

Central Alabama High-Field NMR Facility
Structural Biology Shared Facility (Cancer Center)
Center for Structural Biology
 Dept of Chemistry, 901- 14th St. South, Birmingham, AL 35294

NMR Facility Director: Prof. N. Rama Krishna (Ext. 4-5695),
Dept of Biochem & Molec Genetics

NMR Research Capabilities
 (Extremely Diverse Range of Applications in Structural Biology and Drug Discovery)

The facility staff will provide advice and consultation on a wide range of NMR applications

- **Quality Control** in Synthetic Chemistry and Medicinal Chemistry Drug Discovery/Design Projects by 1D/2D-NMR (1H, 13C, 31P etc).
- **Three-dimensional structures of Proteins and their complexes** (protein-protein, protein-nucleic acid).
- **Three-dimensional structures of Protein-ligand complexes** (tight binding to very weak binding).
- **STD-NMR Screening** (a binding assay) of single Compound or Compound Libraries.
- **Binding Epitopes** of the low molecular weight compounds.
- **Fragment-based discovery & design** (lead optimization) of new drugs by: (a) SAR-by-NMR and (b) ILOE
- **Membrane-bound Proteins/peptides.**
- **NMR on cells (in vitro)** and cell extracts, NMR-Metabolomics.

STD-NMR (Saturation transfer difference)

For screening compound libraries

Saturation Time

Ligand/Protein ratios can be 15:1 to 1000:1

Adapted from M. Mayer & B. Meyer, *Angew. Chem. Int. Ed.*, **38**, 1730-1738, 1999.

CORCEMA Analysis of Transferrin/Bovine DHEP-complex

Binding Pocket

Bound (NMR) Transferrin

- (1) Determination of bound ligand structure within the protein binding pocket
- (2) Post-printing of the binding pocket, and/or protein
- (3) Identification of group epitopes on the ligand

NMR Structure of QbV Enzymic Nucleoside

State-of-the-Art Bruker NMR Instrumentation:

- (1) 850 MHz NMR Spectrometer with a TCI-CryoProbe
- (2) 700 MHz NMR Spectrometer with a TCI-CryoProbe
- (3) 600 MHz NMR Spectrometer with a TCI-CryoProbe
- (4) 500 MHz NMR Spectrometer with TXI & TBI Probes

Facility Staff:

N. Rama Krishna, Ph.D., Director, nrk@uab.edu, 4-5695
 Ronald shin, Ph.D., Manager, rsim@uab.edu, 4-5696
 Mike Jablonsky, Ph.D., Res Associate, mjab@uab.edu

Usage Fees: Please contact Dr. Krishna for usage fees

STD-NMR identification of compounds (lig) binding to the HIV-1 capsid protein (CA)

Non-enveloped RNA virus: Hepatitis in Rabbits, binds to histo-blood group antigens on cells lining digestive tract, aggregation of tumored blood cells

ChemEM image of the RBEV virus (Shimizu *et al.*, *J. Mol. Biol.*, 279:338-346 (1997))

Epitope Mapping by Cross-saturation transfer

Large Protein

Ligand or Small Protein

rf irradiation

ICS-NMR proposed by Takahashi *et al.* (2000) for mapping protein-protein interfaces

NMR Structure of a monomeric mutant of the HIV-1 capsid protein (26 kDa)



Bound Conformation of Transferrin with the binding pocket of bovine (B)hydroxide reductase (BHR)

(a target enzyme for folate antagonists)

STD-NMR identification of the specific sugar (B) recognized by the virus

NMR "foot-printing" of ligand binding sites on proteins

CdM Peptide: 1:0 (Black), 1:1 (Red), 1:2 (Green)

CdM interaction with FLP Peptide

Apo-A1 mimetic peptide bound to lipid bilayer

Vince Mizell, Ph.D., Medicine

Hepatitis and Primarily Biological Evaluation of High-Dose and Passive Antibody Challenge by the Center for Structural Biology

Sheng C. Xiang, F. Fasella, D. D. Ho, and R. Ramakrishna, and DDD Prasad Center Research Program

Abstract Summary

Transferrin/DHEP Complex: Comparison of Experimental and Calculated STDs

Using the crystal structure of Chicken Liver DHEP complex

After CORCEMA Optimization

Fragment-based Design of Conjugated Ligands with Higher Affinity Binding to Neighboring Binding Pockets

Ligand molecules (fragments) in solution: A and B

Binding pockets

Linker

SAR by NMR: Protein-based, NMR structure of protein required

ILOE: Ligand-based, No need to know the protein structure

HIV-1 infection of human brains: NMR analysis of brain extracts from autopsy samples (Dak Bence, Ph.D.)

NMR on intact cells and cell extracts