IMPACT OF GS-986, PGT121 AND N6-LS ON CNS IMMUNE ACTIVATION IN SHIV-INFECTED MACAQUES

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BACKGROUND:

- Kick and kill strategies using TLR-7 agonist and broadly neutralizing antibodies (bnAb) have shown promise in non-human primates, but effects on the central nervous system (CNS) have not been evaluated.
- The blood-brain barrier limits the penetration of antibodies into the CNS.
- Thus there is a potential for kick and kill strategies to increase immune activation without elimination of infected cells.

METHODS:

- Male rhesus macaques (negative for protective MHC allele Mamu A-01, B-08, B-17) were inoculated with SHIV-1157ipd3N4 and initiated on ART (PMPA, FTC, DTG) on Day 14.
- Active group (n=8) received at least 7, 2 and 2 doses of GS-986, PGT121 and N6-LS (number of bnAb administrations were limited by the development of anti-drug antibodies).
- ART was ceased 2 wks after plasma bnAb Levels <0.25ug/mL.
- Control group (n=8) received saline and ART was ceased at wk 40.
- Plasma and cerebral spinal fluid (CSF) SHIV RNA levels were measured by PCR and soluble markers of immune activation by multiplex assay using Luminex.

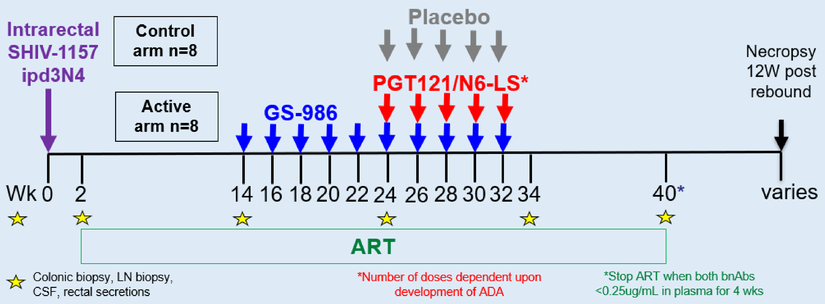

Figure 1. Study Schema

No increase in CSF SHIV RNA or markers of immune activation after TLR-7 agonist and bnAb kick and kill

RESULTS:

Viral dynamics

- Median wk 2 (pre-ART) plasma and CSF SHIV RNA was 5.7 (range 4.1-6.8) and 3.1 (range 2.2-4.2) log_{10}copies/mL.
- Plasma SHIV RNA was undetectable in all animals by wk 8 and remained undetectable until ART interruption.
- CSF SHIV RNA was undetectable in all animals at wks 14 and 24.

Soluble markers of Immune activation

- Levels of CSF IL-15, MCP-1, IL-8, IL-1RA, IL-2, and G-CSF increased post infection, and decreased after ART initiation.
- No increases in CSF markers of immune activation were seen after GS-986 or bnAb administration.

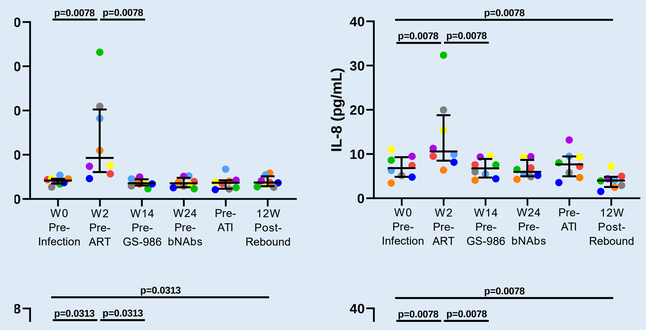

Figure 3. Markers of selected soluble markers of immune activation measured in CSF of active group (n=8). Lines represent median and interquartile range. Each color represent data from an individual animal.

RESULTS (cont.):

Viral Rebound

- Median time to viral rebound was 6 wks in the active group vs 3 wks in the control group (p=0.024).

Figure 2. Time to viral rebound

Hsu et al., Delay in Viral Rebound with TLR7 agonist, N6-LS and PGT121 in SHIV-infected Macaques. CROI 2020. Session: Targeting the Persistent HIV Reservoir, Tues, March 10, 2020.

- At 12 wks post rebound, median plasma SHIV RNA was 1.2 (range 1.0-2.2) and 2.1 (range 1.0-2.8) log_{10}copies/mL in the active and control groups respectively.
- CSF SHIV RNA was only detectable at low levels in 1 active and 1 control animal.

Conclusion:

- Administration of GS-986, PGT121 and N6-LS did not increase SHIV RNA or markers of immune activation in CSF, suggesting that this strategy may be pursued in humans without impacting CNS activation.

Material has been reviewed by the Walter Reed Army Institute of Research. There is no objection to its presentation and/or publication. The opinions or assertions contained herein are the private views of the author, and are not to be construed as official, or as reflecting true views of the Department of the Army or the Department of Defense. Research was conducted under an approved animal use protocol in an AAALACi accredited facility in compliance with the Animal Welfare Act and other federal statutes and regulations relating to animals and experiments involving animals and adheres to principles stated in the Guide for the Care and Use of Laboratory Animals, NRC Publication, 2011 edition.