## Jun Xi

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**Research Theme:** All biological events, such as cell signaling and gene regulation are accomplished by biomacromolecular complexes. I am interested in dissecting these complexes to develop a fundamental understanding of the formation and regulation of these biological machineries. Such studies are critical to the success of identifying drug targets and developing potential therapeutics.

**Research approach:** Chemical and molecular biology are the corner stones of my research. Chemical biology approach includes but is not limited to pre-steady and steady state enzymology, functional genomics, proteomics, mass spectrometry, NMR, single molecule fluorescence spectroscopy, protein engineering, organic synthesis, and combinatorial chemistry. Molecular biology approach involves functional assay development and mutagenesis.

## **Research projects**

Mechanistic study of heat shock protein Hsp90. Heat shock protein Hsp90 plays a key role in the response of cells to stress and participates in producing and maintaining the active states of many important regulatory proteins of signal transduction, cell cycle, differentiation and survival, and share the functional necessity to form multiprotein complexes. These include many proteins involved in cancer development. Therefore, Hsp90 has become a unique target for cancer therapeutics. In recent years, much progress has been made to understand the structure and function of Hsp90. However, some fundamental questions remain to be answered. I am interested in defining the functional domains and ATPdependent domain movements of Hsp90, examining the effect of the binding of cochaperones and substrate proteins on conformational changes of Hsp90, and determining the sites of interaction between Hsp90 and its cochaperones and its target proteins.



Figure 1.Dynamic conformational switching of Hsp90.

**Mechanistic study of Mismatch Repair in** *Escherichia coli.* DNA mismatch repair plays a major role in safeguarding the integrity of the genome by recognizing and correcting errors that arise from base misincorporation or damages. Although the *Escherichia coli* methyl-directed pathway is best understood among all the known mismatch repair systems, many questions remain in the areas of mismatch recognition, signaling pathway and repair

process. I am planning to investigate the dynamic processes of the protein-protein and protein-DNA interactions involved in all three areas with a unique fluorescence approach. The functions of some of the key protein components will be reevaluated based on current understanding of the signal propagation and the repair process. The connection between mismatch repair and DNA replication will also be explored. I would also like to eventually expand my research to include eukaryotic system which is potentially more meaningful to life and human health.



Figure 2. Model for mismatch recognition in E. coli MMR system.

Mechanistic study of DNA replication in Bacteriophage T4. The T4 replication system is a model for DNA replication in general. By far, there is very limited knowledge concerning the repetitive lagging strand DNA synthesis, including the handoff of the primer from primase to its next recipient and the subsequent assembly of the lagging strand holoenzyme. Another area of T4 research is to explore the molecular mechanism employed by T4 replisome to achieve a coordinated replication between leading and lagging strand DNA synthesis. This could have implications to DNA replication in other organisms.



Figure 3. T4 replisome.

## Selected publications

• Interaction between the T4 Helicase Loading Protein (gp59) and the DNA Polymerase (gp43): Unlocking of the gp59-gp43-DNA Complex to Initiate Assembly of A Fully Functional Replisome. (2005) *Biochemistry* 44, 7747-56.

• Interaction between the T4 helicase-loading protein (gp59) and the DNA polymerase (gp43): a locking mechanism to delay replication during replisome assembly. (2005) *Biochemistry* 44, 2305-2318.