

Kenneth A. Johnson, Ph.D.

Roger Williams Professor of Biochemistry
Institute for Cellular & Molecular Biology
University of Texas at Austin

Title: DNA Polymerase Dynamics and Specificity in the Treatment of AIDS

Abstract: The specificity of nucleotide incorporation during DNA polymerization is governed by conformational changes induced by nucleotide binding to the enzyme-DNA complex. A correct nucleotide causes a change in enzyme structure from an open to a closed complex in which the substrate is bound tightly so that release is slow while the active site is organized to facilitate fast catalysis. In contrast, binding of a mismatch leads to a novel structure in which the active site residues are misaligned and substrate release is fast. Accordingly, the conformational change acts like a gate to select or reject the substrate. Nucleotide selectivity governs the effectiveness versus toxicity of nucleoside analogs used to treat HIV infections and can be assessed by measurements using HIV reverse transcriptase to quantify effectiveness and the human mitochondrial DNA polymerase to quantify toxicity.