Presentation title: INVESTIGATING PREVENTATIVE AND THERAPEUTIC INTERVENTION STRATEGIES AGAINST HUMAN T-LEUKAEMIA VIRUS 1 (HTLV-1) IN A HUMANISED MOUSE MODEL OF INFECTION

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Synopsis

Human T leukemia virus 1 (HTLV-1) infection remains refractory to known preventative and therapeutic interventions. Humanised mice are an important tool to study the efficacy of drugs against infectious diseases and are instrumental in progressing promising drug candidates into the clinic. The work presented here focusses on the development of a humanised mouse model of HTLV-1 infection and the efficacy of anti-viral and cell death inducing compounds against HTLV-1.

Our humanised mouse model of HTLV-1 infection recapitulates key aspects of human disease including persistent HTLV-1c pro-viral load (>10^6 copies/10^6 PBMC), lymphocytosis of mature $CD25^+CD45RO^+CD4^+$ and $CD8^+$ T cells (>10^7 T cells/ml blood), splenomegaly and lobed 'flower-like' nuclei of infected cells. This model is therefore suitable for the study of preventative and therapeutic intervention strategies against HTLV-1.

The HTLV-1 reverse transcriptase may be susceptible to some anti-retroviral compounds developed for HIV, a related retrovirus. We examined the efficacy of the HIV anti-viral, tenofovir alafenamide (TAF), in preventing HTLV-1 infection in a humanised mouse model of infection. Administration of TAF by daily oral gavage significantly reduced transmission of HTLV-1 in this model at clinically relevant doses of drug ($p=0.004$). This data seeks to inform clinical use of TAF in preventing HTLV-1c transmission. However, TAF demonstrated no efficacy in clearing an established infection in this model.

To clear established HTLV-1 infection from the host, infected cells must die. Therapeutically targetting cell death machinery to specifically kill HTLV-1-infected cells is the focus of current work in this model. Inhibitor of apoptosis proteins (IAPs) are critical for cell survival in certain conditions. The IAP antagonist, birinapant, is effective at killing HTLV-1-infected cells in this model and is a proof-of-concept for the use of IAP inhibitors against HTLV-1.

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