Oral Session IV

Respiratory Infections

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Structural Analysis of the Non-nucleoside Binding Site of HIV-1 Reverse Transcriptase

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Among the many approaches being pursued in the design of new AIDS therapies, inhibition of the viral enzyme reverse transcriptase (RT) represents a particularly attractive strategy. Several classes of non-nucleoside RT inhibitors have been reported to inhibit the enzyme in a non-competitive manner, binding at a site proximal to but distinct from the catalytic site. A variety of techniques, including photoaffinity labeling, site directed mutagenesis, X-ray crystallography, and molecular modeling, have been used to study binding interactions between the enzyme and nevirapine, a prototypical non-nucleoside RT inhibitor. These studies, and in particular the three-dimensional structure of the enzyme-nevirapine complex, provide a basis for understanding the resistant mutations that arise in response to nevirapine and other non-nucleoside inhibitors. Such an analysis has important ramifications for the design of second-generation RT inhibitors.