HUMANIZED ANIMAL MODELS FOR HIV, DENGUE AND ZIKA

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The new and improved humanized mouse (hu-mouse) models harboring a transplanted human immune system permit study of human pathogens in a setting mimicking the human host. The hu-HSC model is made by engrafting human hematopoietic stem cells whereas BLT mice are prepared by transplanting human fetal liver and thymic tissues in addition to HSC. Using this unique platform, our ongoing studies are focused on various aspects of viral pathogenesis, evolution, latency and human immune responses to HIV, Dengue and Zika.

HIV-1: In the context of achieving a complete cure for HIV/AIDS, in vitro viral out growth assays (qVOA) are currently the gold standard for measuring latent HIV-1 but these assays often fail to detect very low levels of replication-competent virus as shown with the “Boston patients”. Here we investigated an alternative in vivo approach for sensitive viral detection using hu-mice (hmVOA). Peripheral blood CD4+ T cell samples from HIV subjects on stable ART with undetectable viral loads by RT-PCR were first assayed by in vitro qVOA. Samples in which no virus was detected were injected into hu-mice. Viral outgrowth was seen in the hmVOA assay suggesting that it is more sensitive in detecting latent HIV-1.

HIV-2: Since no animal model exists to study HIV-2, another causative agent for AIDS, hu-mice were evaluated for their susceptibility to HIV-2 infection and testing a three drug formulation of anti-retrovirals (NRTIs abacavir and lamivudine, integrase inhibitor dolutegravir) (trade name, Triumeq®). Results showed that hu-mice are susceptible to HIV-2 infection showing persistent viremia and CD4 T cell loss, key hallmarks of AIDS pathogenesis. Oral drug treatment led to full viral suppression and protection from CD4 T cell depletion. Cessation of therapy resulted in viral rebound and CD4 T cell loss indicating re-emergence of the latent virus.

Dengue: There is no ideal animal model for Dengue pathogenesis and evaluating human immune response. In our dengue viral pathogenesis studies, hu-mice were shown to be permissive for productive infection resulting in viremia lasting up to three weeks. Fever characteristic of dengue was noted, with infected mice developing human neutralizing anti-dengue IgM and IgG antibodies.

Zika: While a variety of mouse and NHP models were shown to be susceptible to Zika viral infection, an in vivo model permitting human cell infection and human immune responses is lacking. Our recent experiments showed that hu-mice are susceptible to Zika virus with chronic viremia lasting more than 250 days. Human antibody response is seen. Virus could be detected in multiple organs with histopathology. Renal hemorrhage was a prominent feature in BLT mice.

SIV evolution into HIV: HIV-2 is thought to have originated from an SIV progenitor native to sooty mangabeys. We modeled the initial human transmission of SIVsm and its evolution to HIV-2 in hu-mice. Productive infection was seen during the initial challenge followed by chronic viremia and gradual CD4 T cell decline. Upon sequential serial passages, viral loads increased by the 5th generation leading to a more rapid CD4 T cell decline. Genetic analysis of human adapted virus revealed several amino acid changes in the nef, env and vpr regions.
Based on these studies above and from other laboratories, the new humanized mouse models show great promise for viral pathogenesis studies with new and emerging viruses, testing of novel therapeutics and prevention strategies.