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ADS-J1, A NON-PEPTIDIC LOW MOLECULAR WEIGHT HIV FUSION INHIBITOR TARGETING GP41, WITH NO CROSS-DRUG RESISTANCE WITH PEPTIDIC HIV FUSION INHIBITORS T-20 AND C-34, AND HIV BINDING INHIBITORS

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BACKGROUND: ADS-J1 is a low molecular weight compound selected for its ability to interfere with the association of the N- and C-terminal heptad repeat regions of HIV-1 gp41 envelope glycoprotein. Since ADS-J1 is a polysulfonic acid compound, it is interesting to know whether it, like other polyanionic anti- HIV compounds, blocks the binding of HIV-1 to CD4 cells through electrostatic interactions and to test the anti-HIV activity of ADS-J1 against HIV strains that have been made resistant to polyanionic HIV binding inhibitors.

METHODS: Evaluation of anti-HIV activity in MT-4 cell culture against wild-type and drug-resistant HIV-1 strains. Cell culture selection of HIV drug resistance to known inhibitors of gp41-dependent fusion (T-20 and C-34). Flow cytometry evaluation of drug interaction with HIV co-receptors.

RESULTS: Here, we show that ADS-J1 was active against T-20- and C-34-resistant HIV-1 isolates with similar potency to the wild-type HIV-1 NL4-3 strain (EC₅₀ 0.6, 0.3 and 0.4 µg/ml, respectively). ADS-J1 (10 µg/ml) could not block the binding of an HIV strain that was made resistant to AR177, a negatively charged oligonucleotide that blocks HIV binding, and is cross-resistant (>100-fold) to dextran sulfate (DS), a known polysulfonic HIV binding inhibitor. However, ADS-J1 blocked AR177-resistant virus fusion and replication (EC₅₀ 1.5 µg/ml), suggesting that ADS-J1 has a mechanism of action different from the polyanionic HIV binding inhibitor AR177.

CONCLUSIONS: If the activity of polyanionic compounds on HIV binding is 'bypassed' by selection of resistance, compounds such as ADS-J1 may exclusively act on gp41-dependent fusion. Our results support the hypothesis that ADS-J1 binds to a

hydrophobic cavity region within gp41 for preventing fusion-active gp41 core formation. ADS-J1 may serve as a lead low molecular weight compound to develop new anti-HIV agents.

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