www.ncrr.nih.gov

NATIONAL INSTITUTES OF HEALTH • NATIONAL CENTER FOR RESEARCH RESOURCES

NCRR Reporter

Spring 2007

Critical Resources for Your Research

U.S. Department of Health and Human Services

Critical Connections Enhance Research Capacity

FROM THE DIRECTOR

Connecting Investigators and Communities with Research Opportunities

I am honored to be named director of NCRR and welcome the opportunity to work with my very talented and dedicated colleagues as we capitalize on NCRR's long-standing investments in clinical and translational science.

The NCRR budget of greater than $1 billion enables investigators throughout the country to conduct research that ranges from basic and clinical projects to community outreach and education. One of the key ways in which NCRR ensures support to biomedical researchers in all geographic areas across the nation is through the Institutional Development Award (IDeA) program, which is featured in this issue of the *NCRR Reporter.*

This program was developed to provide support for training and research in states that have historically received a relatively low amount of NIH funding due to the challenges of serving rural or dispersed populations. By funding faculty development and enhanced infrastructure, the IDeA program fosters health-related research and improves the competitiveness of investigators at research institutions in 23 states, ranging from Alaska to Vermont and North Dakota to Mississippi, as well as Puerto Rico. As you'll read in the article that follows, the program provides research opportunities, science education, and economic development and extends high-speed connectivity to IDeA grantee institutions to facilitate research collaborations.

It is this kind of support and outreach that is integral to our efforts as we transform clinical and translational research across the complete spectrum of NCRR programs. Central to this effort, I look forward to the ongoing development of the Clinical and Translational Science Award (CTSA) program—a national consortium of academic health centers that will transform the conduct of clinical and translational research. Through the CTSA consortium, the IDeA program, and many other collaborations and networks, NCRR will continue to integrate its programs, bring together innovative research teams, and leverage the power of shared resources—multiplying the opportunities to improve human health.

Barbara Alving, M.D.

Barbara Alving, M.D.
Director, NCRR

(Information about Barbara Alving's appointment as NCRR Director can be found in the "News from NCRR" section on page 13.)

INSIDE

SPRING 2007, VOL XXXI, NO. 2

CRITICAL RESOURCES

SCIENCE ADVANCES

NCRR Reporter

This quarterly publication of the National Center for Research Resources fosters communication, collaboration, and resource sharing in areas of current interest to scientists and the public.

Editor
Joyce McDonald, NCRR

Managing Editor
Laura Bonetta,
Palladian Partners, Inc.

Publication Design
Palladian Partners, Inc.

Please send comments and ideas about future articles to:

Office of Science Policy and Public Liaison, NCRR/NIH
One Democracy Plaza
6701 Democracy Blvd., 9th floor
Bethesda, MD 20892-4874
Telephone: (301) 435-0888
Fax: (301) 480-3558
E-mail: info@ncrr.nih.gov
Web site: www.ncrr.nih.gov

On the Cover: Pancho Monroy and Francesca Pine, students at Little Big Horn College in Montana, collect water samples from the river that flows through the Crow Indian Reservation. Testing for contaminants in the water is one of many projects supported under NCRR's Institutional Development Award (IDeA) program, which is designed to expand research opportunities to rural and other underserved populations.

Above: Francesca Pine examines the water testing instrument.

PHOTOS BY LYNN DONALDSON

NIH Clinical Center Collaborates with CTSAs

The NIH Clinical Center (CC), NIH's clinical research hospital in Bethesda, Maryland, offers unparalleled opportunities for collaborations through the Clinical and Translational Science Award (CTSA) program. About 1,500 clinical studies are currently being conducted at the CC, the world's largest clinical research complex.

"Collaboration is the foundation for the bench-to-bedside clinical research conducted here, and the CTSA program provides new possibilities for partnerships that will ultimately improve health and health care," said Dr. John I. Gallin, CC director. "Our goal is to share expertise, provide models for effective programs, and improve access to specialized resources." One such example is a collaboration between the CC and the CTSA at Rockefeller University to survey research subjects about their perceptions of the clinical trial experience. The effort is currently being expanded to include all interested CTSAs.

Re-engineering the clinical research enterprise is a key objective of the NIH Roadmap for Medical Research. Several recommendations in the 2004 NIH Director's Blue Ribbon Panel focused on the CC's role in providing education in the discipline and in fostering partnerships in the extramural community. In response, the CC has developed or expanded a range of programs to support and nurture clinical research.

CLINICAL RESEARCH TRAINING

"Investigators need a firm grounding in the increasingly complex conduct of clinical research, and the CC developed formal coursework because the training was not widely available," said Dr. Gallin. Course topics include clinical research practice, ethics, and pharmacology. Many students take the courses from remote sites via teleconference or using lectures on DVD. Information is available online at http://clinicalcenter.nih.gov/researchers/training.shtml.

