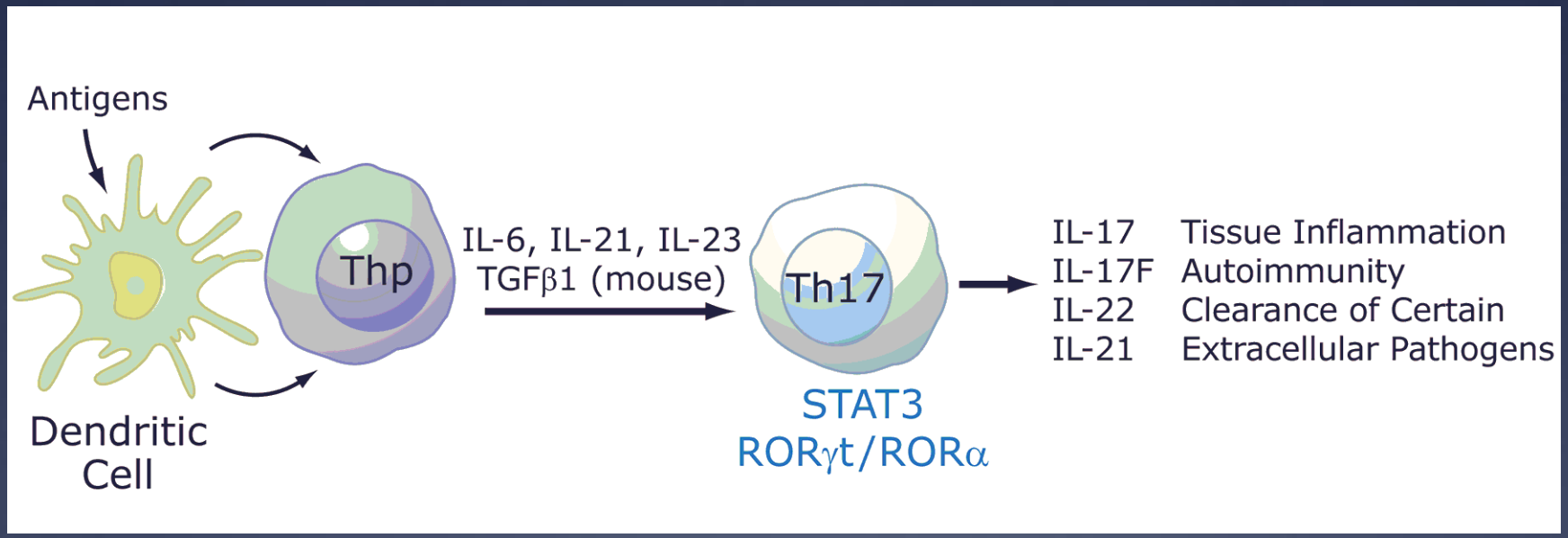
IL-23 and IFN-γ deficiency in immunodeficient HIV patients who achieved a long-term increase in CD4 T-cell counts on highly active antiretroviral therapy

Silvia Lee, Martyn A.H. French and Patricia Price

- Th17 phenotype requires IL-23
- HIV infection associated with decrease in IL-23 prod^{n}, IL-23 signaling
- IL-23 prod^{n} restored following HAART, but still no Th17 cells…

Hypothesis

In addition to perturbing IL-23 production by APC in response to TLR ligation, HIV and its regulatory proteins disturb Th17 function and/or differentiation by modulating IL-23-activated intracellular signaling pathways

