DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
NATIONAL CENTER FOR RESEARCH RESOURCES

NATIONAL ADVISORY RESEARCH RESOURCES COUNCIL
MEETING MINUTES
SEPTEMBER 11, 2007

The National Advisory Research Resources Council convened for its 137th session at 8:00 a.m. on Tuesday, September 11, 2007, in Conference Room 10, Building 31. Dr. Barbara M. Alving, Director, National Center for Research Resources (NCRR), National Institutes of Health (NIH), presided as Chair. The meeting was open to the public until 1:00 p.m., at which time it was closed to the public for the review, discussion, and evaluation of grant applications as provided in Sections 552b(c)(4) and 552b(c)(6), Title 5, U.S. Code, and Section 10(d) of Public Law 92-463.

COUNCIL MEMBERS PRESENT

Dr. Nancy J. Brown
Dr. James P. Collins, Liaison Member, NSF
Dr. Valerie Copié
Dr. Kenneth G. Cornetta
Dr. James E. Heubi
Dr. Roland F. Hirsch, Liaison Member, DOE
Dr. Kevin B. Johnson
Dr. Cynthia E. Keppel
Dr. Barbara B. Knowles
Dr. Henry Lewis III
Dr. Bettie Sue Masters
Col. (Dr.) Debra M. Niemeyer (ex-officio)
Dr. Richard A. Rudick
Dr. Janet L. Smith
Dr. M. Roy Wilson
Ms. Sheila C. Zimmet
Dr. Stuart M. Zola

COUNCIL MEMBERS ABSENT

Dr. Kelly D. Garcia (ex-officio)
Dr. Mark V. Pauly
Dr. Thomas J. Rosol
Dr. Arthur W. Toga
Dr. Tilahun D. Yilma

SPECIAL INVITED GUESTS FOR OPEN SESSION

Dr. Sherine E. Gabriel, Mayo Clinic, Rochester, MN
Dr. W. Timothy Garvey, University of Alabama, Birmingham
Dr. Steven I. Hirschfeld, NICHD, Bethesda, MD
Dr. Jennifer M. Puck, University of California, San Francisco

STAFF OF OTHER NIH COMPONENTS

Dr. Nuria E. Assa-Munt, CSR
Ms. Irene E. Dorsey, OD
Dr. Kathryn M. Koeller, CSR
Dr. Dana J. Plude, CSR
Dr. Jean D. Sipe, CSR
Dr. Meredith Temple-O'Connor, NIGMS
Dr. Estina Thompson, CSR

OTHERS PRESENT

Mr. Robert J. Berendt, Consultant, Robert J. Berendt Associates, Washington, DC
Ms. Margaret Blasinsky, President, The Madrillon Group, Inc., Vienna, VA
Dr. Luis A. Cubano, Assistant Professor, Anatomy and Cell Biology, Microbiology and Immunology, Universidad Central del Caribe, Bayamón, Puerto Rico
Dr. Robert P. Dottin, Director, Hunter College Center for Study of Gene Structure and Function, New York, NY
Dr. Mary C. Dufour, Senior Vice President, The Madrillon Group, Inc., Vienna, VA
Dr. Marilyn F. Dunlap, RCMI Coordinator, Pacific Biosciences Research Center, University of Hawaii at Manoa
Dr. Matthew Gdovin, RCMI Center Director, University of Texas at San Antonio
Dr. Barbara E. Hayes, Dean, Pharmacy School, Texas Southern University, Houston, TX
Mr. Stephen J. Heinig, Senior Staff Associate, Division of Biomedical and Health Sciences Research, Association of American Medical Colleges, Washington, DC
Dr. Robert Kirken, Deputy Director, Border Biomedical Research Center, University of Texas at El Paso
Dr. Perry M. Kirkham, Project Officer, Purdue University, West Lafayette, IN
Ms. Marilyn Massey-Ball, President and CEO, MasiMax Resources, Inc., Rockville, MD
Dr. Valerie Montgomery Rice, Professor & Chair, Obstetrics and Gynecology, Meharry Medical College, Nashville, TN
Dr. Eddy O. Ríos-Olivares, Universidad Central del Caribe, Bayamón, Puerto Rico
Dr. Karam F. Soliman, RCMI Program Director, College of Pharmacy andPharmaceutical Sciences, Florida A&M University, Tallahassee
Dr. Paul B. Tchounwou, Associate Dean/Professor, Biology Department, Jackson State University, Jackson, MS
Dr. Joseph A. Whittaker, Dean and Professor, School of Computer, Mathematical, and Natural Sciences, Morgan State University, Baltimore, MD

OPEN SESSION

I. Call to Order: Dr. Barbara M. Alving, Director, NCRR

Dr. Alving welcomed Council members and guests to the 137th meeting of the National Advisory Research Resources Council.

