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2001 Program
New Investigator (3-year project)

Project Title: Structure mechanisms of RNA processing enzymes

Project Summary: Biological molecules exhibit amazing specificities in molecular recognition and enzyme catalysis. The project investigated how specific recognition between two biomolecules lead to enzyme catalysis. The subject of the study is an essential enzyme in eukaryotic cell (cells die without this enzyme), called splicing endonuclease. This enzyme is responsible for the removal of intervening gene sequences (nucleic acids) that interrupt otherwise mature sequences in a manner similar to editing of movie films. In order to understand how this enzyme or enzymes of similar functions selects out and removes the target sequences among the many it encounters in the cell, the project has been working towards obtaining three dimensional structures of this enzyme bound with its target nucleic acids. The project has also been engaged in using quantitative assays to define the specificity of this enzyme outside cells. Findings from these studies will advance the understanding of biomolecular recognition in gene expression. It has recently been determined that a partial structure of this enzyme bound with its target nucleic acids which will soon reveal the exact atomic placement of the entire enzyme with respect to the target nucleic acids. As the results of this support, work on another related molecular complex has been worked. It is involved in making mature nucleic acid products by chemically modifying nucleic acids. The study has revealed, at atomic resolution, how this large molecular complex is assembled and how it catalyzes the reaction.

Project Successes: The impact of this study is high. The enzymes that the project has been working are essential to the survival of cells. Defects in these enzymes lead to either low or no expression of functional genes and thus cause diseases. In addition, many of these essential gene expression pathways in uncontrolled proliferating cells (e. g. cancer cells) are amplified. Therefore, studying the chemical properties of these enzymes has the potential in leading to anti-cancer drug discovery. Three dimensional structures of molecular complexes hold the key to address the principles of molecular recognition and catalysis.

Selected publications from BRP funded research in Peer Reviewed Journals:

Aittaleb M, Visone T, Fenley MO, **Li H.** Structural and thermodynamic evidence for a stabilizing role of Nop5p in S-adenosyl-L-methionine binding to Fibrillar. *J Biol Chem.* 2004;279(40):41822-41829.

Zhang Y, **Li H.** Structure determination of a truncated dimeric RNA splicing endonuclease in pseudo-centered space group P2₁2₁2. *Acta Crystallogr.* 2004;D60:447-452.

Moore T, Zhang Y, Fenley MO, **Li H.** Molecular basis of box C/D RNA-protein interactions: Co-crystal structure of the archaeal sRNP. *Initiation Complex Structure.* 2004;12(5):807-18.

Aittaleb M, Rashid R, Chen Q, Palmer JR, Daniels CJ, **Li H.** Structure and function of archaeal box C/D sRNP core proteins. *Nature Structure Biology.* 2003;10: 256-63.

Rashid R, Aittaleb M, Chen Q, Spiegel K, Demeler B, **Li H**. Functional requirement for symmetric assembly of archaeal box C/D small ribonucleoprotein particles. *J Mol Biol.* 2003;333:295-306.

Selected presentations from BRP funded research:

Moore M, **Li H**. "Co-crystal structure of box C/D RNA bound with L7Ae". (Invited oral presentation) Biophysical society meeting 2004, Baltimore, Washington.

Oruganti S, **Li H**. "Oligomerization Studies of Yeast Nop56p and Nop58p proteins by Biochemical and Analytic Ultracentrifugation Methods". Symposium on RNA Biology V: RNA, Tool and Target, North Carolina, 2003

Rashid R, **Li H**. "Asymmetric Assembly Mode of An Archaeal box C/D sRNPs in Methylation Reactions". *2003 RNA Society Meeting*, Vienna Austria

Zhang Y, **Li H**. "Crystallographic Studies of RNA Splicing Endonucleases" *ACA 2003*, Cincinnati, OH, 2003

Moore TL, **Li H**. "Co-crystal structure of box C/D RNA-L7Ae Complex at 2.9 Å", *RNA Society Meeting*, Vienna Austria, 2003.

Lam TT., Xu F, Emmett MR., **Li H.**, Marshall AG. Fibrillarin:Nop5p Complex Binding Surface Mapped by H/D Exchange and LC Micro-Electrospray Ionization Fourier Transform Ion Cyclotron Resonance Mass Analysis. *MRE Functional Genomics Conference*. Sweden, 2002

Cox R, **Li H**. "Bioinformatics of the Bulge-helix-bulge RNA Motif in Archaea". *SERMACS 2001*, Savannah, Georgia, 2001

New grants based in part on BRP-funded work:

NIH

Title: Structural Assembly and Catalytic Mechanism of SnoRNPs

Project period: July 1, 2003 – June 30, 2008

Award amount: \$1,203,899

NIH

Title: The Mechanism of evolutionarily conserved t(r)RNA splicing enzymes

Project period: pending

Award amount: \$1,300,000

NSF

Title: Integrating structural biology research of RNA splicing endonuclease with Biochemistry education

Project period: pending

Award amount: \$851,914