Conclusions: These data demonstrate that the majority of CMX001 treated patients had $a > 99\%$ decrease in viral load compared to baseline after 2 weeks of therapy. Antiviral activity of CMX001 was reduced in patients with high level resistance to CDV, all of whom had received prior treatment with CDV. Finally, higher plasma exposure to CMX001 appeared to correlate with a more rapid response. CMX001 is a promising antiviral for severe adenovirus infection.

doi:10.1016/j.antiviral.2011.03.020

Poster Session 1: Retroviruses, Respiratory Viruses, Emerging Viruses and Antiviral Methods Chairs 4:00–6:00 pm Sofia 3 and Kyota

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Design, Synthesis and West Nile Protease Inhibitory Activity of Novel Isatin Derivatives

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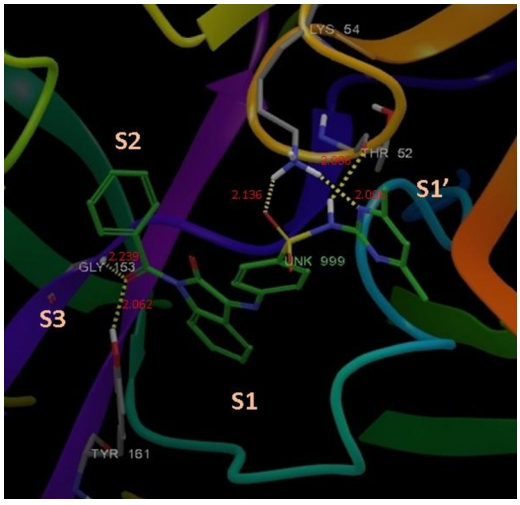
Background: The mosquito-borne viral pathogens of global significance include the members of flavivirus genus of Flaviviridae family. Two important human pathogens are dengue and West Nile viruses which cause considerable morbidity and mortality throughout tropical and subtropical regions of the world. No vaccines or antiviral therapeutics are available for these two pathogens. The overall goal of our study is to develop potent inhibitors of West Nile virus serine protease, which is a quintessential viral target as it is required for viral replication. In this study, we examined whether derivatives of isatin (2,3-dioxoindole) could be versatile lead compounds for structure–activity relationship (SAR) study.

Methods: Novel isatin-sulphadimidine derivative synthesized and screened for their inhibitory activities of WNV protease in vitro.

Results: The N-benzoyl derivative (SPIII-5H-BZ) and 5-chloro-N-acetyl derivative (SPIII-5Cl-AC) exhibited significant inhibitory activities against the WNV protease (IC_{50} values of 15 μM and 8.4 μM, respectively).

Conclusions: To our knowledge, this is the first report regarding the inhibitory activities of isatin derivatives against the WNV serine protease. Further work on SAR study for lead optimization is in progress.



doi:10.1016/j.antiviral.2011.03.021

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Effects of the Addition of Hiltonol® (Poly-ICLC) to a SARS-CoV S Protein Vaccine in Lethal SARS-CoV Mouse Model

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The principal containment strategy for emerging diseases has been rapid diagnosis/isolation followed by immunization, but there is often a gap between isolation/identification and immunization. Host-targeted therapeutics that could provide immediate, broad-spectrum resistance to disease could fill this gap in protection to allow time for agent specific immunization to take effect. Hiltonol® is a stabilized dsRNA therapeutic viral mimic or pathogen-associated molecular pattern (PAMP) that activates 2′5′ OAS, PKR, RIG-I, mda-5, DCs, natural killer cells interferons and various cytokines and chemokines, while at the same time accelerating and enhancing the quality of adaptive cellular/humoral immunity. It induces a broad-spectrum innate-immune antiviral state lasting up to 3 weeks. The current study was done to see if Hiltonol® could be used to protect during the time between the isolation/identification of an agent and adaptive immunization. Mice immunized i.m. twice with S Protein vaccine in alum, 14 days apart, were protected against death from viral challenge 14 days after the last immunization. A one time Immunization with varying doses of vaccine (0.3, 1, 5 μg/mouse) along with simultaneous Hiltonol® (10 μg/mouse) intranasally also significantly protected mice against death ($P < 0.001$). Mice treated with 5 μg of vaccine and only 1 μg of Hiltonol®, showed diminished survival to only 60%. These data suggest that the co-administration of Hiltonol® at higher doses of the S protein vaccine enhanced the protection of mice against death. When mice were challenged with SARS-CoV 3 days after one immunization with vaccine (0.3, 1, 5 μg/mouse) plus Hiltonol® at 10 μg, both given i.n., then all mice survived the infectious challenge. Mice receiving one course of vaccine plus alum and challenged on day 3 all died; mice receiving Hiltonol® at 10 μg/mouse and challenged on day 3 all survived. Thus, it appears that Hiltonol® provided an immediate protection against disease that allowed time for the more specific vaccination strategy to take effect.

Acknowledgement: Supported by Contract No. N01 AI-15435 and HHSN272201000039I/HHSN27200002/A14 from NIAID, NIH.

doi:10.1016/j.antiviral.2011.03.022

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Synthesis and Anti-HIV Activity of D-peptide Analogs as HIV Fusion Inhibitors

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The identification of new anti-HIV molecules remains an important challenge. To date, HIV viral entry becomes a promising target for HIV drug development as illustrated for example by the approval of Enfurvitide by regulatory agencies as HIV fusion inhibitor, and more recently, Maraviroc as HIV entry inhibitor. Although highly effective, Enfurvirtide, a C-peptide of 36 amino acids mimicking the CHR region of gp41 has several serious