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DNA-eCD4-Ig Decreased HIV-1 Reservoir on ART & Delayed Viral Rebound in Humanized Mice

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BACKGROUND

AAV-delivered eCD4-Ig can prevent infection with more breath than individual broadly neutralizing antibodies (bNAbs). This approach can block multiple challenges of SHIV in NHP and HIV in hu-mice models in the absence of anti-AAV serology. However, the ability of eCD4-Ig to impact HIV levels during ART or following ART interruption have not been studied. DNA Launched (DL) eCD4-Ig with co-delivery of enzyme IgE-TPST2 in vivo leads to expression of this highly structured molecule and allows for in vivo enhanced sulfation, which is functional and neutralizes the HIV-1 Global Panel with high potency. In this study, we tested DL-eCD4-Ig co-delivered with IgE-TPST2 in HIV-infected bone marrow-liver-thymus (BLT) humanized mice under ART suppression and after ART interruption.

METHODS

AAV delivered human cytokine-differentiated BLT hu-mice were infected with transmitted/ founder (T/F) virus HIVsuma. Following 4 to 5 weeks of viremia and subsequent suppression on cART (FTC+TDF+RAL), DL-eCD4-Ig/IgE-TPST2 was delivered IM three times (Fig 1). In-vivo expression of DL-eCD4-Ig was detected by ELISA and dosing optimized. Leukocyte subsets and activation were measured by flow cytometry. Plasma viral load (sensitivity >100 copies/ml), CD4+T cells and NK cells were monitored weekly. Proviral DNA size was measured by total HIV DNA assay. Differences between and within groups were determined by two-sided nonparametric tests with 0.05 alpha. Survival analysis used to evaluate time of viral rebound between groups.

In vivo delivery of DNA-eCD4-Ig/IgE-TPST2 reduces persistent HIV-1 reservoir size and delays viral rebound after ATI in HIV infected BLT humanized mice.

RESULTS

We confirmed hu-mice plasma levels with eCD4-Ig can elicit strong ADCC by NK cells against HIV-1 infected cells. DL-eCD4-Ig/IgE-TPST2 delivery in vivo into ART-suppressed humanized mice (Fig 1) resulted in a significant delay of the viral rebound after ART interruption (Fig 2) with a retention of weight and CD4 T-cell frequency during ATI. An acute temporal mean 12.5% CD4+ T cells decline and mean 5-fold increase in NK% in CD45+ cells were observed 1 week after the first dose of electroporation on ART without any detectable change in viral load. Two weeks after first dose, total HIV proviral DNA in PBMC (Fig 3) showed a significant decrease (p=0.0497) consistent with delay in viral rebound.

CONCLUSIONS

- DNA Launched eCD4-Ig co delivered with IgE-TPST2 administered to hu-mice on ART was able to reduce the cellular levels of HIV-1 and delay viral rebound after ART interruption.
- DNA-eCD4-Ig/IgE-TPST2 could be pursued as a strategy to achieve a cure or ART-free remission of HIV infection.

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Fig. 1

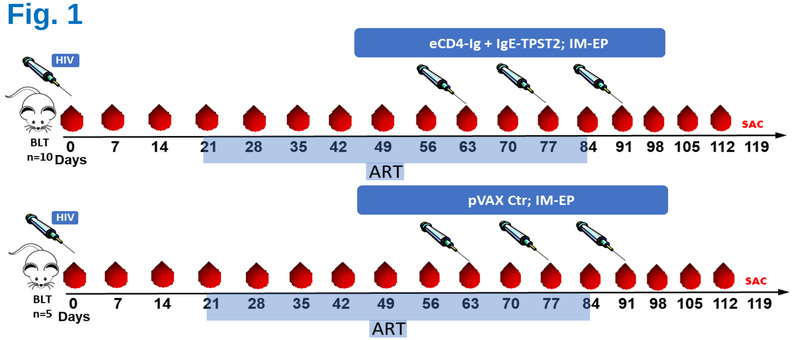


Fig. 2

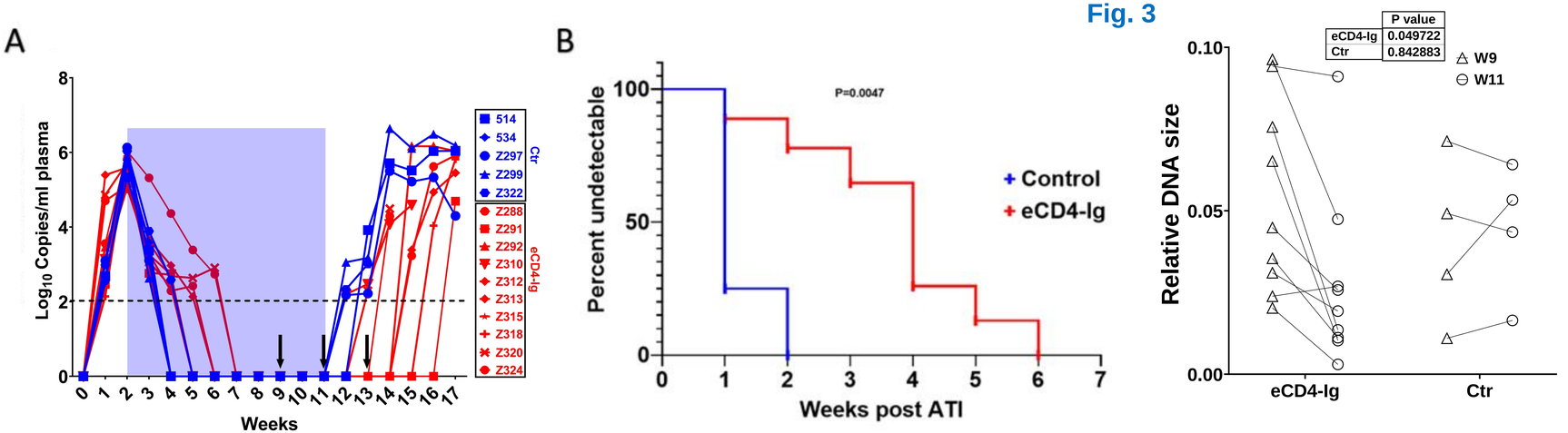


Fig. 3