Keynote Lecture

KN02

Triumphs of Crystallography in Tackling HIV/AIDS: Drugs by Design

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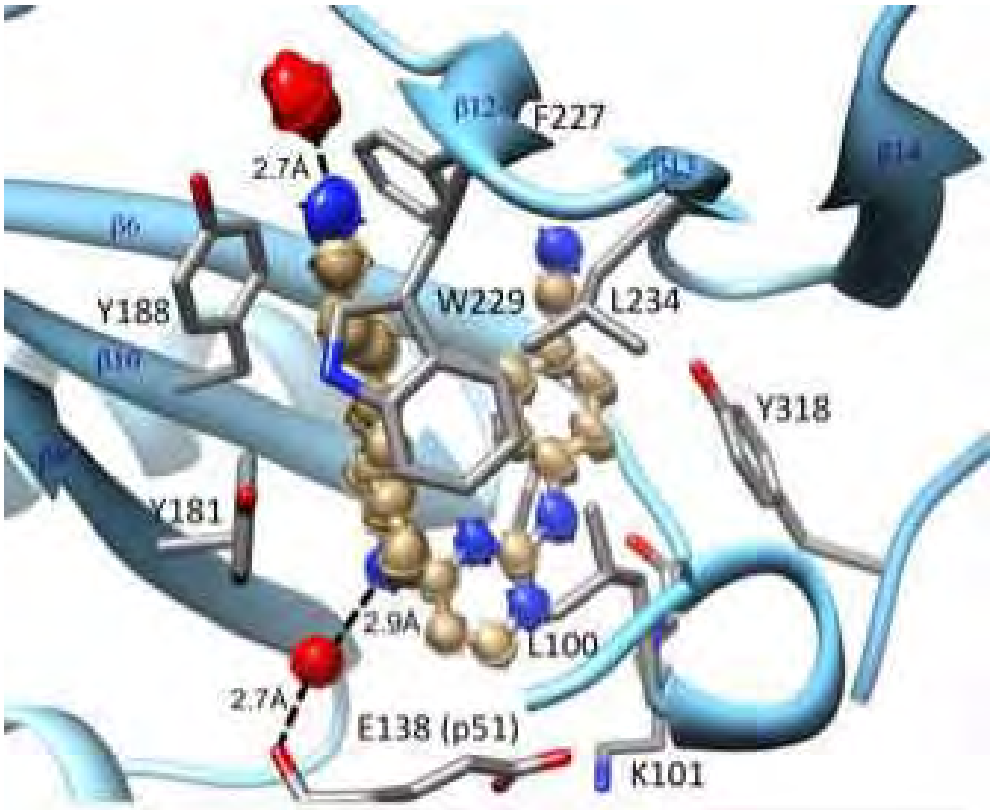
Crystallography has made extraordinary contributions to our understanding of the biology and chemistry of HIV. Judicious applications of structure-based drug design against HIV-1 protease and reverse transcriptase (RT) has led to the discovery of key drugs that are used in combinations to treat HIV infection. Extensive research and development efforts by pharma, academia, and government have made it possible for an HIV-infected person to live a nearly normal life. I will summarize the elegant structures that have been determined of components of HIV, with an emphasis on the enzyme RT, which my laboratory has studied since 1987. HIV-1 RT is responsible for converting the viral 10-kilobase single-stranded RNA genome to double-stranded DNA. This fascinating and essential enzyme is the target of 13 approved anti-AIDS drugs: 8 nucleoside analog RT inhibitors (NRTIs) and 5 non-nucleoside RT inhibitors (NNRTIs). We have determined crystal structures of wild-type and drug-resistant RTs in complexes with nucleic acid and/or inhibitors. We participated in structure-guided discovery and development of two anti-AIDS drugs with exceptional potency against drug-resistant variants. Crystal structures combined with biochemical data help to elucidate intriguing molecular mechanisms by which HIV-1 develops resistance to different anti-AIDS drugs. Recent crystallographic fragment screening has revealed new allosteric inhibitory binding pockets for future drug discovery. I am very grateful to my many co-workers, colleagues, and friends for their contributions, synchrotron resources at CHESS, BNLS, and APS, and generous funding from NIH in support of research on HIV-1 RT.

[1] *S.G. Sarafianos, B. Marchand, K. Das, et al., 2009, Journal of Molecular Biology, 385, 693-713,* ***[2]*** *K. Das, S.E. Martinez, J.D. Bauman, E. Arnold, 2012, Nature Structural and Molecular Biology, 19, 253-259,* ***[3]*** *J.D. Bauman, D. Patel, C. Dharia, et al., 2013, Journal of Medicinal Chemistry, 56, 2738-2746*



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