II. Commemoration of the Terrorist Attacks on September 11, 2001: Dr. Barbara M. Alving

Dr. Alving acknowledged the tragic events that took place on this date six years ago. She spoke about the importance of honoring the memory of the people who died, those who sacrificed their lives for others, and those who continue to suffer from the tragic events of that day. To help prevent future tragedies such as these, she called on scientists, with their extensive contacts in other countries, to help build common goals with communities around the world.

III. Consideration of Minutes: Dr. Barbara M. Alving

The minutes of the Council meeting held on May 22, 2007, were approved as written.

IV. New Council Members: Dr. Barbara M. Alving

Two new Council members were introduced: Dr. James E. Heubi and Dr. James P. Collins.

Dr. James E. Heubi is the Director of the General Clinical Research Center at Cincinnati Children's Hospital Medical Center and Associate Dean for Clinical Research at the University of Cincinnati College of Medicine; he has been a practicing pediatric gastroenterologist since 1979. Dr. Heubi's practice includes the treatment of all disorders affecting the gastrointestinal tract, liver, biliary tract, and pancreas. His areas of interest include liver disease, complications related to end-stage liver disease and liver transplantation, and the management of patients with "short gut" or compromised gut function requiring prolonged enteral or parenteral nutritional support.

Dr. James P. Collins is Assistant Director for Biological Sciences at the National Science Foundation (NSF) and is replacing Dr. Machi F. Dilworth as the NSF liaison member. Dr. Collins oversees NSF's nearly $580 million annual investment in fundamental biological research and serves on the Foundation's senior management team. Dr. Dilworth, a long-time liaison to the Council, has been selected to be director of the NSF office in Tokyo, Japan.

V. Personnel Update: Dr. Barbara M. Alving

Division of Clinical Research Resources

- **Dr. Donna Jo ("DJ") McCloskey** joins NCRR from the National Institute of Nursing Research where she was the Director of Training for the Intramural Research Program. Dr. McCloskey is a Ph.D. nurse and has had extensive experience at the NIH Clinical Center where she worked with NIH physicians, their protocols, and patients. As a Health Scientist Administrator, Dr. McCloskey will manage a portfolio of research grants in support of the Clinical and Translational Science Awards (CTSA) program.

Division of Research Infrastructure

- **Dr. Padma Maruvada** recently worked at the National Cancer Institute, where she served as a Program Director in the Cancer Biomarkers Research Group in the Division of Cancer Prevention. As a Health Scientist Administrator, Dr. Maruvada manages a portfolio of research grants, particularly in support of the Institutional Development Award program.

VI. **Meetings, Activities, and Other Events**: Dr. Barbara M. Alving

RCMI Annual Principal Investigator's Meeting, September 10, 2007
Dr. Alving updated the Council on the Research Centers in Minority Institutions (RCMI) Annual Principal Investigator's Meeting, which was organized by Dr. Sidney A. McNairy and his staff. The meeting highlighted RCMI activities and accomplishments and focused on topics ranging from technology transfer and intellectual property to community outreach.

As part of the RCMI meeting, Dr. Douglas M. Sheeley, Health Scientist Administrator in NCRR's Division of Biomedical Technology, described his recent visit to the University of Puerto Rico Medical Sciences Campus for the opening of the RCMI Clinical Research Proteomics Facility. He discussed the opportunities for exchange programs and sabbatical projects between RCMI and biomedical technology investigators as well as possible technology transfers through the Biomedical Technology Research Resources program.

Also at the RCMI meeting, Dr. Anthony R. Hayward, Director, Division of Clinical Research Resources, NCRR, spoke about encouraging a synergy between the CTSAs and RCMIs and highlighted some of the community engagement activities that are ongoing at CTSA institutions. He noted that the opportunities for RCMI and CTSA collaborations will likely expand as the programs continue to mature.

Building the CTSA Consortium and Expanding Communication Activities
Dr. Alving informed the Council that the next cohort of CTSA recipients will be announced on September 18, 2007. The "Class of 2007" will enrich the program in new ways, bringing diverse strengths that will contribute to the overall success of the CTSA consortium. NCRR will be sponsoring a CTSA Consortium Oversight Committee meeting on October 3, 2007, to jump-start interactions between the classes of 2006 and 2007.

