Poster Session II:
Respiratory Virus, Hepadnavirus, Papillomavirus Infections

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Inhibition of Influenza Neuraminidases by RWJ-270201: Mechanistic Analysis and Comparison to Zanamivir and GS4071

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The rationally-designed influenza neuraminidase inhibitor RWJ-270201 was examined in enzymatic assays to determine its potency and mechanism of action, using purified neuraminidase (NA), hemagglutinin-neuraminidase complex (HANA), and whole virus of various influenza A and B strains. Kinetic analysis using HANA from influenza B/Lee/40 demonstrated that inhibition was competitive with the substrate 2'-(4-methylumbelliferyl)-α-D-*N*-acetylneuraminic acid. Using nine influenza A viruses, the median IC_{50} and IC_{90} values were 0.2 nM and 1.0 nM for RWJ-270201, 0.8 nM and 5.5 nM for zanamivir, and 0.2 nM and 2.3 nM for GS4071 (the active agent of oseltamivir). Thus, for these Type A neuraminidases, inhibition by RWJ-270201 assessed by IC_{50} and IC_{90} values was comparable to GS4071 and 4-5 fold more potent than zanamivir. All three compounds were less effective against Type B compared to Type A neuraminidases. Using four influenza B viruses, the median IC_{50} and IC_{90} values were 1.0 nM and 20 nM for RWJ-270201, 1.6 and 22 nM for zanamivir, and 9.0 nM and 150 nM for GS4071. Thus, inhibition of these Type B neuraminidases by RWJ-270201 was comparable to zanamivir and 7-9 fold more potent than GS4071. The inhibitory profile of RWJ-270201 renders it an excellent candidate for evaluation in the treatment of influenza virus infections.

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A Pharmacodynamic Evaluation of a Murine Model of Influenza Predicts Efficacy for Once Daily Dosing of RWJ-270201, a Novel Neuraminidase Inhibitor.

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Challenge with A/Shangdong/09/93 (H3N2) virus produces a lethal infection in a BALB/c mouse challenge model. We examined the protective effect of doses of RWJ-27021 ranging from 1 to 10 mg/kg/day and also examined the effect of schedule (Q8h vs Q 12h vs Q24h) in two different sets of experiments. The time to death was examined in a Cox Proportional Hazards model. Dose and schedule of administration were examined for significance of impact on time to death. Dose significantly altered the time to death ($p << 0.001$). Schedule of administration was not significant when evaluated either as a covariate or as a stratification variable. Based upon these modeling experiments we predict that RWJ-270201 should be efficacious on a once daily dosing schedule in man. Clinical trials that evaluate once a day schedule of administration are warranted.