COLLABORATIVE RESEARCH

To encourage collaborations among basic scientists and clinical investigators, the CC created the Bench-to-Bedside Awards to speed translation of promising laboratory discoveries into new medical treatments. Recently, this program was opened to teams including extramural partners. This pilot was such a success that a formal evaluation is under way to determine opportunities for expansion. For more information, visit http://clinicalcenter.nih.gov/ccc/btb/awards.shtml.

INFORMATICS

The CC's Clinical Research Information System (CRIS) facilitates clinical care while supporting the collection of clinical and research data. The system's next phase is a data mart, which will pool data, text, and images from CRIS and make them available to intramural researchers. Future plans include a repository to enable data sharing with extramural researchers.

ProtoType is a Web-based clinical protocol writing tool—available to the extramural community—that provides investigators with a standard protocol structure, online help, and templates of suggested language. Investigators use it to put ideas for new protocols into the proper format to satisfy regulations and facilitate review.

■ John I. Gallin, director of the NIH Clinical Center, talks with one of his patients, Amanda Young of Georgia.

SPECIALIZED RESOURCES

Innovative product development services in both pharmacy and cell processing support the NIH clinical research mission while meeting the rigorous requirements of drug, biologic, and tissue manufacturing regulations. The CC programs serve as a model for extramural researchers. Resources also include investigation-focused surgery, imaging capability, and specialized patient-care components.

All CC patients participate in a clinical research protocol and half have rare diseases. These special cohorts of patients provide unique opportunities for partnerships with the extramural community, some of which have been funded by the Office of Rare Diseases (http://rarediseases.info.nih.gov/asp/resources/intr_res.asp). A list of current CC studies at http://clinicalstudies.info.nih.gov is another information source for extramural investigators.

For more information, contact Dr. Gallin at cc-director@cc.nih.gov. ■

PHOTO BY JOHN CRAWFORD

Critical Connections

Collaborations among disparate research institutions enhance biomedical research and the nation's health. **BY LAURA BONETTA**

Little Big Horn College is a two-year community college settled on two acres in a wooded river valley at the heart of the Crow Indian Reservation in south central Montana—a vast, mountainous state with the third-lowest population density in the country. Despite the college's isolated setting, scientists at Montana State University in Bozeman, 200 miles away, are mentoring some of its students on a research project to identify contaminants in the water of the Little Big Horn River that flows through the reservation.

This research effort, one of many across the country, is funded by NCRR's Institutional Development Award (IDeA) program, which aims to increase the research capability of states with historically low success rates of obtaining NIH grants. "We knew that by just supporting peer-reviewed grants to research institutions we would not be effective," says Fred Taylor, NCRR's IDeA program director. "To effect change in a state and make it more competitive on a national level, we needed to reach out to undergraduate universities and other educational institutions and get the community involved."

Through the IDeA program, NCRR supports institutions and communities in 23 states and Puerto Rico with grants that fund multiple areas of biomedical research and reach out to unique populations. Regardless of its actual area of biomedical inquiry, each grant fulfills five main goals to: build and strengthen the research capabilities at participating institutions by hiring staff and purchasing research equipment; support faculty, postdoctoral fellows, and graduate students; provide research opportunities for undergraduate students; develop outreach activities; and enhance the science and technology knowledge of the state's workforce.

ENGAGING TRIBAL COLLEGES

Little Big Horn College is one of seven tribal colleges in Montana brought together under the IDeA program to collaborate on biomedical research projects with undergraduate and research universities across the state. In the southern portion of the state, along with Little Big Horn College, is Chief Dull Knife College, serving the Cheyenne Tribe. On the northern side are Blackfeet Community College (Blackfeet Tribe), Fort Belknap College

■ Biology teacher Mari Eggers (third from left) supervises students at Little Big Horn College performing research on water quality, one of the IDeA research projects bringing tribal colleges together with Montana universities. Shown in the photo from left to right are Pancho Monroy, Leslie Plain Feather, Mari Eggers, Francesca Pine, Brandon Good Luck, and Candy Felicia.

(Gros Ventre and Assiniboine Tribes), Fort Peck Community College (Assiniboine and Sioux Tribes), Salish Kootenai College (Confederated Salish and Kootenai Tribes), and Stone Child College (Chippewa Cree Tribe). The colleges are each hundreds of miles away from Montana State University and the University of Montana in Missoula, the state's two major research universities.

Because of Montana's large size, few opportunities existed for the faculty and students from different educational institutions to come together. Much of the credit for obtaining participation from tribal colleges goes to Sara Young, outreach coordinator for the Montana program and a member of the Crow Tribe. "It is really important to have someone who has credibility with the tribal colleges," says Young, who had worked on Indian reservations for more than 30 years before joining Montana State University. Young understands the challenges facing Native American students who wish to pursue research careers. All but one of the seven Montana tribal institutions are two-year colleges, which means that to obtain a bachelor's degree, students must leave the reservation. "Most students who live on reservations have very strong family ties," says Young. "It is challenging for a student to move away and not be able to maintain these ties on a daily basis."