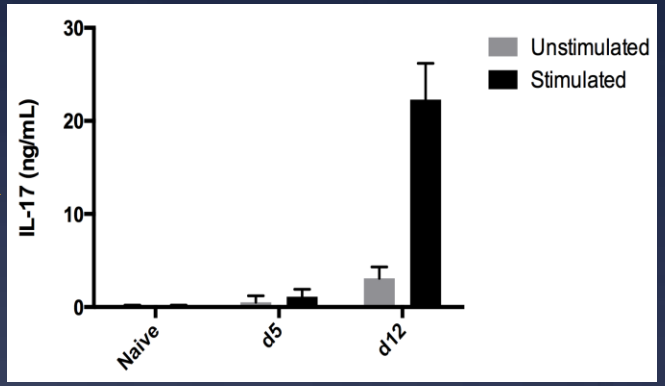


Th17 cells

In vitro differentiation

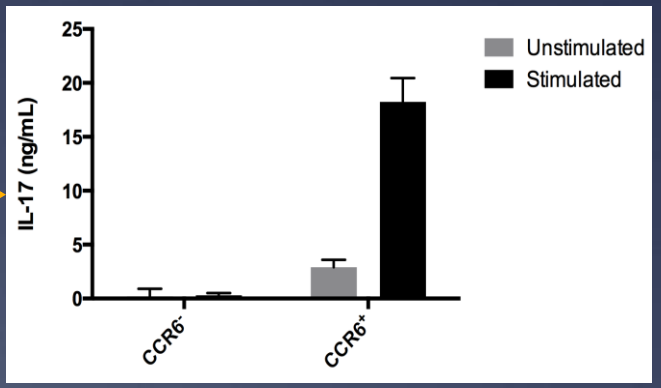
Step 1 (5 days)
•aCD3/CD28 beads
•IL-1β, IL-6
•aIL-4, aIFN-γ

