

15th International HIV Drug Resistance Workshop



13-17 June 2006, Sitges, Spain

IDENTIFICATION AND CHARACTERIZATION OF NOVEL REVERSE TRANSCRIPTASE INHIBITORS

Antivir Ther. 2006, 11:S20 (abstract no. 15)

O Jegede^{1,2}, A Khodyakova¹, M Chernov¹, A Gudkov¹ and ME Quiñones-Mateu¹

¹Cleveland Clinic Foundation, Cleveland, OH, USA; ²Kent State University, Kent, OH, USA

BACKGROUND: Current therapeutic efforts have been effective in improving the quality of life of HIV-infected individuals. However, the increasing prevalence of multidrug-resistant HIV strains requires the development of a new generation of antiretroviral compounds. Here, we have identified and characterized lead compounds which could be used to develop novel and effective alternatives to HAART.

METHODS: We developed a novel cell-based anti-HIV drug screening system that uses a GFP-tagged recombinant lentiviral vector. This assay was used to screen a chemical library of small molecules for potential antiretroviral agents. After passing several filters, selected "hits" were evaluated, i.e., viral susceptibility (IC₅₀) of wild-type and drug resistant viruses, cellular toxicity (CC₅₀), *in vitro* selection of viruses resistant to these compounds, and *in vitro* PR, RT and integrase inhibition assays to identify their potential targets and mechanisms of action.

RESULTS: Initial screening of a chemical library of 74,000 small molecules generated a set of 34 primary hits. Six compounds were chosen due to their anti-HIV activity in both MT4 cells and PBMC (IC₅₀ values ranging from 0.17 to 1.9 μM) and low cellular toxicity (CC₅₀ >5μM). Mapping of their anti-HIV activity suggested that these compounds inhibit reverse transcription. For three compounds, resistant viruses selected *in vitro* harboured NNRTI-associated mutations (i.e., L100I, T128N, E138K, and Y181C). Interestingly, the chemical structure of the other three compounds was similar to that of the novel NcRTI-1 (Tibotec). However, unlike NcRTI-1, these compounds selected for viruses with the A62V mutation in the RT. More important, the compounds were highly active against NRTI- and NNRTI-resistant viruses.

CONCLUSIONS: Our cell-based drug screening system proved to be efficient to discover new antiretroviral agents, allowing us to expand the screening of our small molecule library. To this point, we have identified three novel NNRTI, one of them active against common NNRTI-resistant viruses. Interestingly, we identified three small molecules related to NcRTI-1, which selected for a different RT mutation profile. Ongoing experiments will help us to further characterize these compounds with the intention to begin phase I studies in the near future.

2006-06-13
15

Copyright © 2006 - [International Medical Press Ltd.](#) Reproduction of this abstract (other than one copy for personal reference) must be cleared through the International Medical Press Ltd. 2-4 Idol Lane, London EC3R 5DD UK.