NCRR continues to focus on creating and expanding communications products and tools to inform stakeholders about CTSA activities and to foster opportunities for research collaborations. The revamped Web site, CTSAweb.org, provides access to critical, current information for the consortium and is a focal point for information on the individual CTSA institutions. NCRR is also in the process of negotiating a support contract for this activity. A monthly CTSA e-newsletter has also been established to circulate critical information to NIH staff and consortium participants. It highlights major activities and accomplishments, identifies upcoming workshops and meetings, and directs people to CTSAweb.org for the latest information. Council members will be added to the CTSA e-newsletter listserv in the near future. Dr. Alving encouraged the Council to visit CTSAweb.org to keep current on the activities of the consortium.

In other communications efforts, the *NCRR Reporter* and the *e-Reporter*, the electronic version of the magazine, reach more than 10,000 readers, including Council members. The magazine now includes a section titled "CTSAs in Focus," featuring a specific CTSA activity or topic. The current issue describes CTSA training and career development opportunities.

Information Sharing through the CTSA Wiki

In addition, to encourage collaboration across the consortium, Dr. Alving announced the launch of the CTSA Wiki. Members can now access the Wiki through CTSAweb.org to share information and ideas in a collaborative workspace. The current class of 2006 grantees can share progress as well as "lessons learned" with the new class of CTSAs, and the Wiki will provide a forum to continue the dialogue started at the Consortium Oversight Committee Meeting on October 3.

Informatics Pilot Projects on Information Exchange

Dr. Alving noted that a limited solicitation for informatics pilot projects among CTSA institutions will be announced this fall. These pilot projects will advance the development, adoption, implementation, and dissemination of tools, standards, and practices for information exchange and facilitate the performance of clinical researchers and their collaborators within, among, and beyond the CTSA consortium. Each pilot project will require collaboration of three or more CTSAs and encourage the leveraging of ongoing national informatics efforts. Awards will be for $500,000 – $1 million in total costs per year for two years; two to four awards will be funded. In addition, a CTSA subcommittee has been established to focus on how the CTSAs should proceed in the area of informatics.

Outreach to the Research Community

Dr. Alving noted the importance of direct, face-to-face communication and highlighted her participation at several research meetings. As part of the Multidisciplinary Clinical Conference at the University of Minnesota, she spoke to 100 investigators who are clinical research scholars, part of the NCRR-funded K12 Program. She spoke to them about strategies for career success, such as seeking out mentors, selecting research projects, and setting academic benchmarks. Dr. Alving also discussed opportunities provided by NIH, such as loan repayment, and the CTSA program.

Dr. Alving also presented at the Workforce Innovations Conference in Kansas City, Missouri, by participating in a discussion on working with federal partners to build regional economies. Sponsored by the Department of Labor, the meeting focused on the resources, programs, and expertise needed to meet the challenges that regional economies face together. Dr. Alving was able to share information about how NCRR-funded programs have had a positive impact on state economies across the country, such as through the Institutional Development Award (IDeA) program.

NCRR Five-Year Strategic Plan: Dr. Barbara M. Alving

Dr. Alving updated the Council on NCRR's plans to produce a Strategic Plan covering the five-year period from 2009 to 2013. A timeline was presented in order to recap the process.

In July 2007, NCRR posted a strategic planning Web page that requested input from the scientific community on key research and resource questions to determine the promising areas of biomedical research. Over the past two months, more than 500 responses have been received, representing a wide range of interests. Examples of these responses included interest in fostering collaborations between CTSA institutions and NCRR Centers; integrating informatics resources; increasing the availability and range of animal models; enhancing training opportunities for clinicians and veterinarians; enhancing opportunities for developing institutions to partner with research-intensive institutions and increase technology database development; expanding imaging resources; and encouraging partnerships with industry and pharmaceutical companies.

These responses will help NCRR identify and prioritize themes for the Strategic Planning Forum, which will take place December 3–4, 2007, at the Hilton Executive Meeting Center in Rockville, MD. The participants will include a cross-section of investigators, clinicians, NIH and other federal partners, and those who comprise the core constituencies. The Forum will be an opportunity to identify scientific trends while sharing recommendations on meeting critical needs. Dr. Alving expressed a desire to have the first draft of the strategic plan completed in time for the January 2008 Council meeting. She stressed that the plan will be continually updated, even after finalization, to allow for changes in focus and priorities.

