T regulatory cell depletion in controller macaques reactivates SIV while boosting CTLs

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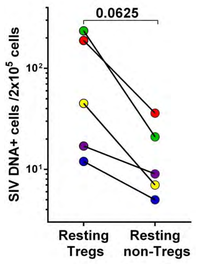
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Background

T regulatory cells (Tregs) can be latently infected with HIV and may represent a potentially important HIV reservoir

- they expand in blood and tissues in chronically HIV-infected patients and SIV-infected macaques (Moreno-Fernandez et al., 2012)
- HIV/SIV DNA positive cells are more abundant in Tregs than in non-Tregs in patients on ART and in rhesus macaques (RMs) (Tran et al., 2008; Allers et al., 2010)
- Tregs are less susceptible to cell death than conventional T cells



T regulatory cells (Tregs) have a critical contribution to the shape of the viral reservoir

- During acute infection, Tregs decisively contribute to the establishment of HIV reservoir by reversing CD4⁺ T cell immune activation status
- During chronic infection, Tregs contribute to the impairment of CTL responses, as their expansion correlates with loss of CTL function and their *ex vivo* depletion enhances T cell responses to HIV/SIV antigens.
- The HLAB27⁺and B57⁺ HIV-specific CD8⁺ T cells from elite controllers evade Treg suppression

These observations support a major involvement of Tregs in suppressing protective effector immune responses against HIV

This Treg effect may be critical for the "shock and kill" strategies, which require increased virus killing of the reactivated virus

Hypothesis

Treg depletion is a valid HIV cure approach, as through a a single intervention we can

reduce the size of the reservoir

- **reactivates the virus**
- **boosts cell-mediated immune responses**

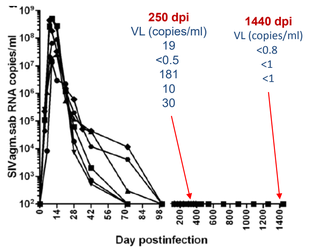
Study design

•Treg depletion with Ontak (Denileukin diftitox, recombinant IL-2 combined with diphteria toxin A chain) in 2 spontaneous controller RMs infected with SIVsab

•Two Ontak treatments (with a duration of 5 days each) were initiated at 360 days post-infection

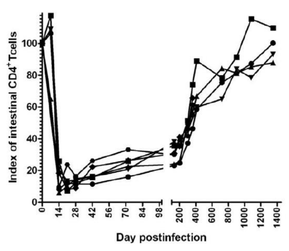
SIVsab infection of RMs as a model of functionally-cured SIV infection

Plasma Viral Loads



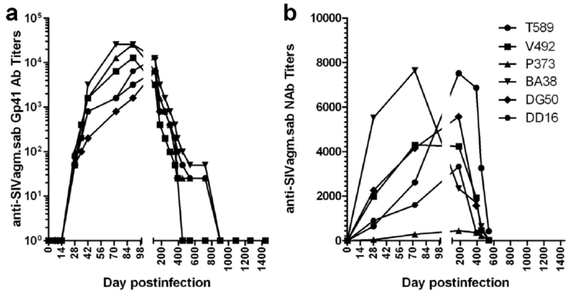
High levels of viral replication during acute infection, followed by complete control during the chronic stage (6 years p.i.)

Mucosal CD4⁺ T cells

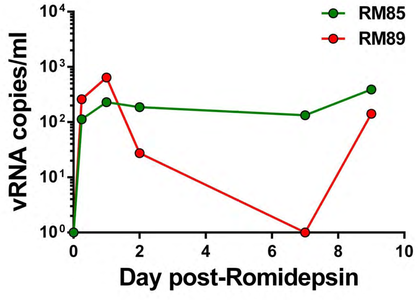


Massive mucosal CD4⁺ T cell depletion during acute infection, followed by COMPLETE mucosal CD4⁺ T cell restoration

Control of SIVagm in RMs is a functional cure and not an elite controlled infection

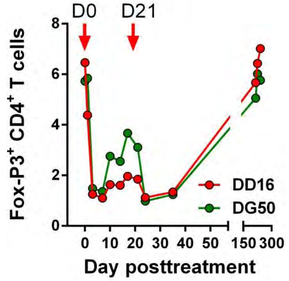


SIVsab can be induced *IN VIVO* from latently infected cells

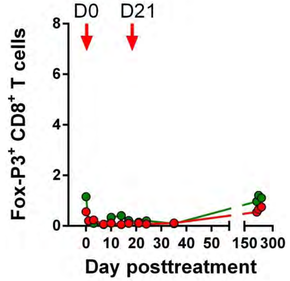


Ontak successfully depletes Tregs in RMs

CD4⁺ T cells

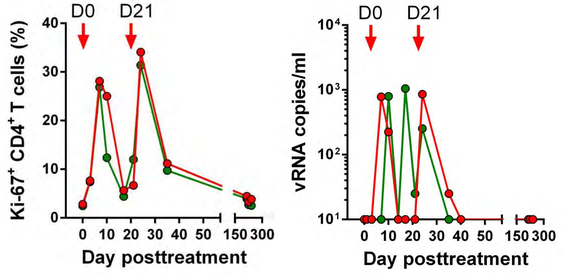


CD8⁺ T cells

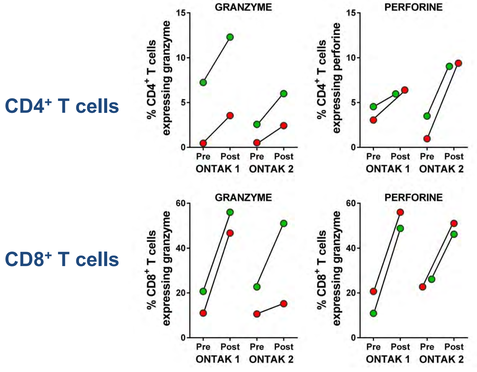


Impact on CD8⁺ T cells is minimal, as only a small fraction of CD8 T⁺ cells express Fox-P3

Ontak activates CD4+ T cells and reactivates the latent virus

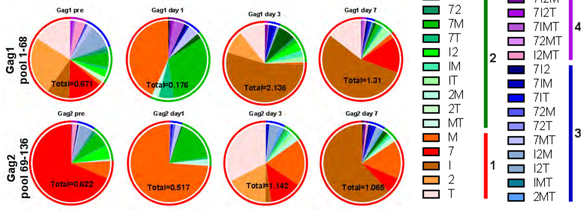


Treg depletion boosts the cytolitic activity of CTLs

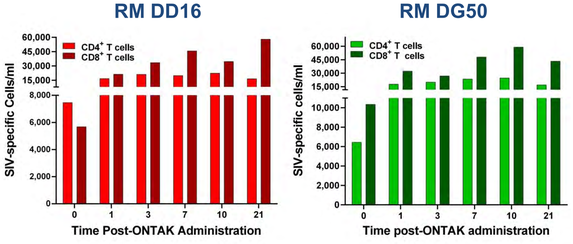


Treg depletion boosts the SIV-specific CD4⁺ and CD8⁺ T cells

SIV-specific CD8⁺ T cells (RM DD16)



Overall SIV-specific T cell responses



Conclusions

- **Treg depletion in chronically SIV-infected superelite controller RMs, results in both reactivation of latent virus and boost of CTL responses**
- **The overall Treg ability to control immune responses was significantly impaired in spite of the fact that Treg depletion was incomplete**
- **As none of the LRAs in development has been reported to have such a dual activity, our strategy holds great promises for cure research**
- **Combination between Treg depletion and latency reversing agents may exert a significant impact on the viral reservoir**