Structural Biology NMR Facility Strategic Plan
Executive Summary

I. Facility Functions and Personnel

A. Research Focus

- Particular emphasis on high-resolution NMR solution structure; other areas of strength include metabolomics, pharmaceuticals, and solid-state NMR of membranes and other biological assemblies

B. People

- Dr. David Thomas, Director; Dr. Beverly Ostrowski, Manager; Dr. Chin Ju Park, Assistant Manager; Todd Rappe, NMR Spectroscopist; Nathan Traaseth, Solid-state Assistant Manager
- Fifty-four principal investigators from fifteen different departments depend on facility for research needs, over 160 users
- User and Steering Committees ensure broad input.

C. Training and Education

- Personnel run educational workshops for new user and advanced training, practical NMR lab course for credit in May and June
- Provide extensive consultation for internal and regional community

D. Interactions with Other University Facilities

- Contractual agreement with Med. Chem. for 2 - 400 MHz maintenance
- Contractual agreement with CDD for 600 MHz NMR maintenance

II. Instrumentation

A. Spectrometer Consoles

- Four of seven consoles 12 years old
- **Replacement of all four by 2010 is very high priority**

B. Probes

- Cryoprobe acquired for 800 MHz in 2005
- Additional cryoprobe (carbon enhanced, salt tolerant) a priority for 600 MHz to be purchased by 2011

C. Computers

- Six Sun workstations to be replaced by 2010, four new offline workstations in 2007

D. New Instrumentation

- 700 MHz solid state spectrometer added in 2007
- 700 MHz solution instrument donated from 3M in 2007
- Current space could site future shielded 800-900 MHz magnet
- Other new major instrumentation would require significant new space

III. Space

- Current space for offices, instruments is fully occupied; additional expansion space is critical for future personnel or instrumentation

IV. Income and Funding

- Annual income from internal use, subsidy, Med Chem and CDD contracts, workshop fees, solid-state use
- User rates increased at approximately 3% per fiscal year
- Potential grant sources include Minnesota Medical Foundation, NIH Shared Instrumentation Grants (SIG), NIH High-End Instrumentation, NSF Major Research Instrumentation (MRI), Minnesota Partnership Infrastructure

At the core of the NMR Facility is the instrumentation and personnel whose goal is to provide state-of-the-art NMR resources to researchers at the University.

I. Facility Functions and Personnel

The primary mission of the facility staff is to help keep Minnesota at the forefront of biomedical NMR research, by maintaining the performance of the complex research instrumentation (both hardware and software), working with investigators to develop improved methods for the use of these instruments, and promoting education in the area of NMR. The facility personnel make substantial contributions to the education and training of students and postdocs through workshops and extensive one-to-one interactions.

A. Research Focus

The NMR Facility operates as an internal service organization serving the entire University of Minnesota and a very diverse set of researchers. The facility has particular emphasis for work in high-resolution NMR solution structure, with other strengths in the areas of metabolomics, small molecule studies in pharmaceuticals, and solid-state NMR of membranes and other large assemblies. The demanding area of high-resolution NMR structure work creates constant pressure for newer technology, especially in the area of cryoprobes and for higher field instruments. Major growth in metabolomics and other biomedical applications is stimulating the facility to enhance its capabilities in high-throughput NMR of biological liquid samples and in solid-state NMR of tissue samples.

B. Training and Education

Organized practical training workshops are held by the NMR facility to provide formal training for users, typically 5-6 times a year. These workshops are open to the local community and encourage participation from outside the University. Participants from as far away as Canada and Harvard have attended these workshops as well as many from the University of Minnesota in Duluth. In addition, users from groups both with and without a primary focus on NMR, rely heavily on training, input, and scientific advice from the facility staff. Two recently established courses, Intro to Structural Biology and Laboratory in Practical NMR Techniques, provide an introduction to NMR. Laboratory in Practical NMR was developed and is taught through the NMR facility for undergraduate (Bioc 4225) and graduate (Bioc 5225) credit. Sponsorship of visiting lecturers or symposia in the field would also further the NMR program and will require additional financial support. Following the solid-state NMR 700 MHz instrument and liquids 700 MHz instrument installations, along with major new instrumentation in the adjacent EPR facility, a symposium should be organized to showcase these outstanding resources (e.g., fall 2009).