VII. Budget Update: Dr. Barbara M. Alving

The FY 2008 NCRR President's Budget funding level is $1.112 billion. This level reflects the reinstatement of the Roadmap/Common Fund allocation, which totals $14.775 million. In FY 2007, the Office of the Director received direct funding for the Roadmap/Common Fund, which allowed the ICs to keep their Roadmap/Common Fund allocations in their budgets.

The Full House Appropriations Committee on Labor, Health and Human Services and Education passed the FY 2008 spending bill on July 19, 2007. The FY 2008 NCRR House Mark totals $1.171 billion—a $27 million (+2.4 percent) increase over the FY 2007 Joint Resolution level and a $59 million (+5.3 percent) increase above the FY 2008 President's Budget Request.

The Full Senate Appropriations Committee on Labor, Health and Human Services and Education marked up the FY 2008 spending bill on June 21, 2007, but did not pass the bill before recessing on August 6. The FY 2008 NCRR Senate Mark totals $1.178 billion—a $34 million (+2.4 percent) increase over the FY 2007 Joint Resolution level and a $66 million (+5.3 percent) increase above the FY 2008 President's Budget Request.

Congress reconvened on September 4, 2007. Before these bills can be sent to the President, the House- and Senate-passed bills must be reconciled by mutual agreement. The President has suggested he may veto both of these bills, because they exceed his budget request and because of the stem cell policy change in the Senate bill. Consequently, the likelihood of a continuing resolution at the start of FY 2008 that would provide for the ongoing operation of the government at the FY 2007 spending rate is a real possibility.

VIII. Legislative Update: Dr. Barbara M. Alving

Dr. Alving directed Council members to the Legislative Update in their binders for a review of several recent activities affecting NIH and NCRR.

IX. P41 Evaluation: Dr. Barbara M. Alving

Dr. Alving noted that the Council members had received a copy of a letter that was sent to the members of the Biomedical Technology Research Resources (BTRR) Evaluation Panel. She noted that the panel had provided a thoughtful and insightful analysis of the BTRR program, as reported at the last Council meeting. The letter was provided to update the Council on NCRR plans relative to those resources. This item also will be on the agenda for the January Council meeting.

X. CTSA Education Steering Committee Update: Dr. Sherine Gabriel, Professor of Medicine and Epidemiology, Mayo Clinic, Rochester, MN.

Dr. Gabriel described the CTSA Education Steering Committee and its members. Dr. Wishwa Kapoor co-chairs the committee with Dr. Gabriel. She explained the organization of the committee and the frequency with which its members communicate internally and with the CTSA education leadership, including Drs. Wilde, Merchant, and Schreffler. Regular updates are provided to the CTSA Consortium Oversight Committee.

Dr. Gabriel outlined the highlights and accomplishments of the CTSA Education Program. The program embraces the multidisciplinary, translational approach of the CTSAs. It is focused on developing competency-based curricula to offer a menu of programs of varying intensity and depth to reach a wide range of students and scholars representing many disciplines and stages of training. Degrees available range from certificates in clinical and translational research to the M.S. and Ph.D. The student body is diverse and has many more opportunities for collaboration than previous student groups. Students also have access to education technology, although this is an aspect that requires further expansion. All programs are up and running, and enrollment is strong.

The unique features of each program were briefly highlighted, and examples of multi-institutional collaborations were given. Partnerships with local colleges are encouraging outreach to undergraduate students, and programs have also been developed to encourage community outreach. Some education structures are focusing on translation of biomedical discoveries, and many of the CTSA institutions are attempting to integrate the learning environment among disciplines and specialties.

These programs had some challenges in common that included trying to change institutional culture, creating new medical disciplines, focusing on translation, maximizing use of education information technology, training and support for mentors, building interdisciplinary research teams, improving scholar retention, and ensuring NIH review of interdisciplinary research protocols.

The CTSA Education Steering Committee is focused on developing national curricula that will form the foundation for a new discipline (i.e., clinical and translational science) and define the standards and competencies required for particular degrees and particular groups of learners. This will lead to the creation of Web-based modules for core education that will further ensure consistency among institutions. Together with NIH, the committee is holding a workshop in January 2008 to discuss Core Competencies in Clinical and Translational Research. In addition, the committee will work toward the creation of a Mentor Development Program as well as discussing mechanisms to ensure scholar retention.

An annual national meeting in collaboration with the Association for Clinical Research Training (ACRT) is being planned. Themes of the CTSA-KL2 portion of the meeting will be the creation of a national curriculum as well as scholar retention. This is a serious issue, because current scholars in these programs need to be able to envision their future in this changing environment. The ACRT focus will be on achieving successful interdisciplinary collaboration.