Native American students attending a university in Montana often have to deal with feelings of isolation and, in some cases, misunderstanding from a predominantly white faculty and student body. "It is hard to be the only person of color in a class of 200 students," says Young. But there are signs that the research environment, at least at Montana State University, is becoming more welcoming to tribal students. During the summer of 2006, four Native American students conducted research on the Montana State University campus, and all of them are now pursuing bachelor's degrees in health-related fields.

The IDeA program is also helping to establish research projects within the tribal colleges, in subject areas uniquely relevant to the local communities. For the past several years, students at Little Big Horn College have been collecting river water and monitoring its quality. At the same time, researchers at Montana State University have been analyzing the water and fish tissue samples to identify environmental contaminants, such as mercury, pesticides, and pathogens. Students from the tribal college often visit Montana State University to learn these more

PHOTO BY LYNN DONALDSON

sophisticated laboratory techniques and to carry out the analyses themselves.

"They were really interested in having students involved in basic water quality assessment," says Montana State University professor and microbiology department head Timothy Ford, who directs the NCRR-funded program and serves as the primary mentor for the Little Big Horn College project. "That comes from a strong perception on Crow and other reservations that the water is contaminated and a source of disease." The perception is based, in part, on Montana's history of mineral and energy exploration and indiscriminate use of pesticides and other chemicals in agriculture, coupled with anecdotal reports of cancer clusters, stomach problems, and other ailments among those living on reservations.

To help prioritize these concerns in relation to contamination, an environmental health steering committee was formed on the Crow Indian Reservation made up of community members, utility managers, and tribal health representatives. "What we have done with Crow, we will begin to expand to other reservations," says Ford. Already IDeA funding has been used to hire new faculty and to provide mini-grants to six tribal colleges in the state. The increase in faculty means that science instructors have some time to devote to research projects and to pursue further research training.

Other projects supported by the IDeA program in Montana include studies of microbes involved in human disease, such as *Candida albicans* and hantavirus, and those that threaten Montana's abundant livestock and wildlife, such as the chronic wasting disease agent. For each project, the primary investigator is at one of four baccalaureate schools, and the primary mentor, an NIH-funded scientist, is at Montana State University or the University of Montana. One of the biggest payoffs so far, according to Ford, has been a "change in culture" at both the tribal colleges and the undergraduate institutions. "We talk to the deans and presidents, and they are ecstatic about the way undergraduates are exposed to research," he says.

CONNECTING UNIVERSITIES TO RURAL CLINICS

On the other side of the country, the IDeA program in West Virginia is also enabling critical connections among different institutions and facilities and between mentors and students. Along narrow roads, nestled among the tall peaks of the Appalachian Mountains, the Tug River Health Association has, for many years, been providing health care to residents of the coalfields of southern West Virginia. The small rural clinic, a three-hour drive south of the state's capital, is also participating in a major research effort to identify the genetic underpinnings of heart disease.

The NCRR-funded Appalachian Cardiovascular Research Network project "is a unique research collaboration that includes major research universities, undergraduate institutions, major hospitals, and rural clinics," says Gary Rankin, the grant's principal investigator at Marshall University, located in Huntington. "And it involves all kinds of individuals, from students to molecular biologists to clinicians." It focuses on heart disease, a health problem that is highly relevant to West Virginians. According to statistics released by the U.S. Centers for Disease Control and Prevention in February 2007, the West Virginia population has a high prevalence of obesity, diabetes, and smoking-related illnesses. In fact, the state has the highest proportion of people with heart disease in the nation.

Although heart disease is caused by a mix of genetic and environmental factors, knowing which genes make it more likely for a person to develop the condition could help identify at-risk individuals. "We want to understand a person's susceptibility to disease long before it develops," says Donald Primerano, a professor at Marshall University and the program's director. "These individuals could be advised, for example, on what diet could be beneficial to them."

Those who are eligible to participate in the study have abnormal levels of fats, or lipids, in their blood. "To find out if they want to participate, we either call them or ask them during a regular visit to their physician," says Primerano. Patients are recruited at three major centers (Marshall University, West Virginia University, and Charleston Area Medical Center), as well as from three small rural clinics spread out across the state, extending the program's reach.

The research effort has already had some success in identifying genes involved in obesity-associated cardiovascular disease. For that study, researchers analyzed the sequence of DNA nucleotides within several genes already known to predispose people to heart disease and compared the sequences in overweight and obese individuals to those in normal-weight individuals. They found three genes that differ between the two groups and thus may play a role in obesity-associated cardiovascular disease. An abstract describing the work was presented at the annual meeting of the American Society for Human Genetics held last October in New Orleans (www.ashg.org/cgi-bin/ashg06s/ashg06).