C. Personnel

At present, the facility has three full-time staff. An additional 75% postdoctoral fellow maintains the solid-state NMR instrument. The level of staffing is an issue given the demands on personnel in maintaining the seven facility instruments, computer system administration, training, assisting users, supporting the two 400 MHz instruments in Medicinal Chemistry and the 600 MHz instrument in the Center for Drug Design (10 instruments total). With new research groups, new projects, new instrumentation and general growth in the facility usage, an adequate level of staffing is very important. Currently, the facility is receiving additional staff support through one part-time graduate student assistant and one undergraduate doing directed research. Future additions of more sophisticated instrumentation could require the addition of more highly skilled staff people. Facility

personnel have the option of voluntarily engaging in collaborative projects at a level that does not overwhelm their facility responsibilities. This option provides an opportunity for them to keep current in the field and maintain their scientific standing though currently the demand for NMR collaborators vastly outweighs the supply. Occasional NMR spectral service is provided with the requestor being charged at a premium for personnel time.

D. NMR User Committee

The NMR User Committee currently includes approximately 54 principal investigators who aid in establishing broad policy related to the academic and research usage of the instruments in the facility including special allocations of instrument time, rates, upgrades, and grants submitted on behalf of the facility. Meetings of the user committee are to be held approximately once every two months. All users of the facility are invited to attend these meetings.

E. NMR Steering Committee

This is a smaller committee consisting of the principal investigators of the major user groups within BMBB plus at least one from Medicinal Chemistry and/or the CMMR. This committee meets every one to two months to discuss more detailed technical and strategic issues, their results and recommendations are then reported to the users, by email and/or at the Users Committee meeting.

F. Interactions with Other NMR Facilities

A financial arrangement between the facility and Medicinal Chemistry supports the maintenance of their two 400 MHz NMR instruments and training of their users. The user base on their instruments has increased steadily since our first installation with them in 1999 (300 MHz). The department added a 400 in the Institute for Therapeutic Discovery and Development (ITDD) and a new base of users from Dr. Gunda Georg's group in 2007. Another 400 MHz instrument was installed in 2008 replacing the original 300 MHz instrument creating a more advantageous instrument for the users, but a higher demand on this staff support. This arrangement is reviewed annually so that appropriate adjustments can be made in light of demands. A similar agreement with Center for Drug Design (CDD) provides training and maintenance support for their 600 MHz instrument. The cooperation between the NMR facility, Medicinal Chemistry, ITDD and CDD is a very positive, productive interaction for all parties.

An informal, positive interaction exists with the NMR facility in the Chemistry Department and the Center for Magnetic Resonance Research (CMRR) whereby information, resources, and interest in NMR are shared. Sufficient common NMR research interests exist on campus that a University-wide approach for future enhancements in the area of high-resolution magnetic resonance is possible.

G. Promotion, Public Relations

This facility has grown rapidly in recent years, in stature and productivity, along with the rest of the Structural Biology Program at the University. This is an opportunity for us to increase our national and international profile, through our web site, symposia, courses, recruiting, and other efforts. The Steering Committee is beginning to further discuss this priority and make recommendations.

II. <u>Hardware</u>

A. Consoles

The instrument consoles date from 1996 (500 and 600's) and 1998 (800) and continue to perform well. By 2009, these consoles will be 12 years old, and some components have begun to fail due to age. A newer console model is now available from Varian and has essentially made our current consoles obsolete. Software upgrades for the current consoles are no longer available. Replacement of the consoles is the top equipment priority by 2010.

