A single prophylactic dose of CD388 provides protection against highly pathogenic bovine-origin influenza A(H5N1) virus in the ferret model

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The emergence of highly pathogenic influenza A(H5N1) clade 2.3.4.4b viruses in dairy cattle in the United States has spawned a novel animal-human interface and augmented pandemic concerns. Antivirals play a pivotal role in mitigating the impact of pandemics caused by emerging influenza viruses. Limited therapeutic options are available for treating and/or preventing severe A(H5N1) infections and the search for novel drugs is needed. Here, we studied the prophylactic efficacy of CD388, a first-in-class multivalent conjugate of the approved neuraminidase inhibitor zanamivir linked to a proprietary crystallizable fragment hybrid domain of human IgG, against lethal A(H5N1) infection in ferrets. Control (virus-infected, untreated) ferrets displayed pronounced weight loss, neurological symptoms (ataxia, tremor, seizures, hind limb paresis) and met humane endpoints at 4-8 days post-inoculation (dpi). A(H5N1) virus was present in nasal washes (3-7 dpi, 10^3-10^5 $TCID_{50}$/mL) and in multiple tissues collected at 5 dpi (10^3-10^7 $TCID_{50}$/mL). A single subcutaneous (SC) dose of CD388 (3 mg/kg) administered 24 hours before A(H5N1) virus inoculation protected 75% of ferrets from death; 10 mg/kg provided 100% survival. CD388-treated animals exhibited reduced weight loss and clinical symptoms versus control. Nasal wash titers in CD388-treated animals were reduced versus control after 5 dpi, with no statistical titer differences observed between the 3 and 10 mg/kg doses. CD388 substantially reduced viral titers in the upper and lower respiratory tract of ferrets and prevented viral neuroinvasion and systemic spread to other organs. Pharmacokinetic data demonstrated that SC dosed CD388 rapidly distributed systemically with sustained plasma exposures through the course of infection. Phenotypic testing was used to characterize CD388 inhibitory activity *in vitro* on a panel of bovine- and avian-origin viruses including zanamivir-resistant strains. Our data identify CD388 as a promising antiviral that has the potential to provide prophylactic protection from this highly virulent and systemic viral infection.