Two more ambitious projects are now under way. Researchers are trying to identify variations in genes involved in two common conditions leading to heart disease that seem to run in families: familial combined hyperlipidemia and familial

> Students are keen to work on the project because, for the first time, they are seeing the importance of their research to the health of their community.

hypertriglyceridemia. This time, the scientists are scanning the entire human genome to identify telltale variations between genes, rather than focusing on a set of known candidate genes.

The two projects take full advantage of the resources at the collaborating institutions. Blood samples collected at the clinics are sent to Marshall University, where DNA is isolated from them. The DNA is then sent to Fairmont State University or West Liberty State University—two undergraduate institutions—to determine the nucleotide sequences of specific genes in each DNA sample. The sequence data are then analyzed at Marshall and West Virginia universities using bioinformatics tools to find significant associations between specific sequences and symptoms of heart disease. "The network helps with patient recruitment, but it also helps us bring together people with different expertise, which you need for these types of studies," Primerano says.

■ Biology professor Mark Flood is heading a project to identify variations in genes involved in heart disease. He is shown in his lab at Fairmont State University in West Virginia with Sarah Dodson, assistant professor of biology (standing), and students (left to right) Contessa Hill and Bonnie Freeman.

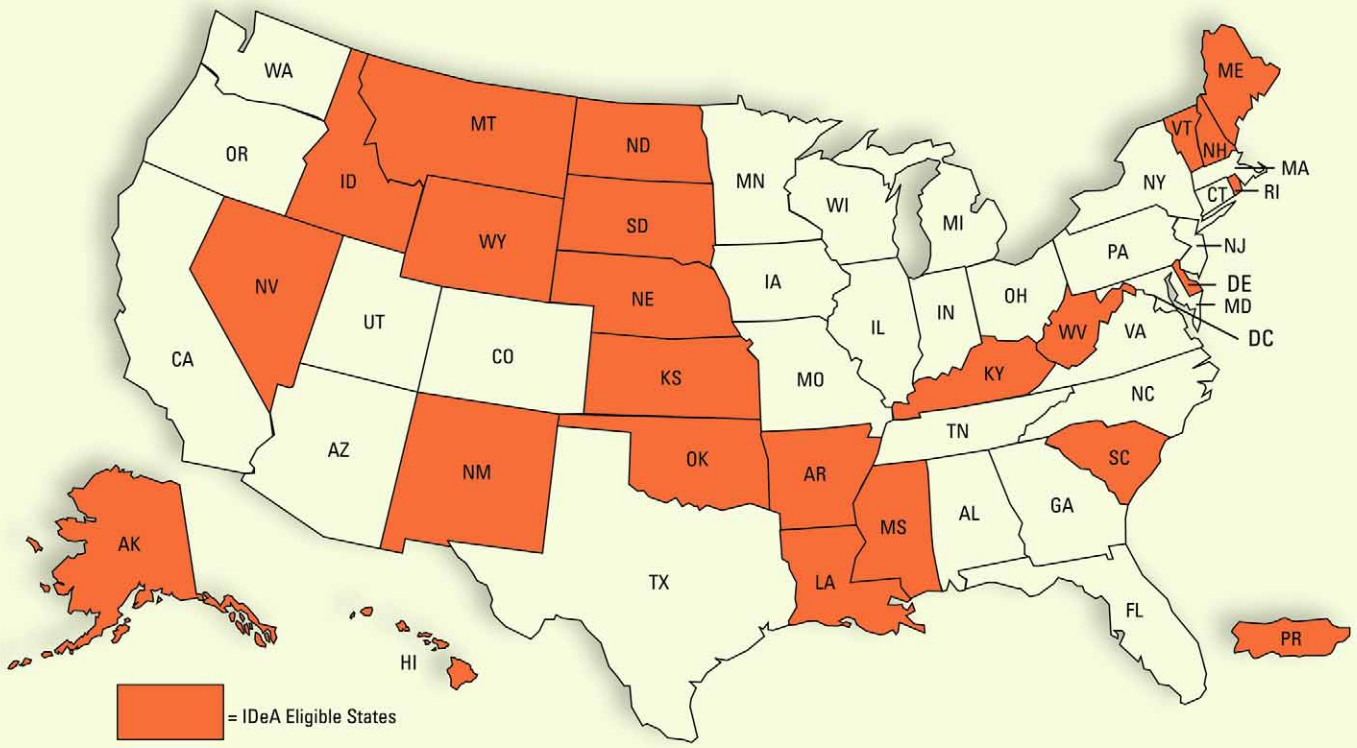
PHOTO COURTESY OF FAIRMONT STATE UNIVERSITY

Mark Flood, an investigator and professor at Fairmont State University, a three-hour drive from Marshall University, directs the familial combined hyperlipidemia study. "We would not have access to patient populations if we did not have these collaborations with Marshall and West Virginia University," says Flood. "My campus has 7,500 undergraduate students; we don't have a medical school or any chance to obtain funding for this kind of research unless we collaborate with investigators from larger institutions."

