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Alternative strategy of the HIV-1 integrase inhibition through the search of allosteric sites: Modeling and beyond

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Integrase (IN) catalyzes the insertion of the viral DNA (vDNA) into host cell chromosomes. IN represents an attractive target for antiretroviral (ARVs) drugs and has been the object of intensive pharmacological research crowned by development of Raltegravir (Ral), which like all known anti-IN inhibitors targets the IN active site. As with other antivirals, resistance mutations rapidly emerge that reduce the susceptibility to the drug. We have previously proposed a mechanism for Ral inhibition and the basic principles of Ral-induced resistance. We describe herein an alternative strategy of IN inhibition based on exploring allosteric sites. We applied a multi-approach protocol combining different computational methods. We found that the conformation of IN before and after 3'-processing differ strongly and we established a pathway between two conformations. Our results, first, provide a description of structure-dynamics-function relationships which supplies an understanding of the IN 3'-process. Second, the calculated intermediate conformations along the trajectories were scanned for molecular pockets - a means of exploring putative allosteric binding sites, particularly positioned on the IN C-terminal domain (CTD). Third, to validate our approach we performed combined *in silico* and *in vivo* studies focused on the CTD. Based on our mutagenesis studies we found that mutations on almost studied residues in the CTD lead to decreased or completely diminished vDNA binding efficiency. These data correlate with the theoretical prediction of vDNA binding with WT and mutated IN. Finally, the pocket profiles we obtained also encourage us to select conformations as targets for molecules in a virtual screening protocol.

Biography

L. Tchertanov has completed her Ph.D at the age of 28 years from Nesmeyanov Institute of the Academy of Sciences, Moscow and ten years later her Habilitation in Life Sciences from University Paris XI, Orsay-France. She is research director at CNRS, founder and leader of BiMoDyM team (http://tinyurl.com/tchertanov) at ENS de Cachan. She has multidisciplinary high level skills with a large experience in structural chemistry and biology, bioinformatics and molecular modeling. She has published more than 90 papers in peer-reviewed journals. She currently supervises 5 Post-Docs and 3 PhD students and coordinates modeling projects in virology and cancerology.