B. Probes

The emergence of new cryoprobe technology offers substantial improvement in sensitivity that translates into reduced experiment time and/or ability to study more dilute or challenging samples. These probes provide the most cost effective way in the near term for increasing the capacity of the data output of the current instruments. A cryoprobe (cold) probe has been installed for the 800 MHz instrument. Since installation this probe has been used non-stop and is currently drastically oversubscribed. The general maintenance of the cold head on this probe adds to the yearly facility expenses. The 700 MHz instrument from 3M is equipped with a cryoprobe, but has not alleviated the current pressure on the 800 MHz cold probe system. Both cryoprobes are currently in heavy use.
A subsequent purchase of a cold probe for a 600 MHz instrument is anticipated as the next top equipment priority following replacement of the instrument consoles. The purchase of a carbon-enhanced, salt-tolerant probe for the 600 will provide additional capability over the 800 cold probe. Cryoprobes are also quickly becoming a staple of metabolomics work providing additional sensitivity for dilute biological fluids.
A new 5mm broadband for a 600 MHz instrument was installed in 2008 and replaced the temperamental 8 mm broadband probe. Funds for the broadband probe are being provided in part by a separate Minnesota Medical Foundation equipment grant essential for a new large, metabolomics grant beginning in 2009.
An upgrade to the current triple resonance probe on the 500 MHz to the improved technology conventional probes providing about a 50% increase in performance should be considered in the next year as well as the addition of deuterium switching capability to this instrument for automation.

C. Computers

The Sun workstations were replaced in 2006 in concert with a major software upgrade to VNMRj. . Offline workstations for solution and solid-state NMR will be added to the computer room in 2007. The host workstations are expected to be upgraded and to Linux workstations upon acquisition of new instrument consoles in 2010.

D. New Instrumentation

1. High-field, solid-state spectrometer. The University committed $1.3 million for the acquisition of a new 700 MHz instrument housed in the facility. This instrument is part of the overall facility, but its finances and operation are organized separately from the solution NMR components. Dr. Veglia, whose group will be the principal user of this instrument, is the primary advisor to the Director for decisions regarding operation of this instrument. Due to the failure of the 700 MHz Oxford magnet delivered in summer 2006, an additional 600 MHz solid-state instrument was installed and is currently on loan with the option to purchase from Varian. At this point, the 700 MHz instrument has been accepted and the University is expected to cover all costs of operating the 600 MHz instrument as well as the 700 MHz instrument. Plans are being developed to promote this instrument as part of a new Center for Magnetic Resonance of Biological Assemblies, in combination with the new high-field pulsed EPR spectrometer in the adjacent Biophysical Spectroscopy Facility. A NIH shared instrumentation grant is planned to obtain funds to purchase the loaner 600 MHz instrument. This instrument is a hybrid liquids and solids instrument. Liquids work on this instrument will be consistent with the rates and policies in place for the existing liquids 600 MHz instruments. Rates and policies for solid-state NMR work on the loaner 600 MHz and the 700 MHz solid state NMR will be developed according to U of M ISO policies.

2. A 700 MHz Bruker liquids instrument with cryoprobe and autosampler was added to the facility in 2007 due to a generous donation of the instrument by 3M. This instrument provided high field access to another cryoprobe and ability to conduct high-throughput metabolomics studies with the availability of a 60 sample autosampler.

3. Replacement consoles for 600s and 800. The aging consoles on the two 600 and one 800 MHz instrument are top priority for equipment acquisitions. The current consoles are beginning to have age-related parts failures resulting in down time and their software upgrades are at an end. The newer VNMRS consoles available from Varian have improved performance and signal-to-noise and will also provide continued ability to use the latest software and NMR experiments available.

4. Additional 600 MHz cold probe. The dramatic improvement of the performance of the 800 MHz spectrometer, due to the addition of a cold probe, and subsequent high-level of demand underlines the second equipment priority of acquiring another 600 MHz cold probe. This accessory could provide additional capability with carbon-enhancement and the improvement of certain experiments at lower field than 800.

