Preclinical evaluation of a subunit vaccine platform for HTLV-1

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Background:
There is no cure or vaccine for the oncogenic HTLV-1. Although related to HIV, HTLV-1 subtypes have remarkably low genetic variability and vaccines targeting the envelope glycoprotein (GP) of the virus have elicited partial protection in several preclinical models. However, none of these vaccine studies have been evaluated in the clinic or reported on the conformation of HTLV-1 GP used for vaccination. Prefusion conformation of GP is required for native HTLV-1 virions to infect cells and likely represents the principal conformational target of GP for antibody-mediated virus neutralization and/or prevention of cell-cell spread. Thus, we aimed to engineer a prefusion conformed HTLV-1c GP using a proprietary, protein trimerization motif called the molecular clamp and report on preclinical investigations of this protein termed, GPclamp.

Methods:
SDS-PAGE, size-exclusion chromatography, LAT-27 affinity ELISA and transmission electron microscopy were used to characterize GPclamp. We immunized first generation cross of C57BL/6 x BALB/c mice with adjuvanted and non-adjuvanted regimens including GPclamp and evaluated immune responses using ELISA and novel, high-throughput flow cytometry based assays.

Results:
Characterization of GPclamp following expression on ExpiCHO cells showed a \textasciitilde 73 kD protein that bound to HTLV-1 neutralizing antibody LAT-27 and adopted the prefusion, trimeric conformation of GP. Intramuscular vaccination of mice with GPclamp and an MF59 like adjuvant, Addavax, elicited robust and broad GP-specific T helper (Th) cell and cytotoxic T lymphocyte (CTL) responses \textit{in vivo} as well as high titres of antibodies that bound to HTLV-1 infected cell lines. We are now in the process of performing passive transfer studies to evaluate vaccine efficacy in humanized mice that will be challenged with HTLV-1 infected cells.

Conclusion:
The molecular clamp platform can be harnessed to develop HTLV subunit vaccine candidates and we aim to develop this platform to be clinically viable for this purpose.

Disclosure of Interest Statement:
The molecular clamp technology was invented by Keith J Chappell, Paul R Young and Daniel Watterson and Intellectual Property is covered by patent WO2018176103A1