One thing that makes the Appalachian population particularly well suited for these studies is that, in addition to the high prevalence of heart disease, individuals tend to live close to other family members. As a result, it is relatively easy for researchers to obtain DNA samples from several related individuals within a family, something that greatly aids genetic analysis. "We recently recruited a 22-member family at West Virginia University," says Primerano. So far, the familial combined hyperlipidemia project has recruited about 50 participants, out of a possible 200 that will be needed to complete the study.

IDeA funding was used to buy specialized equipment at Fairmont—a pyrosequencer and several polymerase chain reaction (PCR) machines—and to hire another faculty member, relieving some of Flood's teaching duties and freeing up more time for research. Students are also reaping the benefits. Since the start of the program, Flood has had 10 undergraduate students working in his lab, learning to do PCR and DNA sequencing. "We are seeing some successes with them getting into medical and graduate school or obtaining jobs in the biotech industry," says Flood, adding that students are keen to work on the project because, for the first time, they are seeing the importance of their research to the health of their community.

Another outcome of the IDeA funding is that there is now an office of grants management at Fairmont. "We are seeing many more regional and national grants being submitted by our faculty, and our president has set aside money specifically to support undergraduate research," says Flood.



NCRR's Institutional Development Award (IDeA) program provides research opportunities, science education, and economic development and extends high-speed connectivity to grantee institutions to facilitate research collaborations. Twenty-three states and Puerto Rico participate in the program.

LINKING RESEARCHERS THROUGH "VIRTUAL" NETWORKS

Many IDeA states face the challenge of rural or isolated locations. To overcome the distance between institutions and enhance the research capacity in the state, Louisiana State University (LSU) in Baton Rouge constructed a network to encourage partnerships. The network uses cutting-edge technology, called Access Grid, so that research groups at different sites can interact over high-speed Internet connections. For example, using audio and video conferencing, people can meet "virtually" for lab meetings, classes, and mentoring. The effort is led by Harold Silverman, a professor at LSU in Baton Rouge, and his team of faculty and staff. "One reason for having the Access Grid is that we have programs running at bigger institutions that we thought some of the smaller institutions could take advantage of," says Silverman. "We also wanted to be able to move large packets of real-time data between researchers and to facilitate collaborations."

The project had an interesting start. The State of Louisiana had set aside some money from the 1997 tobacco settlement to create health centers of excellence. The LSU main campus in Baton Rouge and the LSU Eye Center decided to spend the money to build an Access Grid network. "The process was working nicely," recalls Silverman. "So, when we saw the initial NCRR call for creating networks, we thought it would be a good chance to bring the primarily undergraduate institutions onto the grid."

Access Grid, funded by the IDeA program, enables research groups at different sites in Louisiana to interact over high-speed Internet connections. The network has been particularly helpful to researchers who were displaced because of Hurricane Katrina.

PHOTO COURTESY OF LOUISIANA STATE UNIVERSITY

When Silverman and his colleagues began building the physical infrastructure for the Access Grid, most campuses had little or no equipment in place to support the effort. Today the Access Grid links four large research centers—two medical schools in New Orleans, including Tulane University; one in Shreveport; and the LSU main campus—and four primarily undergraduate institutions—Southern University, a historically black university in Baton Rouge; the University of Louisiana in Monroe; Louisiana Tech University in Ruston; and Louisiana State University in Shreveport.

In 2006, the governor of Louisiana pledged more than $40 million over 10 years to support the Louisiana Optical Network Initiative (LONI), a high-capacity network connecting mainframe computers at Louisiana's major research universities. "LONI is required for computational and informatics advances to drive research," says Silverman. "IDeA funding and collaboration were a nucleus for these advances in Louisiana."

Sumeet Dua, an assistant professor of computer science at Louisiana Tech University in Ruston, found a mentor at LSU in New Orleans, 300 miles away. Together, Dua and Hilary Thompson, associate professor in the Department of Public Health at LSU, are developing new bioinformatics tools to analyze the expression of all genes in the eye to identify patterns associated with loss of vision and other disease states. When Dua joined the program in 2002, his university did not yet have an Access Grid node. "That is something I helped establish," he says. "The Access Grid has given us unique opportunities. I can work with leading mentors around the state and beyond without leaving my institution."

Thompson and Dua were able to continue their collaboration, even when Thompson was displaced from his laboratory in New Orleans for several months as a result of Hurricane Katrina. This was possible through the Access Grid communication between Louisiana Tech and Baton Rouge, where Thompson had temporarily moved. Based on the research he has carried out so far and the equipment he has been able to purchase with IDeA funding, Dua says he is now in a position to apply for more NIH grants.