Dr. Gabriel listed the accomplishments of the CTSA Education Steering Committee:

- The first 12 CTSA education programs have been launched.
- A range of competency-based, multidisciplinary, translational education programs aimed at a wide variety of students/scholars representing many disciplines and stages of training has been implemented.
- A large, diverse *national* student body has been enrolled.
- Many multi-institutional collaborations are under way, particularly involving minority-serving institutions.
- Novel use of education technology has been instituted.

She stressed that the CTSA Education Program was critical to achieving the goals of improving the nation's health, coping with economic realities, and remaining globally competitive. She noted that training the next generation of investigators to excel in the changing world of research is imperative and must be sustained in order to ensure the success of the CTSA initiative.

XI. **Challenges in Pediatrics Research: Dr. Jennifer M. Puck, Chair of the CTSA Pediatrics Committee, University of California, San Francisco**

Dr. Puck addressed the Council via an audio recording. She summarized the unique aspects of pediatric research, which include the vast changes from infancy through the teen years; rare disorders that manifest during childhood; lags in drug development and approval; the logistics of dealing with children and families; and lack of normative data. Because some pediatric conditions are rare, no single institution can accrue enough participants for a sufficiently powered study, so collaboration is essential for progress.

A specific research issue that has received more interest recently is the challenge of navigating institutional review boards (IRBs) for pediatric protocols. Dr. Puck encouraged viewing the CTSA program as an opportunity to form consortia for common research agendas, encourage collaboration, assist the development and sharing of normal control data, and establish sample biobanks. She also sees the CTSAs as a way to extend existing pediatric research networks and establish new ones across CTSA sites.

The Pediatric Oversight Committee holds quarterly working group meetings to discuss specific agenda items, including topics such as regulations on research with infants and children, ways to foster pediatric research careers, and academic rewards for team pediatric research. The first working group meeting, via a nationwide Web conference and scheduled for the same time as the Council meeting, is titled "Challenges in the Review of Pediatric Research for Institutional Review Boards." Its focus includes regulatory, ethical, and content issues of pediatric protocols. Attendees include pediatric researchers, IRB members, and regulatory officials. The format will include case discussions to identify critical issues and to build trust among IRBs.

XII. **Report on Planned Conference from Clinical and Translational Science Awards Program Pediatrics Oversight Committee: Dr. Steven I. Hirschfeld, Associate Director for Clinical Research, National Institute of Child Health & Human Development (NICHD), Bethesda, MD.**

Dr. Hirschfeld elaborated on the discussion of the meeting cited above, "Challenges in the Review of Pediatric Research for Institutional Review Boards," introduced by Dr. Puck. The meeting is being held as a hybrid live and Web-based conference—with registrants across nine time zones—that focuses on panel discussions through a structured presentation with expert panels. Actual cases submitted by CTSA institutions were modified and de-identified for this exercise. The moderators for the conference are Dr. Puck and Dr. Alexander Kon from the University of California, Davis.

The goals of the meeting are to highlight some of the challenges in assessing pediatric research proposals, build a culture of harmonization and trust among institutions involved in pediatric research, and demonstrate the feasibility of multi-institutional teams to communicate and collaborate in reaching common

objectives. CTSA pediatric researchers believe that improved collaboration among IRBs will improve pediatric research and that IRBs should be encouraged to enhance their expertise and use appropriate processes for assessing pediatric clinical research projects. The expert panels include individuals from several NIH ICs and ethics and research experts from universities across the country with specific support from the National Institute of Child Health and Human Development and NCRR. Representatives of the Food and Drug Administration and the Office for Human Research Protections will be present to answer any questions.

The meeting will be available through CTSAweb.org. The intent is to produce one or more publications, depending on the themes that emerge from the meeting. Dr. Hirschfeld concluded that this workshop format can serve as a model for inter-institutional and public discussion of issues related to clinical research.

XIII. Synchrotron Resources for Biomedical Research: Dr. Amy Swain, Health Scientist Administrator, Division of Biomedical Technology, NCRR, Bethesda, MD.

