 OA05.01

Durable Suppression of Established Transmitted Founder Replication in Infected BLT Humanized Mice by Vectored ImmunoTherapy

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Background: Recent reports in humanized mice and monkeys have found that broadly neutralizing antibodies (bNAb) can suppress the replication of laboratory strains of HIV and SHIV while bNAB concentration remains high. Vectored ImmunoProphylaxis (VIP) results in long-lived bNAB expression following a single intramuscular (IM) injection of a specialized viral vector, and this approach has been demonstrated as a means of durably suppressing viral load. However, previous reports of VIP-delivered bNAb for HIV therapy required prior antiretroviral drug therapy to reduce viral load to prevent escape.

Methods: Humanized BLT mice were infected IV with the REH/r.c transmitted molecular founder strain of HIV. A low dose of combination antiretroviral therapy (cART) was administered to these animals for 5 weeks, followed by a single IM injection of VIP expressing VRC07 or luciferase. Mouse plasma was analyzed by ELISA to determine antibody concentration and by qPCR to determine viral load. Cellular fractions were analyzed...
by flow cytometry to quantify human CD4 cells over time. After sacrifice, plasma was subjected to a clinically validated ultrasensitive PCR-based viral load assay.

**Results:** We detected viral loads of $10^5$ copies/mL in infected mice prior to low-dose ART treatment, which resulted in a transient reduction and rebound to pre-therapy loads. Following VIP administration, we observed a rapid increase in the blood concentration of VRC07. Mice expressing VRC07 exhibited a sharp decline in viral load to undetectable levels and an increase in CD4 cells over four weeks and this effect was sustained for the remaining 8 weeks of the study. In contrast, mice expressing luciferase exhibited increasing viral loads with concomitant decreases in CD4 cells throughout the study.

**Conclusions:** Our results demonstrate that VIP expressing VRC07 is sufficient to suppress actively replicating transmitted founder virus at high viral load and support efforts to move Vectored ImmunoTherapy into clinical trials with infected patients.

**OA05.03**

**Efficitation of Immune Responses by a DNA/MVA Vaccine in ART Treated Patients in a Treatment Interruption Trial**

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**Background:** GV-TH-01, a Phase 1 open-label trial of GOVX-B11, a DNA/MVA prime-boost regimen, in HIV infected patients on ART was undertaken to evaluate safety and vaccine-elicited T cell responses, and to explore viral rebound during analytical (treatment interruption (TI)).

**Methods:** Patients who began ART within 18 months of seroconversion and had sustained plasma HIV-1 RNA < 50 c/mL for at least 6 months were enrolled. Patients received a total of 4 inoculations at intervals of 8 weeks. 2 of GpA/JS7 DNA (3mg) followed by 2 of MVA/HIV62B (10^7 TCID50). At 8 weeks after the last immunization, plus an efavirenz wash-out if needed, patients entered a TI phase of 12 weeks, after which ART was reinstituted. T cell responses were scored for IFN-γ or IL2 by flow cytometry following stimulation with Gag, Env and Pol peptides. Responses were considered positive if ≥2-fold higher than pre-vaccination.

**Results:** 8 of 9 men completed all vaccinations. For the 8, median age was 37.5 yrs, baseline CD4 count was 691/µL (501-1612/µL) and all had HIV-1 RNA < 50 c/mL. Median viral load prior to ART was 5.1 log10 c/mL (2.6-7.2 log10 c/mL). No serious adverse events occurred. After the 1st or 2nd MVA/HIV62B immunization, Gag-specific CD8 T cells were boosted over pre-vaccination levels in 7 out of 8 (P < 0.05) whereas Gag-specific CD4 T cells were boosted in 5 of 8 patients (P = 0.2). 6 of 8 patients elicited previously undetectable CD8 responses whereas 5 of 8 elicited previously undetectable CD4 responses to Gag epitopes. Gp120 or gp41-specific antibody responses were boosted in 3 of 8 patient and 2 of 8 patients respectively. Excluding one acute seroconverter, the median reduction in HIV-1 RNA at weeks 2, 6, and 12 compared to pre-ART levels was $-2.2$, $-1.3$ and $-0.8$ log10 c/mL.

**Conclusions:** This trial demonstrates the potential for GOVX-B11 to boost both T cell and antibody responses in a therapeutic setting. A placebo-controlled trial will be required to further assess the therapeutic benefit of the vaccine.