"The barriers to collaboration tended to be distance and a lack of understanding of the roles and missions of other institutions and what constraints they work under," says Silverman. Putting the network together forced university administrators and information technology specialists to visit each others' institutions and communicate, both in person and by using the virtual connection. The process has, in turn, enabled a greater understanding among institutions. "The evidence of success is when you can transfer what we have done to the political realm of the state," says Silverman. "When the governor jumps on board and says, 'I would like to continue putting money in to build the network,' the small steps we took initially among a few institutions have now multiplied."

■ Sumeet Dua, assistant professor of computer science at Louisiana Tech University, discusses data with student Pradeep Chowriappa. High-speed Internet connections funded by the IDeA program link together researchers and students at eight Louisiana research centers and undergraduate institutions.

Louisiana, Montana, and West Virginia illustrate the diversity of the IDeA programs. Each is facing unique challenges and developing different strategies to overcome them, but the grantees are making strides. "In the future, we hope to see these states participate fully in the research endeavor and successfully compete for NIH funding across the board," says NCRR's Taylor. "We would like to see pipelines established to produce homegrown researchers. Our goal is to address the health disparities of the local populations in IDeA states and, ultimately, improve the health of the nation." ■

TO LEARN MORE: For more information about the IDeA program, visit the NCRR Web site at www.ncrr.nih.gov/resinfra/ri_idap.asp.

PHOTO COURTESY OF THE COLLEGE OF ENGINEERING AND SCIENCE, LOUISIANA TECH UNIVERSITY

Cholesterol Buster

Physicians uncover a new way of reducing high cholesterol in patients resistant to standard drug treatments. **BY LIZ STILLMAN**

As is often the case with those suffering from a rare condition, patients with homozygous familial hypercholesterolemia (FH) have few treatment options available to them. A genetic condition that strikes one in a million individuals, FH causes abnormally high levels of "bad cholesterol," also known as low-density lipoprotein (LDL), in the blood of patients. The LDL deposits in the walls of arteries that feed the heart, making it harder for the blood to flow through them. As a result, FH patients frequently develop heart disease before their 25th birthdays.

Although they help millions of individuals each year, the cholesterol-lowering drugs currently on the market, such as the statins, provide relatively little relief to homozygous FH patients. "Right now the standard care for these patients, LDL apheresis, is at best an invasive, expensive, and temporary solution," says Daniel Rader, a professor of Medicine and Pharmacology at the University of Pennsylvania (Penn) and director of the NCRR-funded Clinical and Translational Research Center. Apheresis is a process of physically removing cholesterol from the blood that must be repeated every one to two weeks in a clinic or hospital.

Rader has spent his career studying factors that regulate the formation and breakdown of lipoproteins—large particles consisting of fats, such as cholesterol and triglycerides, and specialized proteins. In the early 1990s, while in the intramural research program of NIH's National Heart, Lung, and Blood Institute in Bethesda, he was part of a research team that discovered the gene responsible for another rare inherited disease called abetalipoproteinemia. This disease is associated with extremely low quantities of cholesterol and lack of LDL in the blood. The responsible gene encodes a protein, called microsomal triglyceride transfer protein (MTP), that works in the liver to "package" triglycerides and cholesterol with apolipoprotein B to produce LDL in the blood. Without MTP, LDL cannot be produced.

"The discovery of MTP as the genetic basis of abetalipoproteinemia suggested that MTP could be a novel therapeutic target for lowering LDL," Rader asserts. "My extensive experience in working with patients with homozygous FH convinced me that an MTP inhibitor could be useful in these patients." Investigators at the pharmaceutical company Bristol-Myers Squibb developed the first MTP inhibitor, and Rader collaborated with them in an early study to demonstrate its effectiveness in lowering elevated LDL levels in otherwise healthy individuals. But the company decided to stop further development of the drug because of some gastrointestinal and liver-related side effects and concern that it would not compete with statins for the treatment of high cholesterol in the general population. "I then persuaded them to essentially donate it to Penn so that we could continue working with it in our patients with homozygous FH," says Rader.

His persistence is starting to pay off. Taking advantage of the resources available at the Institute for Translational Medicine and Therapeutics (ITMAT) at Penn—one of the first recipients

This translational research shows how investigations into rare genetic diseases can lead to important advances that influence many more people.

of NCRR's Clinical and Translational Science Awards (CTSAs) launched in October 2006 and supported by additional funding from the Doris Duke Charitable Foundation—Rader carried out a protocol in which the MTP inhibitor was given to six homozygous FH patients at four increasing dosages, each for four weeks.

