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EDWARD ARNOLD

DRUG DESIGN TARGETING HIV-1 REVERSE TRANSCRIPTASE: OVERCOMING RESISTANCE BY INHIBITOR STRATEGIC FLEXIBILITY

27 SEPTEMBER - 11:00

SARDEGNA RICERCHE
Loc. Piscinamanna – Edificio 2 – Pula

Moderator: Prof. Enzo Tramontano, UniCa

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In 1987, Professor Arnold's laboratory began collaborating with the laboratory of Dr. Stephen Hughes (NIH NCI in Frederick, Maryland) to study the structure and function of HIV-1 reverse transcriptase, believing that knowledge of the structure would facilitate the design of drugs targeting HIV-1 RT, in addition to provide a basis for understanding the function of this fascinating and versatile enzyme. The team has solved a variety of crystal structures representing different functional states of HIV-1 RT. These structures include: HIV-1 RT in complex with a double-stranded DNA template-primer; HIV-1 RT complexes with RNA:DNA template-primers; structures of RT with AZTMP-terminated primer, representing pre-translocation and post-translocation complexes; and ternary complexes of wild-type and drug-resistant RT/DNA and tenofovir-diphosphate. The team has also determined the structures of numerous HIV-1 RT complexes with non-nucleoside inhibitors and with RNase H inhibitors, as well as structures of unliganded HIV-1 RT and a variety of drug-resistant mutant HIV-1 RT structures. The team has also established the unusual structural basis of AZT resistance by ATP excision. These structures complement the valuable HIV-1 RT structural information that has been obtained by the groups of Thomas Steitz at Yale, Stephen Harrison at Harvard, and David Stammers and David Stuart at Oxford. Through collaboration with the late Dr. Paul Janssen they participated in a structure-based drug design effort that resulted in the discovery and development of two non-nucleoside drugs (diarylpyrimidine, or DAPY analogs) with high potency against all known drug-resistant variants of HIV-1 RT. Etravirine/TMC125/Intelence was approved for treatment of HIV infection by the FDA in 2008, andrilpivirine/TMC278/Edurant was approved in May 2011. The team has hypothesized that strategic flexibility of the DAPY inhibitors may account for their potency against a wide range of drug-resistant variants: compound may "wiggle" and "jiggle" in a binding pocket to accommodate mutations. Through a systematic protein engineering effort they obtained high-resolution crystals of HIV-1 RT and demonstrated that strategic flexibility of rilpivirine/TMC278 was responsible for its resilience against drug-resistant RT variants.

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