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GENERATION AND CHARACTERIZATION OF HIV-1 VARIANTS RESISTANT TO BMS- 806, A NOVEL HIV-1 ENTRY INHIBITOR

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BACKGROUND: The HIV entry process involves key interactions between the HIV-1 envelope glycoproteins gp120 and gp41, cellular receptors, CD4, CCR5 and CXCR4, and the viral membrane. BMS-806 is a novel, small molecule, oral bioavailable HIV-1 entry inhibitor that targets the viral envelope protein, and inhibits viral entry through blocking gp120/CD4 binding. The compound exhibits potent HIV-inhibitory activity against a panel HIV-1 laboratory strains (M- and Ttropic) as well as clinical isolates. This new class of inhibitors is selective for HIV-1, inactive versus HIV-2 and other viruses and exhibits no significant cytotoxicity. Studies were undertaken to generate BMS-806 resistant virus in vitro to identify resistance markers and to map the binding site of BMS-806.

METHODS: Resistant variants were selected in cell culture using two T- and two M-tropic HIV-1 virus strains. The phenotypic and genotypic profiles of the resistant variants that emerged were subsequently characterized. Recombinant viruses carrying the drugselected mutations in envelope were generated to study the role of selected substitutions in drug sensitivity. Susceptibility of HIV-1 variants resistant to reverse transcriptase or protease inhibitors to BMS-806 was analysed using standard cell based assays.

RESULTS: Four strains (NL4-3, LAI, JRFL and Bal) of HIV-1 variants with reduced susceptibility to BMS-806 were selected in cell culture by sequential passage in the presence of increasing concentrations of BMS-806. Genotypic analysis of the selected variants showed that resistance mapped to several amino acid residue substitutions, including A204D, F423Y, M434I/V/T, M475I, situated primarily near the CD4 binding sites of gp120 based on the published X-ray crystal structure of the HIV-1 envelope

protein. One mutation (I595F) is located within the gp41 subunit of the viral envelope. The BMS-806 selected mutations conferred reduced susceptibility when inserted into recombinant viruses and HIV-1 envelope proteins carrying the drug selected substitutions demonstrated reduced sensitivity to compound inhibition in an ELISA based gp120/CD4 binding assay. Some of the envelope variants were shown to bind with a decreased affinity to the radio-labelled BMS-806. Finally, the BMS-806 resistant HIV-1 retains susceptibility to other classes of antiretrovirals (efavirenz, didanosine, stavudine, zidovudine, lamivudine, lopinavir, nelfinavir, indinavir and atazanavir). Reciprocal studies using variants resistant to other classes of antiretrovirals showed that susceptibility to BMS-806 was fully retained. A cross-resistance study involving variants resistant to other classes of HIV-1 entry inhibitors is in progress.

CONCLUSION: Genotypic and phenotypic analysis of the BMS-806 selected HIV-1 variants confirmed the results of biochemical studies showing that the binding target of this novel inhibitor is the HIV-1 envelope glycoprotein gp120. The lack of cross-resistance between BMS-806 and other classes of inhibitors suggests the potential utility of this compound class in HIV drug combination therapy.

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