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***IN VITRO* ESCAPE OF R5 PRIMARY ISOLATES FROM THE CCR5 ANTAGONIST, UK-427,857, IS DIFFICULT AND INVOLVES CONTINUED USE OF THE CCR5 RECEPTOR**

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BACKGROUND: The CCR5 antagonist, UK-427,857, is currently in clinical development as a member of a new class of antiretrovirals targeting HIV co-receptor binding. We have performed *in vitro* serial passage experiments of R5 isolates in the presence of increasing concentrations of the compound in an attempt to understand the pathways that may lead to UK-427,857 resistance.

METHODS: Six R5 HIV-1 primary isolates were serially passaged through mitogen-stimulated PBL in the presence of increasing concentrations of UK-427,857 for up to 20 weeks. Virus cultures that replicated in the presence of high concentrations of UK-427,857 (>1000-fold the parental virus) were generated and stocks were characterized for co-receptor tropism. Env-recombinant pseudotyped viruses were also generated from these stocks and their susceptibility to UK-427,857 was assessed using the PhenoSense HIV Entry Assay. Individual *env* clones of resistant variants were sequenced and compared to sequences of parental viruses and drug-free passaged controls.

RESULTS: High-level resistance to UK-427,857 was achieved in 3/6 virus cultures. Two resistant viruses (CC1/85^{res} and RU570^{res}) continued to use the CCR5 co-receptor. The third virus (SF162^{res}) acquired reduced susceptibility to UK-427,857 in both the drug-treated and drug-free passaged control cultures: in each case the resistant variants selected during passaging were able to use CXCR4 as its entry co-receptor. The CC1/85^{res} and RU570^{res} viruses exhibited increased sensitivity to a CCR5-specific mAb (2D7), suggesting altered envelope recognition of the external face of the co-receptor. The infectivity of the RU570^{res}, but not the CC1/85^{res}, virus was impaired relative to the parental virus. Strain-specific mutations were identified in the gp160 V3 loop regions of

CC1/85^{res} and RU570^{res}. Resistance to UK-427,857 could not be generated in three R5 virus cultures (92BR017, 92BR018 and 92BR023) during the course of this study.

CONCLUSIONS: Resistance to UK-427,857 was either slow to emerge or did not develop during this study, suggesting there is considerable selective advantage *in vitro* for continued use of the CCR5 co-receptor in a UK-427,857-sensitive manner. Furthermore, our results indicate that gp160 mutations associated with UK-427,857 resistance may be strain-specific, suggesting that the context of the V3 loop is crucial for CCR5 recognition. These results offer promise for the efficacy and durability of UK-427,857-containing HAART.

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