Step 2 (7 days)
IL-2, IL-23

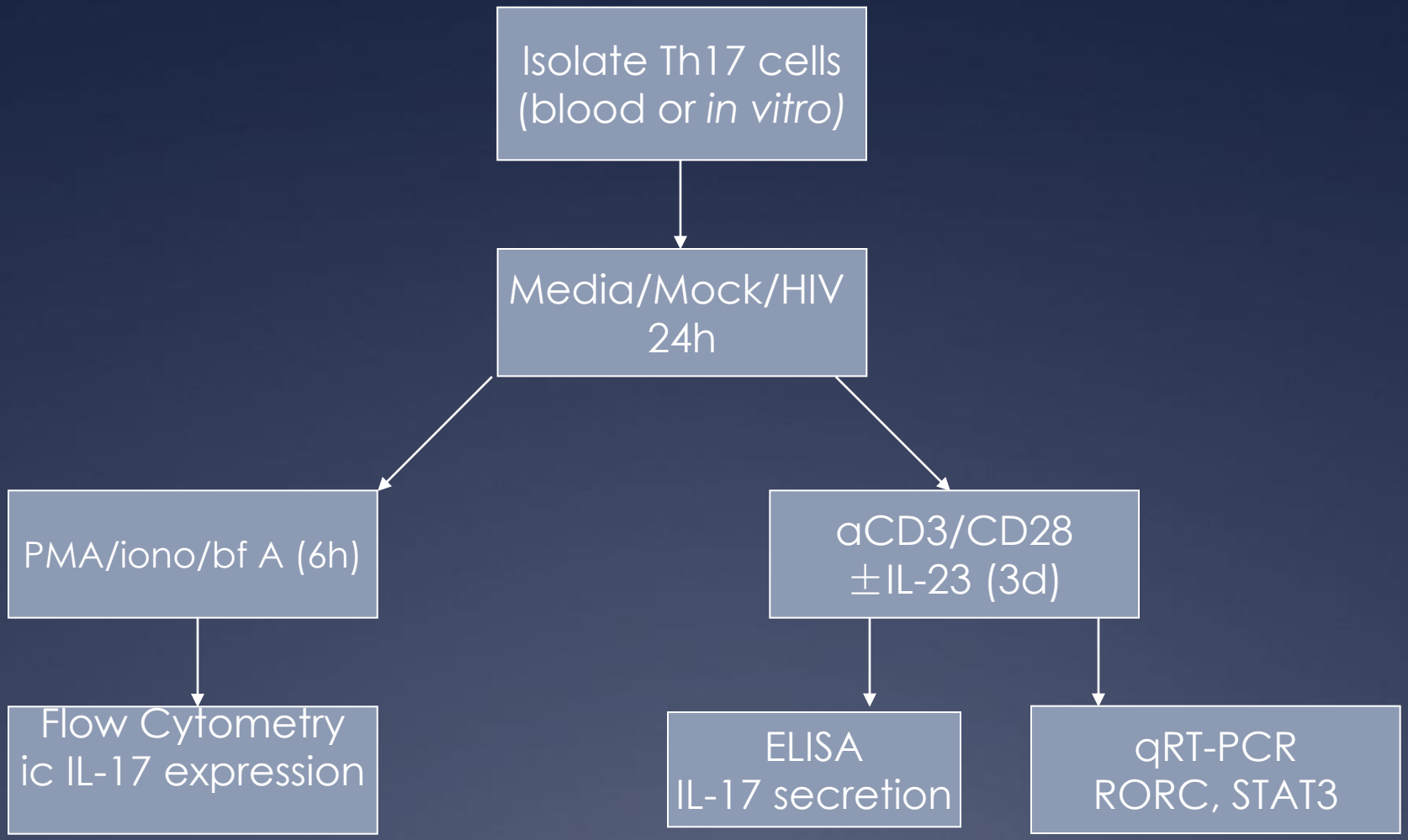


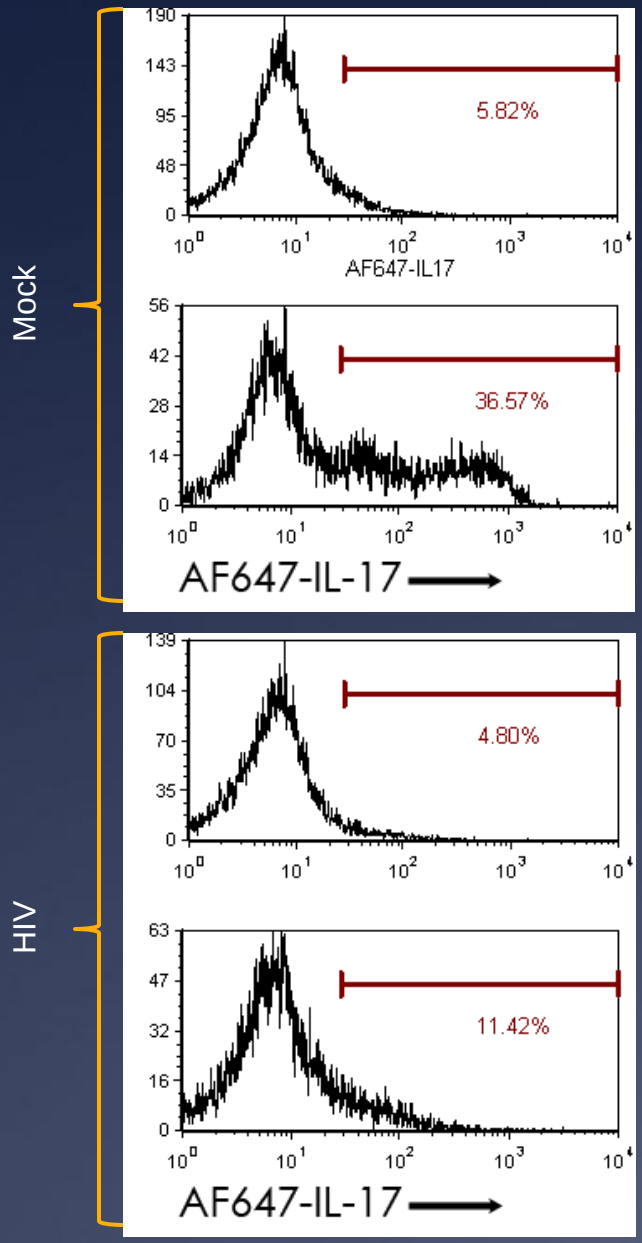
