



ORAL PRESENTATION

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# Detection of HTLV-1 replication and CD4+ proliferation in the humanized BLT mouse model

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Human T-lymphotropic virus type-1 (HTLV-1) is the causative agent of adult T-cell leukemia/lymphoma (ATL) and a number of lymphocyte-mediated inflammatory conditions including HTLV-1-associated myelopathy/tropical spastic paraparesis. Development of animal models to study the pathogenesis of HTLV-1-associated diseases has been problematic and the mechanisms driving disease remain poorly understood. Here we report our findings of HTLV-1 infection in humanized nonobese diabetic (NOD) severe combined immunodeficiency (SCID) common gamma chain knockout (NSG) mice that have been implanted with fetal bone marrow-liver-thymus tissue (BLT). BLT mice were injected with lethally irradiated CD4+ HTLV-1 producing cells. Blood samples were collected every four weeks to monitor CD4 and CD8 phenotypes and DNA isolation. Concomitant with an increase in the number of CD4+CD25+ T-lymphocytes in exposed animals compared to controls, we observed a significant increase in the HTLV-1 viral DNA load. Surprisingly, unlike what we observed in macaques, HTLV-1 virus mutated to knockout Orf-I protein expression was able to infect BLT mice and high viral DNA loads were detected. However, after sequencing the orf-I region of proviral DNA from infected animals, we found reversion of the point mutation to wild type. This was observed as early as four weeks after exposure, indicating *in vivo* viral replication and selection for Orf-I expression. Thus, the BLT mouse model successfully recapitulates HTLV-1 infection and may serve as an important tool for investigating *in vivo* mechanisms of HTLV-1 disease pathology and in evaluating drugs and treatment strategies.

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