Dr. Swain introduced the topic of synchrotrons and synchrotron radiation. Synchrotron X-rays are generated from a small and focused electron beam circulating in a large storage ring, approximately 1 km in circumference. These X-rays are captured in beamlines that house the appropriate optics to direct and focus the beam for experiments. Synchrotron X-rays form a powerful and widely used method for solving molecular structures, because they are many times brighter than laboratory source X-rays and offer the added advantage of wavelength tenability. Advances in synchrotron technology include the development of fast, sensitive detectors, automation (which dramatically increases throughput), the ability to perform time-resolved studies and remote data collection, continual software development, advances in X-ray optics, and improved biosafety containment facilities. The demand for synchrotron applications, such as crystallography, spectroscopy, and solution scattering, is high, but only five major synchrotron facilities exist in the nation with several beamlines for biomedical research.

NCRR has supported synchrotron technology since 1980. The NCRR P41 BTRR program serves the unique purpose of developing new technologies and making resources available to the research community. Among the many NCRR BTRRs are seven that develop synchrotron technologies for biomedical research. They are funded by a cooperative model in which the Department of Energy (DOE) Basic Energy Sciences Division or the National Science Foundation serves as a steward that builds and operates the synchrotron at a cost of $500,000 to $1 billion for building and $20 million to $50 million annually for operation. Within this cooperative model, partner agencies such as NIH, the DOE Biological and Environmental Research Division (BER), institutional consortia, or industrial consortia, support the building and operation of beamlines and experimental

stations, at a cost of $102 million for building and $1 million annually for operation.

Although use of the facilities is divided roughly equally between the physical and the life sciences, DOE/BER and NCRR primarily support synchrotron beamlines for the life sciences. The National Institute of General Medical Sciences, the National Institute of Biomedical Imaging and Bioengineering, and the National Cancer Institute also contribute.

As is intended by the P41 BTRR program, the entire research community has access to the synchrotrons at these facilities. The service and training component of the program is especially important, as a large number of molecular and cellular biologists interested in using synchrotrons do not have the relevant training. In 2006, the synchrotron BTRR supported 2,118 investigators working on 695 individual projects and produced 536 publications.

XIV. Synchrotron Radiation: An Essential Tool for Biomedical Science: Dr. Janet L. Smith, Professor, University of Michigan, Ann Arbor; and Director, GM/CA Collaborative Access Team, Advanced Photon Source, Argonne National Laboratory, Argonne, IL

Dr. Smith pointed out that the field of structural biology, which has grown dramatically over the last decade, remains a largely experimental science. Unlike DNA, the folding of proteins is not readily determined by their sequence, so the structure cannot be predicted unless it is highly homologous to a protein whose structure is previously known. The theory relating a crystal's diffraction pattern to the final determined structure makes virtually no assumptions and is one of the most definitive experiments in molecular biology.

Although there are many biological applications for synchrotron technology, the predominant one is crystallography. Beamlines can be used to examine an organized lattice of proteins in the form of crystals, which exhibit specific and unique diffraction patterns. These patterns can be used to build an electron density map and, finally, an atomic model or structure. Solving the structures of key molecules has led to many advances in certain fields of science; for example, the structure of immunoglobulin G has revolutionized immunology. Synchrotron radiation is used to determine the vast majority of protein crystal structures published today.

Dr. Smith explained the differences between different X-ray sources. The X-ray beam from an undulator synchrotron source is the most intense and nearly parallel, and it can be used on extremely small crystals (5–100 µm). Larger crystals are needed for a synchrotron bending-magnet source (50–200 µm) and a rotating-anode laboratory source (200–500 µm). A new advance in synchrotron technology involves micro-beams for use with micro-crystals, which allow researchers to analyze portions of suboptimal crystals to determine protein

structure. This micro-focus can also reduce background noise and allows analysis of crystals not possible 5 years ago.

The application of synchrotron radiation to structural biology is a critical technology for biomedical research. Discovery of the potential drug targets, the key molecules and mechanisms underlying disease, occur in academia, and solution of the three-dimensional structures of these molecules often is done at beamlines supported by NCRR. These structures can be used by company and academic laboratories to analyze how drugs bind to proteins and to refine and accelerate drug development. Dr. Smith cited interactions between Lipitor and human HMG-CoA reductase and between nevirapine bound to an escape mutant of HIV reverse transcriptase as examples.

Historically, structural biology has been used to understand the molecular basis of genetic diseases, such as sickle cell anemia. Structural biology now is employed early in the search for a molecular explanation for these diseases. Dr. Smith discussed Charcot-Marie-Tooth disorder (CMT) as an example. CMT is a peripheral nervous system disease that manifests in childhood or adolescence, initially as problems in gait and then in loss of gross motor function. A protein studied in mice and yeast, FIG4, showed no homology to any other characterized protein, but a group of investigators at the University of Michigan noted that mice lacking FIG4 display a phenotype similar to human CMT. Working with scientist clinicians at Baylor College of Medicine, who had biological specimens from human patients with CMT, these investigators identified a similar protein in humans with an amino acid variation found in CMT patients but not in healthy controls. Determination of the function of this section of the protein, as well as determination of the structural differences between the normal and CMT variants, will yield important information about the CMT disease process and could ultimately lead to therapeutic options.