Blood Th17 isolation

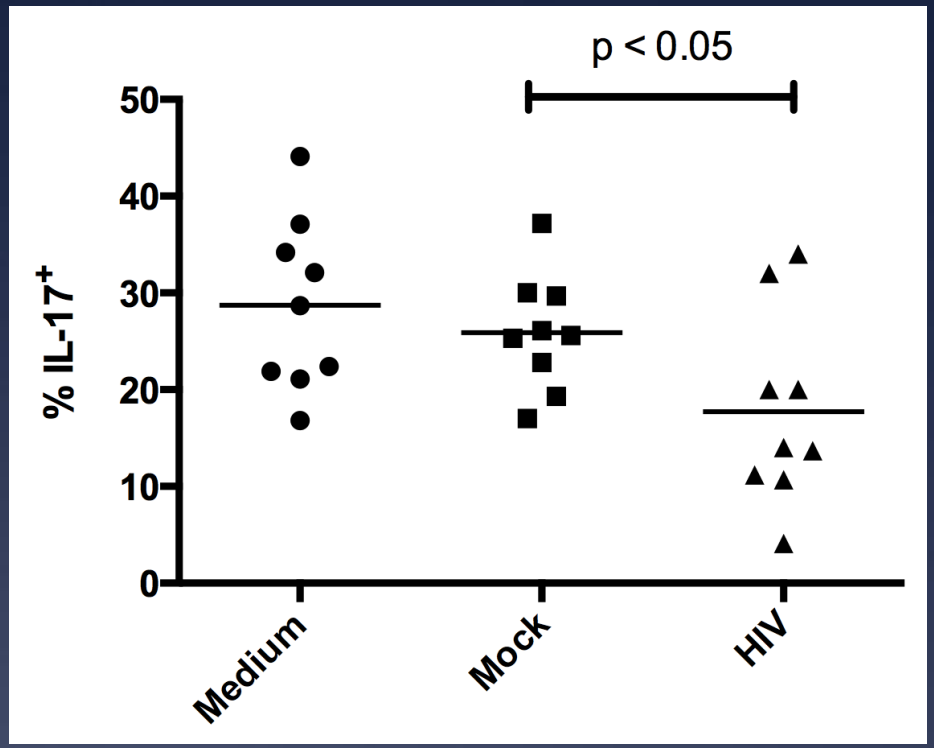
Magnetic Isolation
$CD4^+/CCR6^+/CXCR3^-$



