Retrovirology

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Oral presentation

Monoclonal antibodies and small-molecules as distinct subclasses of CCR5-targeted therapies for HIV-1

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The chemokine receptor CCR5 provides a portal of entry for HIV-1 and serves a target for potential new antiretroviral therapies. CCR5 monoclonal antibodies (mAb) and small-molecule CCR5 antagonists potently block HIV-1 entry in vitro, and controlled clinical trials have provided initial proof-of-concept for this mode of therapy. PRO 140 is a humanized CCR5 mAb that broadly and potently blocks CCR5-mediated HIV-1 entry in preclinical settings, and this product has entered phase 1b testing in HIV-infected individuals. In this study, PRO 140 and small-molecule CCR5 antagonists in development were compared in terms of patterns of viral resistance, synergistic interactions, competition for CCR5 binding, and related properties. In studies that examined forced viral resistance to CCR5 inhibitors in vitro, we observed limited or no viral cross-resistance between PRO 140 and small-molecule CCR5 antagonists. Potent antiviral synergy was observed between PRO 140 and small-molecule CCR5 antagonists in vitro. In contrast, modest synergy or additive effects were observed between PRO 140 and enfuvirtide and between different small-molecule CCR5 antagonists used in combination. Synergy between PRO 140 and small-molecule CCR5 antagonists was explained in part by their non-reciprocal patterns ofA competition for CCR5 binding. Additional studies indicate that PRO 140 may act as a competitive CCR5 inhibitor while the small-molecule CCR5 antagonists act via allosteric mechanisms. Collectively, the findings suggest that mAb and small-molecule CCR5 drugs may provide complementary HIV-1 treatment subclasses.