

## **Novel Insights from the High Resolution Structure of HIV-1 RT Containing a Nonnucleoside Inhibitor and an RNA/DNA Hybrid**

Wei Yang

Laboratory of Molecular Biology, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, USA

High resolution structures of human immunodeficiency virus Type 1 reverse transcriptase (HIV-1 RT) containing either duplex DNA and an RNA/DNA hybrid have provided important mechanistic insights into both the DNA polymerase and ribonuclease H (RNase H) activities of this multifunctional retroviral enzyme, which remains a central target for antiviral therapy. While the structures of several RT/DNA complexes have been solved, only a single binary complex containing an RNA/DNA hybrid has been reported, namely a duplex containing the polypurine tract (PPT) primer of (+) strand, DNA-dependent DNA synthesis. An unusual feature of this structure was a series unpaired and mispaired bases, collectively referred to as the “unzipped” portion of the PPT. In the absence of additional data on RT-RNA/DNA complexes, the role/necessity of such anomalous base-pairing remains obscure. Moreover, it remains to be established whether such structural distortions are a common consequence of the interaction of HIV-1 RT with RNA/DNA hybrids or they are unique to the unusual sequence of the PPT primer. To address these important issues, we have successfully crystallized HIV-1 RT in the presence of a nonnucleoside inhibitor and a non-PPT-containing RNA/DNA hybrid. Features of this complex will be compared and contrasted with the currently-available RT structures.