Experimental Design

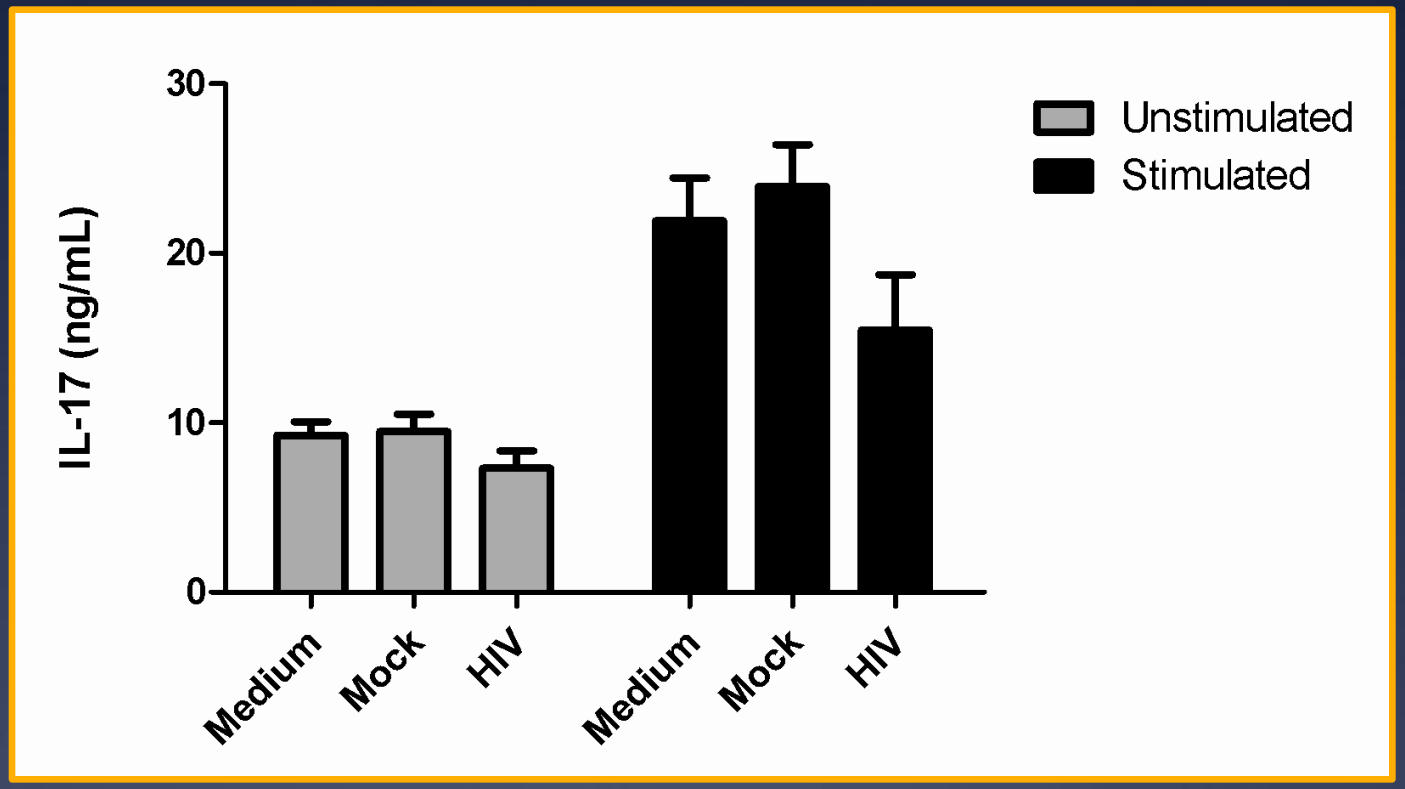




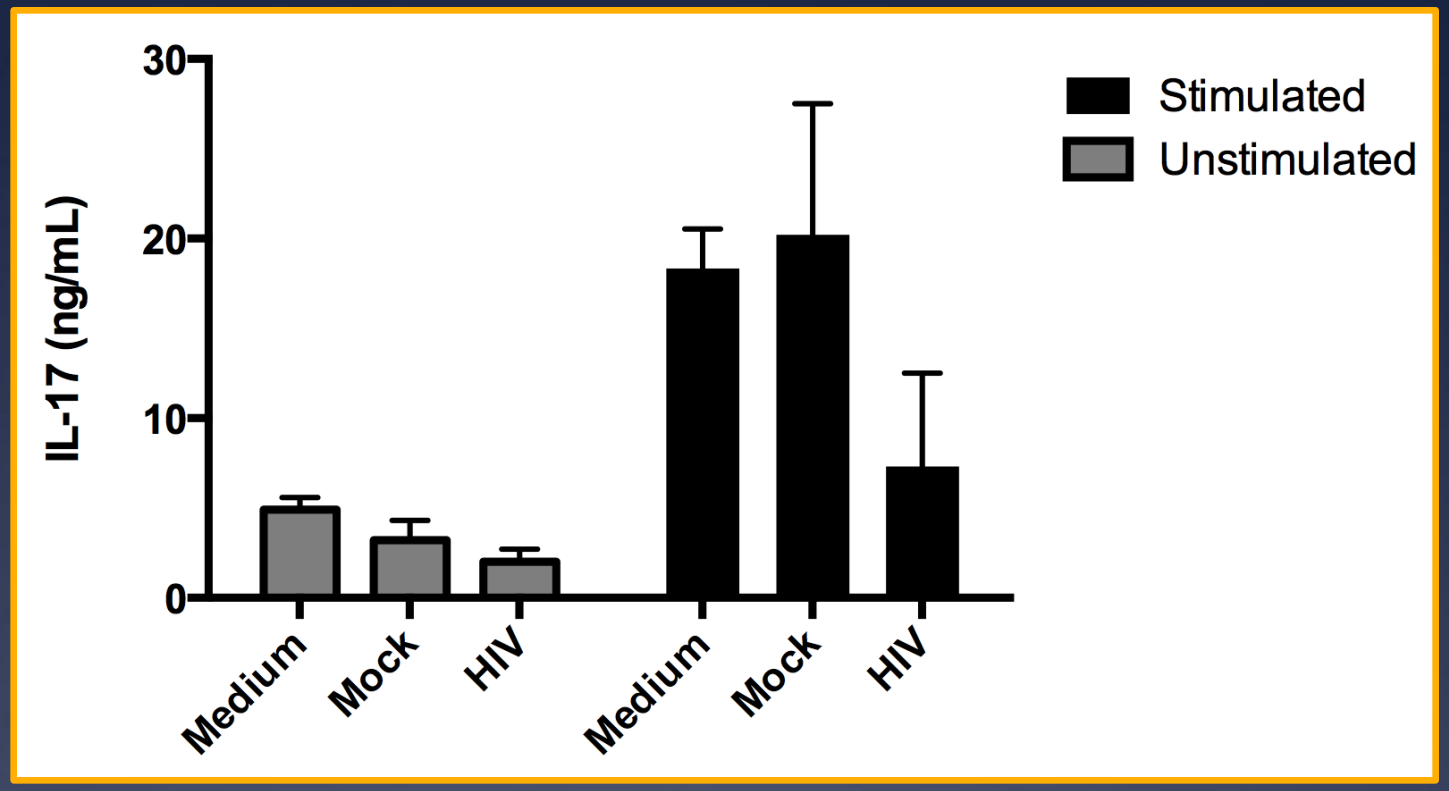


- *in vitro* Th17 cells
- PMA/iono/Bfa (6h)
- n=9
