[ORAL]

RESISTANCE TO A NOVEL HIV-1 INHIBITOR INDICATES DUAL TARGETING OF VPU AND A HOST CELL FACTOR

Mwimanzi, Philip[1]; Tietjen, Ian[2]; Shahid, Aniqa[1]; Miller, Scott C[2]; Fedida, David[2]; Brumme, Zabrina L[1,2]; Brockman, Mark A[1,2]

[1]Burnaby; [2]Vancouver, British Columbia, Canada

BACKGROUND: The discovery of new antiviral drugs is necessary to enhance treatment options and to counter resistance. Here, we examined the mechanism of anti-HIV activity for a novel acylguanidine compound, SM111.

METHODS: GFP-reporter CEM T cell assays were used to test the ability of SM111 to inhibit replication of WT NL4.3, NL4.3ΔVpu (lacking vpu), and recombinant NL4.3 strains encoding major resistance mutations in pol for RTIs, PIs and INIs. Cytotoxicity was evaluated using Via-Count (Millipore). WT NL4.3 was passaged in the presence of SM111 to select resistant mutants. Vpu-mediated downregulation of CD4 and BST-2/tetherin was monitored by flow cytometry.

RESULTS: SM111 exhibited a nontoxic dose-dependent inhibition of HIV replication; including >95% reduction of infected (GFP+) T cells on day 7 following inoculation with WT as well as RTI, PI and INI resistant strains. Three SM111-resistant viruses were selected *in vitro* and all encoded mutations in the transmembrane domain of Vpu. A 5AA deletion (strain A), a stop codon at highly conserved W22 (strain C) or a substitution (I17R) (strain H) impaired Vpu-mediated downregulation of CD4 and BST-2/Tetherin. Notably, SM111 was partially active against NL4.3ΔVpu and resistant strains (52%, 92%, 54%, and 16% reduction for NL4.3ΔVpu, strains A, C, and H, respectively).

CONCLUSIONS: SM111 inhibited replication of WT as well as RTI, PI and INI resistant HIV-1 strains. SM111 selected major mutations in Vpu; however these mutants and a ΔVpu strain remained partially sensitive to the drug. Together, these results indicate that SM111's mechanism of action is unique from current antiretroviral drugs and suggest that SM111 targets an interaction between Vpu and an unknown host cell factor. More studies are necessary to explore this promising prototype.
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