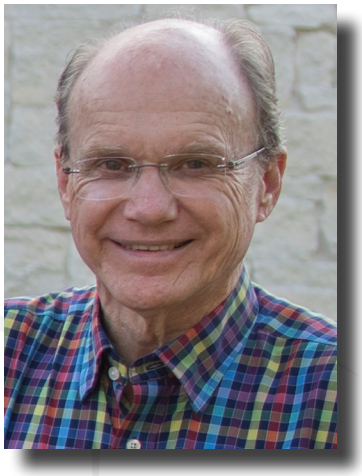
DEPARTMENT OF BIOCHEMISTRY FRONTIERS



PROFESSOR KENNETH JOHNSON

Roger J. Williams Centennial Professor of Biochemistry,
University of Texas, USA

DATE	7 SEPTEMBER 2015
TIME	12PM
LOCATION	MD7 LEVEL 2 SEMINAR ROOM M9
CHAIRED BY	A/P YEW WEN SHAN

Role of Conformational Dynamics in HIV Reverse Transcriptase Specificity and Evolution of Drug Resistance

The role of substrate-induced conformational changes in enzyme specificity has been controversial since the first suggestion of "induced-fit" nearly 60 years ago. In studies on HIV reverse transcriptase, the problem takes on important medical relevance regarding the effectiveness versus toxicity of nucleoside analogs used to treat viral infections. In our studies we use transient state kinetics methods that allow direct measurement of the rates of enzyme closing and opening relative to rates of incorporation of nucleotides during DNA polymerization by HIV reverse transcriptase. This analysis demonstrates that the nucleotide-induced enzyme isomerization is the major determinant of specificity governing both fidelity and selection against nucleotide analogs. In the case of lamivudine (3TC), the two-step binding reaction helps to make the drug more effective by affording a lower Km to compensate for the slower rate of incorporation. Similarly, evolution of resistance to zidovudine (AZT) is attenuated by the two-step binding in that slower chemistry results in a lower Km for incorporation. Molecular dynamics simulations reveal the molecular details underlying the large conformational changes to provide a comprehensive understanding of the role of substrate-induced changes in enzyme structure that are responsible for nucleotide selectivity.

Prof. Kenneth A. Johnson, Ph.D. joined the University of Texas at Austin in 1998 where he serves as the Roger J. Williams Centennial Professor of Biochemistry and is a Member of the Department of Molecular Biosciences and of the Institute for Cell and Molecular Biology. Prior to joining the University of Texas he was the Paul Berg Professor of Biochemistry at Pennsylvania State University. His research is focused on the examination of DNA and RNA polymerases involved in the treatment of viral infections. He has designed and built instruments for transient kinetic analysis and made them available through his company, KinTek Corporation, which he founded in 1987. In earlier work, he established the ATPase pathways of the microtubule dependent motors, dynein and kinesin. In his more recent research he has established the mechanistic basis for DNA polymerase selectivity during polymerization and has shown that the toxicity of nucleoside analogs used to treat AIDS is correlated with their rates of incorporation by the mitochondrial DNA polymerase. Recently he has shown that substrate-induced enzyme conformational changes are the major determinant of enzyme specificity by HIV reverse transcriptase and control the evolution of resistance to nucleoside analogs used to treat HIV infections. He serves as Member of the Scientific Advisory Board of Pacific Biosciences, Inc., and is Fellow of the American Association for the Advancement of Science. Johnson also serves as Chief Executive Officer and President of KinTek Corporation. He received a B.S. in Chemistry from the University of Iowa, and a Ph.D. in Molecular Biology from the University of Wisconsin.

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SynCTI Synthetic Biology Program for Clinical and Technological Innovation