"The patients were eager to try anything and everything that might lower their cholesterol levels without the need of LDL apheresis," says Marina Cuchel, co-investigator of the study, who was supported through an NCRR-funded K-12 Mentored Clinical Research Scholar Award. "Used to the poor response to conventional drug treatment, they were, like us, amazed at how low their cholesterol levels dropped, especially at the highest dosage of the drug." The treatment led to a remarkable 51 percent reduction in LDL levels, 65 percent reduction in triglyceride levels, and 56 percent reduction in apolipoprotein B levels in the patients' blood. The study also demonstrated that, as investigators had suspected, the MTP inhibitor reduced the production of LDL by the liver.

This illustration shows the structure of a low-density lipoprotein (LDL) particle, a form of cholesterol-carrying lipoprotein found in the blood. Mainly composed of lipids, this complex structure includes a large protein (pink) known as apolipoprotein B, which regulates the metabolism of LDL. Also found in the outer coat are phospholipids (stalked spheres) and free cholesterol molecules (yellow). Within the core, cholesterol molecules (yellow) are attached to fatty acids forming cholesteryl esters (green). Researchers believe that high blood levels of LDL particles lead to increased risk of narrowing of the arteries (atherosclerosis), coronary heart disease, and stroke.

Thanks to the study's success, Cuchel has received funding from the U.S. Food and Drug Administration's orphan drug program to carry out a larger and longer phase III trial of the compound in patients with homozygous FH. "One of the key questions for this next trial is: What are the effects on the liver when we test this drug over long periods of time?" says Cuchel. She hopes that the results will support the approval of this MTP inhibitor as an orphan drug for patients with homozygous FH who do not respond to available cholesterol-lowering treatments. It is also possible that lower doses of the drug might be used in patients at high risk of heart disease who are unable to reach the desired LDL levels with conventional treatments. The drug is being developed with this goal in mind by Aegerion Pharmaceuticals, Inc.

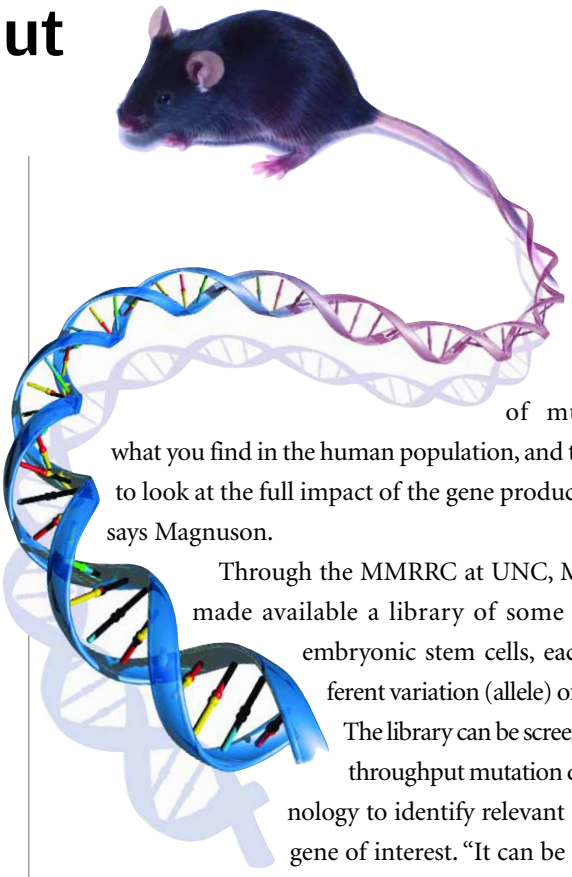
"This translational research shows how investigations into rare genetic diseases can lead to important advances that can influence many more people," says Rader, who, in addition to being ITMAT's associate director and a co-principal investigator (PI) of the Penn CTSA, was previously the PI of a K-12 Mentored Clinical Research Scholar Award from NCRR to prepare and train clinicians for careers in translational research. ■

The research described in this article was funded by NCRR, the Doris Duke Charitable Foundation, and the National Heart, Lung, and Blood Institute. For information on NCRR's Clinical and Translational Science Award program, visit www.ncrr.nih.gov/clinicaldiscipline.asp, and for information on NCRR's Mentored Clinical Research Scholar Award Program, visit www.ncrr.nih.gov/clinical/K12.asp.

ADDITIONAL READING: Cuchel, M., Bloedon, L. T., Szapary, P. O., et al., Inhibition of microsomal triglyceride transfer protein in familial hypercholesterolemia. *N Engl J Med* 356:148–156, 2007.

ILLUSTRATION BY JOHN BAVOSI / PHOTO RESEARCHERS, INC.

For Understanding Human Disease, the Mouse Is a Knockout



With the human genome fully sequenced, the next big question is "What do all those genes do?" The answers will likely be found in the mouse. "The mouse is the only mammalian species in which we have the ability to specifically delete one gene at a time from the genome, which makes it possible to discover what these genes do in normal physiological processes and in pathology," says Kent Lloyd of the University of California (UC), Davis.

