



# P16-08. Combined blockade of the PD-1 and IL-10 pathways synergistically enhance HIV-specific CD4 T cell functions

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## PI6-08. Combined blockade of the PD-1 and IL-10 pathways synergistically enhance HIV-specific CD4 T cell functions

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### Background

HIV-specific T cell dysfunction is a prominent feature of HIV infection. We have reported that the PD-1 and IL-10 pathways mediate a reversible impairment of HIV-specific proliferative T cell responses. However, the responses are frequently modest and not all infected subjects respond to blockade of either pathway. It is therefore crucial to determine whether combined PD-L1 and IL-10R $\alpha$  blockade can overcome these limitations and synergistically revive HIV-specific T cell responses.

### Methods

We investigated 17 persons with HIV infection that were divided into groups according to treatment status. We used Luminex arrays to measure IFN- $\gamma$  and IL-2 secretion in supernatants of CD8-depleted PBMC stimulated for 48 h with a Gag peptide pool or left unstimulated in the presence of isotype control antibody, anti-PD-L1, anti-IL-10R $\alpha$  or combined blockade.

### Results

In viremic individuals (n = 10), blockade of a single or two inhibitory pathways resulted in a significant increase in IFN $\gamma$  secretion by HIV-specific CD4 T cells when compared to the isotype control condition (p < 0.0001, Friedman test with Dunn's post-test). The median fold-increase in IFN- $\gamma$  secretion was 1.8 for PD-L1, 5.1 for IL-10R $\alpha$  and 13.4 for combined blockade. In subjects with higher viral loads, combined PD-L1/IL-10R $\alpha$  blockade resulted in an

occasionally dramatic synergistic effect, even when a limited increase was seen with PD-L1 blockade alone. We also observed a non-significant trend toward increased IL-2 secretion upon inhibitory blockade. In contrast, in aviremic subjects, IL-10R $\alpha$  blockade was not more effective than PD-L1 blockade, and additive effects of combined blockade were inconstant.

### Conclusion

These data indicate that combined blockade of the PD-1 and IL-10 pathways synergize to restore effector functions of HIV specific CD4 T cells and demonstrate the potential of targeting multiple inhibitory pathways to reverse T cell exhaustion in humans. These results may have significant implications for development of novel immunotherapeutic interventions.