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Oral presentation

The chemistry and biology of KP-1461, a selective nucleoside mutagen for HIV therapy

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KP-1461 is a deoxycytidine analogue that is randomly inserted into HIV DNA by reverse transcriptase where it can cause base mispairing and introduce mutations that decrease viral fitness. The nucleoside consists of a natural deoxyribose for efficient use by the viral polymerase and a modified base that undergoes tautomerization between a cytosine form and a thymine form that exclusively causes transitional mutations. In vitro testing showed ablation of HIV when used in a serial passage format [1]. Host cell nuclear polymerases alpha and beta have a high Km for KP-1461 triphosphate that could preclude incorporation into nuclear DNA. KP-1461 has successfully completed preclinical testing including animal toxicology studies, a complete panel of genotoxicity assessments, and acute cardio, pulmonary and neurotoxicity tests. A single dose Phase 1a clinical trial in healthy volunteers showed safety and PK to continue clinical development. A Phase 1b study is currently underway in ARV-experienced HIV+ patients.

References

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