Combined IL-21 and IFNα treatment limits inflammation and delay viral rebound in ART-treated, SIV-infected macaques

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Interleukin-21 treatment in SIV-infected RM 


- Paucity of IL-21-producing CD4+ T cells is associated with Th17 depletion in SIV-infected RM (Micci, *Blood* 2012);

- Loss of function of intestinal IL-17 producing cells contributes to inflammation and viral persistence in SIV-infected RM (Ryan, *PLoS Pathogens* 2016)

- IL-21 treatment in acute SIV infection preserves Th17 cells and reduces microbial translocation (Micci, *PLoS Pathogens* 2014)

- IL-21 treatment in ART-suppressed, SIV-infected RM reduces residual inflammation and viral persistence (Micci, *J Clin Invest* 2015)
IL-21 limits intestinal T cell activation and proliferation

But modestly reduces plasma viremia upon ART-interruption

- No differences in timing of rebound
- No significant differences in viremia at any experimental points

Micci L, J Clin Invest 2015
Rationale and Study design

Time
HIV reservoir
HIV reservoir
HIV reservoir
HIV reservoir
HIV reservoir

Inflammation
Antiviral functions

B: ART + IL-21 + IFNα
A: ART

Weeks Relative to infection
0 1 2 5 6 7 9 11 15 19 23 26 27 29 31 36 39 47 50 56

Gr. 1: ART; #7 RMs
Gr. 2: ART+IL21+IFN-α; #14 RMs

SIVmac239

Phase 1

LOD: 30 copies/mL

p<0.01

ISG expression by RNAseq in total PBMCs
IL-21+IFNα treated RM s maintain low levels of activation on ART

CD4+ T cells

CD8+ T cells

PB

RB
IL-21+IFNα treated RMIs show reduced viral reservoir on ART

Longitudinal measurements – including post IL-21 but pre IFNα – are pending

Additional QVOA analyses in purified CD4+ T cells from LN are pending
IL-21+IFNα treated RMs show delayed and reduced viral rebound after ATI

Measures of viral persistence post ATI are pending

What is happening after IFNα treatment has been discontinued?
Preliminary conclusions

IL-21 + IFNα administration resulted in:

- Reduced mucosal and systemic immune activation
- Reduced cell-associated SIV-DNA in GI tract
- Delayed and reduced viral rebound post ATI (still during IFNα treatment)
- IFNα treatment was not associated with deleterious effects on T cell levels or immune activation, either on ART or after ATI

Multiple immunologic and virologic parameters (including replication competent virus) are pending (longitudinal, blood and tissues)

Impact on viral persistence after discontinuation of IFNα needs to be determined
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