XV. Project Sugar: Genetic and Metabolic Basis of Diabetes and Obesity in Gullah-Speaking African Americans: Dr. W. Timothy Garvey, Professor and Chair, Department of Nutrition Sciences, University of Alabama at Birmingham

Dr. Garvey reviewed the causes of hyperglycemia in type 2 diabetes. Variations in insulin sensitivity in type 2 diabetes shift the curve so that approximately 40 percent of individuals diagnosed with diabetes overlap with healthy individuals. Thus, there appears to be a metabolic syndrome that causes insulin sensitivity in certain individuals.

Secretions from adipose cells affect metabolism, and specific factors, such as free fatty acids, leptin, adiponectin, and restin, are associated with biological mechanisms, such as insulin resistance and adipocyte size, that contribute to type 2 diabetes. These factors and the metabolic syndrome appear to provide a common soil for the development of athlerosclerosis and type 2 diabetes.

From 1980 through 2004, the prevalence of diagnosed type 2 diabetes in several ethnic groups in African Americans and Hispanics is almost twice as high as that for Whites. Yet the prevalence of the metabolic syndrome is not increased in African Americans, compared with Whites. Thus, there is a potential disconnect in the underlying processes of diabetes and in the way diabetes is approached for these minority populations. Dr. Garvey and colleagues proposed that there are racial differences in the pathophysiology of the metabolic syndrome and that the increased risk for diabetes in African Americans has a genetic basis. They designed the Project Sugar study to test this hypothesis, focusing on Gullah-speaking African Americans from the Sea Islands off the coast of South Carolina and Georgia. An important component of the study is that it involved an equal focus on community engagement.

This is an ideal group to study because of the minimal genetic admixture; their geographical isolation and strong cultural identity; the presence of large, stable multi-generational families; the high prevalence of and relative risk for type 2 diabetes, obesity, hypertension, lupus, and prostate cancer; and their uniform diet and lifestyle, which maximize expression of disease in patients with susceptibility genes.

Dr. Garvey and colleagues found that the five factors used to designate metabolic syndrome were all significant predictors of diabetes in Whites, only one, waist size, was significant in Gullah-speaking African Americans. High cholesterol levels did not correlate with type 2 diabetes and obesity in this population. Thus, Dr. Garvey and colleagues proposed that the more genetic admixture in the African American population, the more they genetically resemble Whites in their response to the metabolic syndrome and obesity. They also suggested that the Adult Treatment Panel III criteria used to diagnose metabolic syndrome are insufficient for the Gullah-speaking African American population.

These results led the scientists to ask whether genes unique to African ancestry affect cardio-metabolic risk. One candidate gene is, uncoupling protein 3 (UCP3), a mitochondrial protein that has known polymorphisms and mutations in African Americans. Dr. Garvey and colleagues performed association studies for one polymorphism that yields a splice variant that contributes to an increase in the storage of lipids and an expenditure of the energy garnered from carbohydrates. Individuals carrying this polymorphism are twice as likely to be obese. Dr. Garvey and his group also performed a whole-genome scan of single nucleotide polymorphisms (SNPs), selected for ethnicity, to identify genes associated with type 2 diabetes and obesity. They used 1,000 DNA samples from 426 families and identified some modest to moderate linkages, including regions of chromosomes 3, 7, and 14. Because type 2 diabetes is a complex disease, Dr. Garvey and colleagues also attempted to determine linkages between combinations of genetic regions and environmental factors involved in susceptibility. They found strong correlations for a combination of regions on chromosomes 8 and 9, and 15 and 17; the latter was statistically significant on the order of what is seen in families

with monogenic Mendelian diseases. More fine-tuned mapping of these regions, as well as genome-wide association scans with a high-density SNP map covering the entire genome, are planned.