5. Additional high-field solution spectrometer. With the growth of the current research labs, a large influx of new projects and groups, and the expansion in Medicinal Chemistry, the instruments have reached a usage level where significant waits are sometimes required for time to run experiments. Some users also travel to use the Madison NMR facility and to the University of Georgia due to lack of NMR time in our facility. In the absence of additional space, the mode of expansion within the facility would be the purchase of a shielded 800 MHz system and would be sited in the space previously occupied by an existing 500 or 600 MHz instrument. If new technology allows in the next few years, a 900 MHz instrument may be accommodated by space currently occupied by the 500 or a 600 MHz instrument. Significant additional space would be required to site a higher field instrument in the future. New space would be required in a new building and be specially designed for this purpose. The alternative to new space would be a major renovation to the existing lab.

E. Summary Future Technology, Instrumentation and Expansion Priorities

a. New VNMRS console for 800 MHz/CP
b. New VNMRS consoles for 600 MHz instruments (2)
c. 600 MHz cryoprobe (carbon enhanced)
d. next high field spectrometer (900 MHz or higher)
e. high through-put setup for 600 MHz/CP setup (autosampler)
f. investigate nitrogen separator for Bruker 700 and SS NMRs
g. investigate helium recovery system
h. retain loaner 600 MHz hybrid NMR

III. Space

The space currently allotted to the facility is fully occupied and at capacity. In addition to the main instrument room (1-130), the contiguous wet lab (1-120), offline computer room (1-142), and three offices are all fully occupied space for the facility users and the facility personnel. A larger field instrument (800 or 900 MHz) could potentially be placed in the current 500 MHz location. The NMR facility also will need additional space in the near future to accommodate expansion in new instrumentation and personnel.

IV. Income and Funding

A. User fees and internal income

For FY08, revenue came from annual internal user income from University of Minnesota and external users. Additional internal income is currently generated from the Medicinal Chemistry agreement, the CDD agreement, and workshop fees. The facility currently has a subsidy from the Medical School. Income from user fees on the solid state 700 and loaner, hybrid 600 MHz instruments are estimated to remain flat in the next year.

Rates are developed based on operation expenses, after any subsidies, that include salaries/ fringe

benefits, cryogens, maintenance and repairs, travel, new equipment, computer supplies, and other expenses. Rates are hourly and are adjusted periodically, based on an annual accounting analysis, as required by U of M ISO policies. Rates for the solid-state NMR will be calculated separately based on the nature of the work but will still be based on annual accounting analysis and subject to periodic adjustment according to U of M ISO policies. Solid-state NMR use revenue and expenditures will be routed through a separate account under the NMR ISO.

B. Outside user income

Outside use from a few academic institutions and industrial companies including Medtronic, 3M., and Cargill provided some additional income. 3M use is expected on the donated 700 MHz instrument as part of the agreement for acquisition of the instrument.

C. Grant and funding sources

The next proposed grants to be submitted on behalf of the facility is to the NIH high-end instrumentation grant program.

Contributions from Medical School, CBS, IT, School of Pharmacy, and Graduate School

Minnesota Medical Foundation

Previous awards: $20K for a probe upgrade in winter 1999/2000 (Armitage)
$20K for a cryoprobe in Spring 2002 (Matsuo)
$30K for new HCN probe for 600 2003 (Walters)
$30K for a new HCN probe for 500 Fall 2006 (Veglia)
$30K for a new BB probe for 600 Fall 2007 (Beilman)

Applications are due on Jan. 6, May 1, and Sep. 1. Grants are awarded within two months. Max award $35K.

NIH Shared Instrumentation Grants (SIG)

Deadline March yearly, Minimum $100K, Max $500K.

NSF Major Research Instrumentation (MRI)

Deadline February, Range $100K to $2M.

NIH High End Instrumentation

Deadline October, Minimum $500K, Max $2M.

NSF Multi-User Equipment and Instrumentation Resources for Biological Sciences

Deadline: suspended

University of Minnesota/Mayo Infrastructure Grant: Minimum $50K

Deadline: last one May 23, 2008