- Mean + SEM

- *In vitro* Th17 cells
- aCD3/28, IL-23 (3d)
- n=9
- Mean + SEM

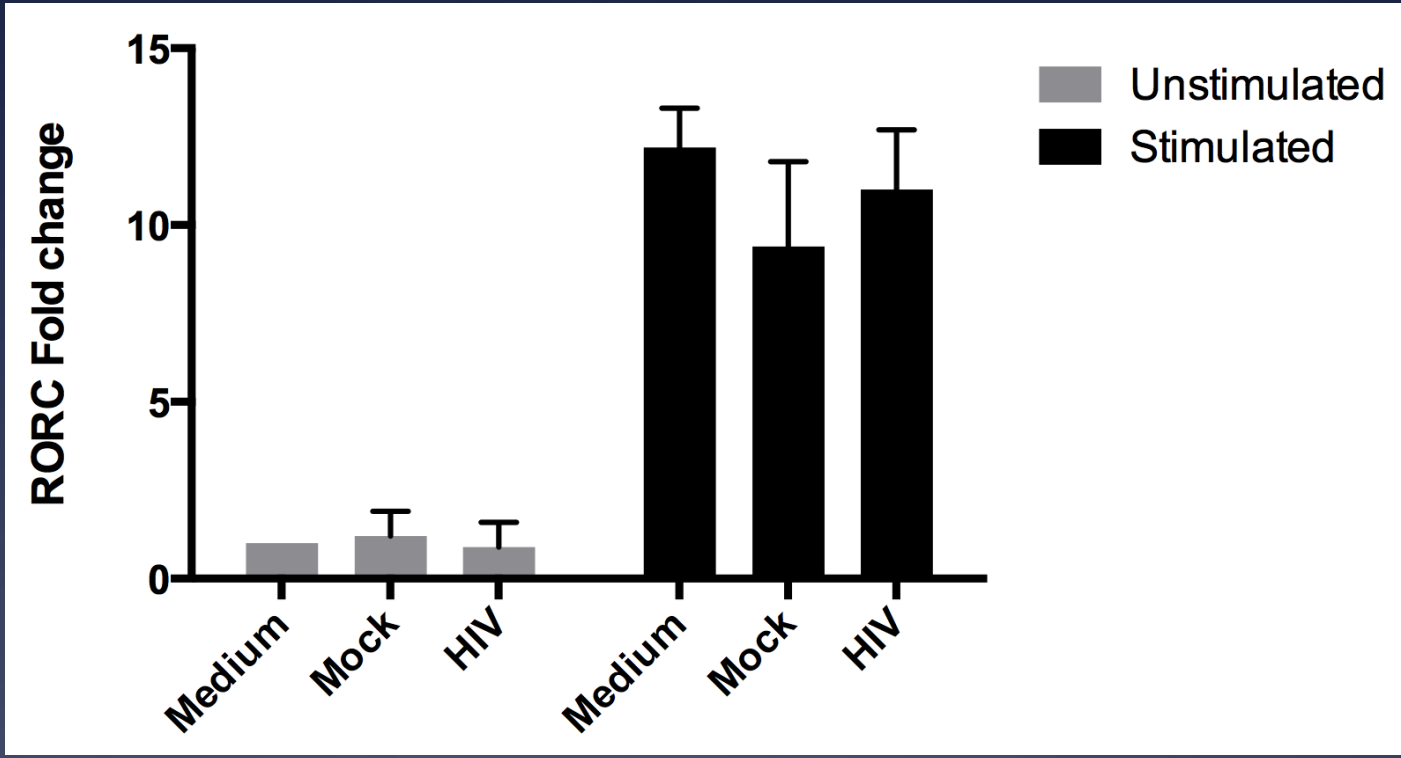


- Blood Th17 cells
- aCD3/28, IL-23 (3d)