XVI. NCRR Workshop: Improving Genetic Resources for The Rhesus Macaque: Dr. John (Jack) D. Harding, Health Scientist Administrator, Division of Comparative Medicine, NCRR, Bethesda, MD

Dr. Harding reported on the May 2007 workshop, "Improving Genetic Resources for the Rhesus Macaque," which followed up a recommendation of a 2006 NCRR workshop focused on an enhanced map that includes new knowledge of the rhesus macaque sequence, population structures, and polymorphisms. A high-resolution genome sequence for the rhesus macaque was published in April 2007. The purpose of the 2007 workshop was to define the next generation of physical and genetic maps for the rhesus macaque, with an emphasis on a SNP map to increase the utility of the rhesus monkey as an animal model of human disease and physiology.

Workshop session topics included an overview of the use of the rhesus macaque in biomedicine; the rhesus genome sequence; the current status of SNP discovery and analysis of population structure; lessons learned from other projects, particularly human research; assay platforms for high-throughput genotyping and advanced sequencing; and databases and outreach.

Workshop participants concluded that large-scale whole-genome studies are not feasible with rhesus macaques, because there are not enough available subjects for a particular condition. Participants therefore suggested a focus on more targeted studies, where factors such as the ability to control the environment and the use of large pedigrees can potentially increase statistical power, making it possible to perform meaningful analysis using relatively small cohorts of animals.

Dr. Harding summarized the workshop recommendations:

- Map at least several hundred thousand random SNPs to better understand polymorphism and population structure.
- Expand studies mapping SNPs associated with specific genes.
- Perform high-resolution sequencing and SNP discovery on complex loci, such as the major histocompatibility complex (MHC).
- Examine copy number differences.
- Design experiments to better understand the effects of various factors on statistical power and sample size.
- Once sufficient information is available, design high-throughput platforms (e.g., chips) and genotype a representative sample of animals in the National Primate Research Centers and from other sources.
- In parallel, phenotype animals using standard criteria.

XVII. Interdisciplinary Research Consortia: Dr. Gregory K. Farber, Health Scientist Administrator, Division of Biomedical Technology, NCRR, Bethesda, MD

Dr. Farber provided a brief history of the Interdisciplinary Research Consortia, which allows collaboration among NIH Institutes and Centers (ICs) to be tracked easily, using a set of linked mechanisms such as the UL1, RL1, and PL1. A September 2003 Request for Applications (RFA-RM-04-004) resulted in 21 awards for 3-year Exploratory Centers in Interdisciplinary Research (FY04–FY06), with a project end date of July 2007. A January 2006 Program Announcement (Pre-application for Interdisciplinary Research Consortium—PAR-06-122) used the X02 pre-application mechanism, for the first time, to select groups that would be invited to submit full consortium applications. Although open to all, 17 groups selected under PAR-06-122 submitted full Interdisciplinary Research Consortium applications in response to RFA-RM-06-008.

More than 80 awards have been made to 32 institutions, at a cost of approximately $42.5 million in total costs per year. Sixteen ICs are participating in the management of these grants. Dr. Farber listed the nine consortia currently funded by U54 applications, which include consortia led by the University of California, Los Angeles; Buck Institute; University of California, Davis; University of Texas Southwestern Medical School; Brigham and Women's Hospital; University of Washington; the Broad Institute of MIT and Harvard; Yale University; and Northwestern University. He noted that the number of awards has changed notably, and that it was clear that NCRR resources played a key role.

CLOSED SESSION

This portion of the Council meeting was closed to the public in accordance with the determination that it was concerned with matters exempt from mandatory disclosure under Sections 552b(c)(4) and 552b(c)(6), Title 5, U.S. Code and Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2).

Council members discussed procedures and policies regarding voting and confidentiality of application materials, Committee discussions, and recommendations. Members absented themselves from the meeting during discussion of and voting on applications from their own institutions or other applications in which there was a potential conflict of interest, real or apparent.

XVIII. Application Review

The Council reviewed 369 applications (with total direct costs of $456,713,543). The Council concurred with the review of all applications.

ADJOURNMENT

The Council adjourned at 3:00 p.m. on September 11, 2007.

CERTIFICATION

We hereby certify that, to the best of our knowledge, the foregoing minutes and supplements are accurate and complete.

Barbara Alving — 10/23/07

Dr. Barbara M. Alving
Chair, National Advisory Research Resources Council
and
Director, National Center for Research Resources, NIH

Date

Louise Ramm — 10/22/07

Dr. Louise E. Ramm
Executive Secretary, National Advisory Research Resources Council
and
Deputy Director, National Center for Research Resources, NIH

Date

These minutes will be formally considered by the Council at its next meeting; corrections or notations will be incorporated into the minutes of that meeting.

Attachment:
Council Roster

NOTE: Open Session materials are available from the Executive Secretary or the Committee Management Office, NCRR.