La Jolla, CA
April 17- 21
2016

hosted by the
INTERNATIONAL
SOCIETY FOR
ANTIVIRAL
RESEARCH
(ISAR)

29th International Conference on Antiviral Research (ICAR)

Program AND Abstracts

184 Evaluation of IQP-0528 Pharmacokinetics in Gels, Intravaginal Rings, and Films

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Although topical microbicides to prevent the sexual transmission of HIV have progressed to pivotal human clinical trials and one ARV (tenofovir) has shown efficacy, additional agents are still required. These products must address the concerns of users with regard to acceptability of the product for use. We have developed the NNRTI IQP-0528 for microbicidal use and have optimized several delivery vehicles to address user perceptions. IQP-0528 was originally formulated as a vaginal gel and intravaginal ring but has also been formulated as a film and as a DuoGel for both vaginal and rectal use. Currently, a suppository based formulation amenable for both vagina and rectal use is being finalized. The various delivery vehicles have been designed to address perceptions of particular subsets of product users. Pharmacokinetic (PK) studies in nonhuman primates with the vaginal and dual vaginal/rectal DuoGel, IVR, and film have determined that sufficient amounts of IQP-0528 are delivered from each vehicle. Four hours following dosing of the 1% wt/wt DuoGel, 1000 to 10,000 times the EC_{50} of IQP-0528 was detected in vaginal, cervical and rectal tissues. A single application of a 1.5% wt/wt film delivered 100 times the EC_{50} of IQP-0528. A 10% wt/wt vaginal ring designed to release 200 ug of IQP-0528 per day delivered 1000- and 10,000-fold the EC_{50} of IQP-0528 to cervical tissue at day 7 and 14, respectively. Thus, IQP-0528 is amenable to multiple delivery devices, achieves highly active concentrations in target tissue, and will be acceptable to the end user population

185 Small Molecule Compounds Inhibit Vpu Mediated Down-regulation BST-2

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BACKGROUND: BST-2(Tetherin/CD317) has been recently recognized as a potent restriction factor that inhibits the release of HIV-1 particles from infected cells. HIV-1 Vpu induces the degradation of BST-2 and allows virus escape from the restriction. Therefore, blocking Vpu-mediated down-regulation of cell surface BST-2 provides clearly an opportunity for developing anti-HIV-1 drugs.

RESULTS: In this study, we identified two small molecule compounds IMB-AZ and IMB-LA, both of which can restore cell surface BST-2 in a Vpu-dependent manner. Interestingly, the compounds had no effect on the degradation of IFNAR1 induced by IFNa, suggesting that their abilities to block BST-2 degradation most unlikely resulted from a general inhibition of lysosome degradation pathway. Mechanism study revealed that IMB-AZ specifically inhibit Vpu-induced ubiquitination of BST-2 without interrupting the formation of Vpu-β-TrCP complex. Unlike IMB-AZ, the treatment of IMB-LA resulted in accumulation of BST-2 within CD63-containing endosomal compartments, suggesting that IMB-LA may impair the translocalization of BST-2 to lysosomes, and consequently inhibit the degradation of BST-2. Furthermore, the results of viral infectivity assay demonstrated that both of IMB-AZ and IMB-LA inhibit the release of HIV-1 particles and the infectivity of progeny virions in cell lines expressing BST-2.

CONCLUSION: In summary, results herein demonstrated that both of IMB-AZ and IMB-LA could specifically inhibit the degradation of BST-2 induced by Vpu, and impair HIV-1 replication in a BST-2 dependent manner, suggesting IMB-AZ and IMB-LA have potent potential to develop a new anti-HIV drug.

186 Anti-Influenza Effect of N-Stearoylethanolamine

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N-stearoylethanolamine (NSE) was shown *in vitro* experiments to suppress viral replication of influenza H1N1 strain in the 3.0 lg $CCID_{50}$ in concentrations 10^{-6} and 10^{-7} mol/l, a chemotherapeutic index NSE against influenza virus H1N1 strain to be 100 that confirms NSE anti-influenza activity. The results of *in vivo* experiments showed that intranasal prophylactic administration of 0.2 ml 10^{-6} mol/l and 10^{-8} mol/l of NSE contributed to the decrease of mortality of infected animals by 40 % and 100 %, respectively. A low titer of influenza virus (<0.5 lg CCID50) under NSE concentration 10^{-8} mol/l was revealed in the lung tissue of mice. The most effective concentrations of NSE which reduced lethality of animals from influenza pneumonia following therapeutic administration were 10^{-6} and 10^{-9} mol/l. NSE inhibited viral replication in the infected lung tissue of mice at 2.0 and 3.5 lg, respectively. Inhibition of H1N1 neuraminidase activity was shown to be one of the mechanisms of NSE anti-influenza effect. Another mechanism of such effect is the induction of IFN synthesis (IFNg — in concentrations of NSE 10^{-6} - 10^{-9} mol/l, and IFNa in concentrations of NSE of 10^{-8} and 10^{-9} mol/l). It was also found that the intranasal administration of NSE in all studied concentrations prevented changes of cholesterol level in liver and lung tissues of mice infected with influenza virus.