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# 16th International AIDS Conference

Toronto, Canada - August 13 - 18, 2006

## THE MECHANISM OF HIV-1 ESCAPE FROM SMALL MOLECULE CCR5 ANTAGONISTS

*Int Conf AIDS. 2006 Aug 13-18;16 Abstract No. MoAa0105*

Pugach P., Kuhmann S., Ketas T., Moore J.P.

*Weill Medical College of Cornell University, Microbiology and Immunology, New York, United States*

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**BACKGROUND:** CCR5 is the principal coreceptor used by the strains of HIV-1 that dominate early infection, and is a major target for development of a new drug class. Two small molecule CCR5 inhibitors, Maraviroc and Vicriviroc, are now in advanced clinical trials in HIV-infected people, and have demonstrated antiviral efficacy. To date, escape from them has not been demonstrated *in vivo*, but it can be anticipated.

**METHODS:** We have studied how HIV-1 escapes from small molecule CCR5 inhibitors *in vitro*, by creating resistant viruses and studying their properties.

**RESULTS:** We report that the drug-resistant viruses have acquired the ability to utilize CCR5 in its inhibitor-bound form. Thus the viruses resistant to the small molecule inhibitors are sensitive to inhibition by PSC-RANTES, but they become significantly resistant to this chemokine derivative when a small molecule inhibitor is also present. In single-round replication assays the drug escape variants exhibit characteristic resistance "plateaus" (*e.g.*, at a maximum of 80% inhibition).

**CONCLUSIONS:** We interpret these findings to indicate that the resistant viruses are utilizing CCR5 receptors to which the small molecule have already bound in a way that blocks PSC-RANTES binding. The appearance of "plateaus" of incomplete resistance suggests that these viruses utilize drug-bound CCR5 less efficiently than drug-free receptors.

2006-08-13  
MoAa0105

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