- n=9
- Mean + SEM



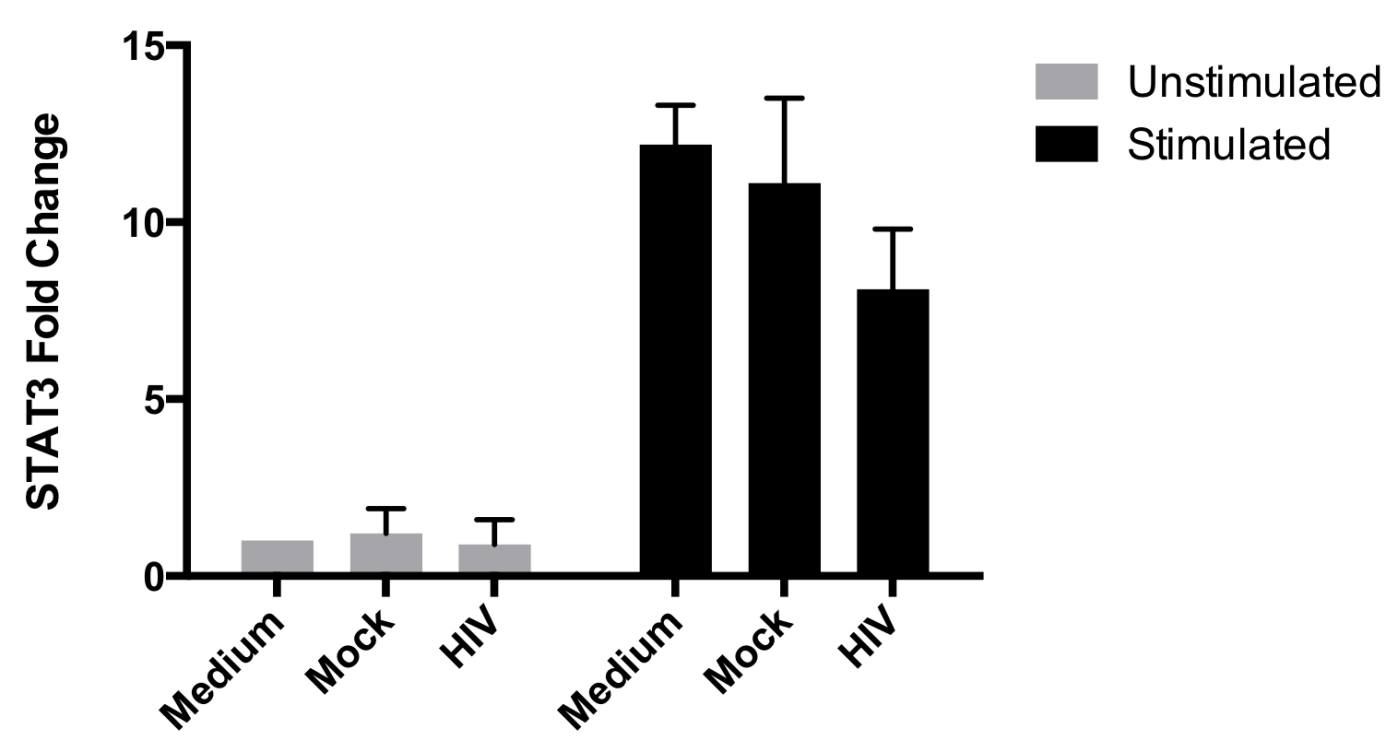
RORC - mRNA

- Blood Th17 cells
- aCD3/28, IL-23 (3d)
- n=9
- ΔΔCt method (semi-q)
- Mean + SEM

