

Abstract Number 73LB - (Oral)

PGT121 COMBINED WITH GS-9620 DELAYS VIRAL REBOUND IN SHIV-INFECTED RHESUS MONKEYS

Basic Science: (D) HIV Reservoirs, Latency, and All Curative Strategies Including Therapeutic Vaccines and Gene Therapy

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Background: Previous studies have shown that broadly neutralizing antibodies (bNAbs) administered at the time of ART discontinuation can provide direct antiviral effects, but whether bNAbs can effectively target the viral reservoir during ART suppression remains to be determined. In this study, we assessed the impact of the V3 glycan-dependent bNAb PGT121 combined with the TLR7 agonist GS-9620 in ART suppressed, SHIV-infected rhesus monkeys.

Methods: 44 rhesus monkeys were infected with SHIV-SF162P3 and initiated ART (TDF/FTC/DTG) on day 7 of infection. Following 96 weeks of continuous daily suppressive ART, animals received 10 mg/kg PGT121 by infusion (every 2 weeks x 5 doses), 0.15 mg/kg GS-9620 by oral gavage (every 2 weeks x 10 doses), both PGT121 and GS-9620, or sham controls (N=11/group). At week 130, which was 16 weeks after the final PGT121 and GS-9620 doses, ART was discontinued and viral rebound was monitored.

Results: PGT121 administration resulted in 10 weeks of therapeutic antibody levels, followed by a decline to undetectable levels in peripheral blood, lymph nodes, and colorectal tissue for >8 weeks prior to ART discontinuation. Autologous cellular immune responses were minimal and were not increased by PGT121+GS-9620 administration. Viral DNA in lymph nodes was markedly lower in PGT121+GS-9620 treated animals as compared with sham controls (P=0.004, Mann-Whitney test). Following ART discontinuation, 100% (11 of 11) of sham controls exhibited rapid viral rebound with a median rebound time of 21 [IQR 21-42] days. In contrast, only 55% (6 of 11) of PGT121+GS-9620 treated animals rebounded by day 140 following ART discontinuation (P=0.03, Fisher's exact test) and demonstrated a substantial delay in median rebound time of 112 [IQR 84-140+] days (P=0.0005, Mann-Whitney test) as well as a 2.64 log reduction of peak viral loads and a 1.52 log reduction of setpoint viral loads as compared with sham controls (P<0.0001, Mann-Whitney test). All PGT121+GS-9620 treated animals exhibited setpoint viral loads <400 RNA copies/ml. Intermediate outcomes were observed in the animals that received PGT121 alone.

Conclusion: PGT121 combined with GS-9620 during ART suppression substantially delayed and controlled viral rebound following ART discontinuation in SHIV-infected rhesus monkeys that initiated ART during acute infection. These data suggest that bNAb administration together with innate immune stimulation during ART suppression may effectively target the viral reservoir.