Bradford K. Berges, J Antivir Antiretrovir 2011, 3:4
doi: http://dx.doi.org/10.4172/1948-5964.S1.6

OMICS Group Conferences
Accelerating Scientific Discovery

International Conference and Exhibition on
VIROLOGY
5-7 September 2011 Baltimore, USA

Humanized mice as a preclinical model for testing a novel HIV-1 fusion inhibitor

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The new generation of humanized mice involves transplantation of human hematopoietic stem cells into highly immunodeficient mouse strains, resulting in multi-lineage hematopoiesis and production of a large variety of human immune cell types. Human $CD4^+$ T cells, monocytes/macrophages, and dendritic cells are detected in blood, lymphoid and non-lymphoid organs and these animals are highly susceptible to HIV-1 infection. Several FDA-approved anti-HIV-1 drugs have been examined for efficacy in humanized mice and have been shown to reduce viral load and to prevent or reverse $CD4^+$ T cell loss in various sites, and the development of viral resistance has also been documented. In the present study, we tested an experimental HIV-1 fusion inhibitor (PIE12-trimer) for efficacy in blocking HIV-1 replication in humanized $Rag2^{-/-}\gamma c^{-/-}$ mice. PIE12-trimer binds to a highly conserved hydrophobic pocket on gp41 and prevents fusion of viral and host cell membranes. This drug functions at picomolar concentrations in vitro, is effective against a broad array of HIV-1 isolates, is refractory to development of resistance mutations, and is composed of D-amino acids and thus is highly resistant to degradation. We have determined the pharmacokinetics of PIE12-trimer in mice, administered it to $HIV\text{-}1^+$ humanized mice and monitored for changes in viremia and $CD4^+$ T cell loss in peripheral blood relative to untreated $HIV\text{-}1^+$ animals. Our results demonstrate the effectiveness of an investigational antiviral drug in vivo, and additionally show the utility of humanized mice to analyze the efficacy of new drugs prior to clinical trials.

Biography

Dr. Bradford K. Berges earned a Ph.D. from the University of Pennsylvania and did post-doctoral work at Colorado State University. He is currently an Assistant Professor of Microbiology and Molecular Biology at Brigham Young University. His research emphasis is on viral pathogenesis, using humanized mice as a model to study how human-specific viruses are transmitted and how they cause disease.