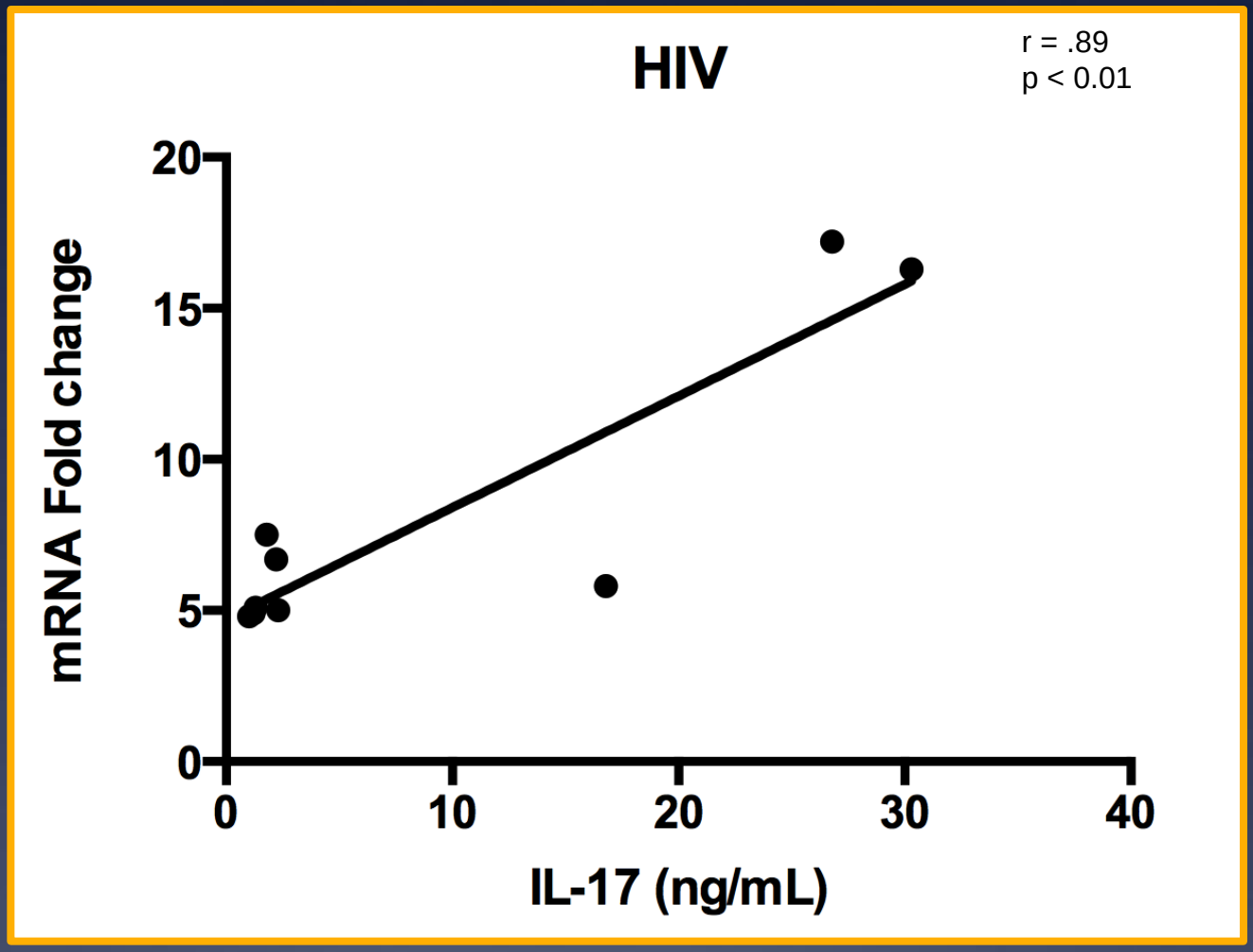


STAT3 - mRNA

- Blood Th17 cells
- aCD3/28, IL-23 (3d)
- n=9
- ΔΔCt method (semi-q)
- Mean + SEM



- Blood Th17 cells
- STAT3 mRNA/IL-17
- aCD3/28, IL-23 (3d)
- n=9



Conclusions

1. Exposure to HIV inhibits expression of IL-17 by *in vitro*-differentiated Th17 cells ($p < 0.05$)
2. Exposure to HIV inhibits secretion of IL-17 by blood-derived and *in vitro*-differentiated Th17 cells
3. Reduction in IL-17 secretion by HIV-treated blood Th17 cells positively correlated with reduced STAT3 transcription ($p < 0.01$, $r = 0.89$)

Significance

- Results indicate HIV capable of inhibiting IL-17 expression by Th17 cells
- May provide targets to reduce immune exhaustion/Th17 deficit in HAART-treated pts
- May explain non-lethal dysfunction of Th17 cells

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