That is why NIH's new Knockout Mouse Project (KOMP) is aiming to eventually disrupt, or "knock out," each of the 20,000 or so genes in the mouse genome. Within the next five years, the effort will create 8,500 to 10,000 new lines of knockout mice, tripling the number currently in existence from all sources.

Although KOMP was officially launched last fall, NCRR-supported researchers have long been laying the groundwork to achieve the project's goals. Since 1999, NCRR has funded a network of public repositories—dubbed the Mutant Mouse Regional Resource Centers (MMRRCs)—that collect, archive, and redistribute mouse strains developed over the years by individual researchers using federal funding.

In June 2006, NCRR expanded this effort by awarding $800,000 to the MMRRCs at UC Davis and the University of Missouri/Harlan in Columbia to develop more lines and to obtain from NIH-funded researchers additional lines that have been created but are not yet widely accessible. With a goal of adding 300 more lines in two years, this effort will significantly augment the public repositories, which already received a boost in October 2005, when NIH purchased 256 lines from two commercial sources.

In addition to providing researchers with mice and embryonic stem cells (from which mice can be generated), the MMRRCs have pioneered new techniques for using knockout mice to investigate normal and disease processes. For example, at the University of North Carolina (UNC) at Chapel Hill, Terry Magnuson has developed a technology to produce mutations in mouse genes that affect proteins in more subtle ways compared to knockouts, in which the protein encoded by the disrupted gene is not produced at all. "These subtle types of mutations are what you find in the human population, and they allow you to look at the full impact of the gene product on biology," says Magnuson.

Through the MMRRC at UNC, Magnuson has made available a library of some 4,000 mouse embryonic stem cells, each with a different variation (allele) of mouse genes. The library can be screened with high-throughput mutation detection technology to identify relevant alleles for any gene of interest. "It can be used to refine the predictions that are being made by proteomics researchers, who use computational methods to try to predict the effect of a given mutation on the protein's structure," Magnuson says. "We can now make the mouse and test the prediction in the actual living system."

The MMRRC at UC Davis, headed by Lloyd, will also play an integral role in the development and cataloging of the new knockout lines targeted by KOMP, as part of a collaboration that also includes the Children's Hospital Oakland Research Institute in California and the Wellcome Trust Sanger Institute in England. Together with Regeneron Pharmaceuticals in Tarrytown, N.Y., the group was awarded $47.2 million by NIH in September 2006 to create the lines. "The effort will contribute enormously, not only to basic science, but also to translational research, by helping us understand the causes so we can find new ways to prevent disease," says Lloyd. **—BRENDA PATOINE**

TO OBTAIN MATERIALS: NCRR funds Mutant Mouse Regional Resource Centers (MMRRCs) at four institutions: the University of California, Davis; the University of Missouri/Harlan; the University of North Carolina at Chapel Hill; and The Jackson Laboratory, which also serves as the Informatics, Coordination, and Service Center for the MMRRC facilities. To learn more, visit www.mmrrc.org/index.html.

Barbara Alving Named Director of NCRR

On April 2, 2007, NIH Director Elias A. Zerhouni, M.D., named Barbara Alving, M.D., as the Director of the National Center for Research Resources (NCRR). As Acting Director of NCRR, Alving oversaw the launch of the Clinical and Translational Science Awards (CTSA) program—a new national consortium of academic health centers that will transform the conduct of clinical and translational research. The goal of the consortium is to ensure that biomedical discoveries are rapidly translated into prevention strategies and clinical treatments for both rare and common diseases.

"Dr. Alving has demonstrated exceptional leadership in the recent efforts of the NIH to energize the discipline of clinical and translational research across the nation," said Zerhouni. "The CTSA program marks the first systemic change in clinical research in 50 years and is a critical component of how we will effectively re-engineer the clinical research enterprise, including training the next generation of researchers. It will be with Dr. Alving's vision, creativity, and leadership that we will be able to maximize our investment in the CTSA consortium, ensure that benefits extend to the greater research community, and that new medical advances are delivered to the people who need them."

A native of Indiana and a graduate of Purdue University, Alving earned her medical degree *cum laude* from Georgetown University School of Medicine, where she also served as an intern in internal medicine. She completed her residency training, followed by a research fellowship in hematology, at the Johns Hopkins Hospital in Baltimore. She began her research career as a Public Health Officer in the Division of Blood and Blood Products at the U.S. Food and Drug Administration (FDA) on the NIH campus. Alving then joined the Walter Reed Army Institute of Research, where she served at the rank of colonel as the Chief of the Department of Hematology and Vascular Biology. In 1997, Alving became the Chief of the Section of Hematology and Oncology at the Washington Hospital Center in Washington, D.C. In 1999, she joined the National Heart, Lung, and Blood Institute (NHLBI) as the Director of the Division of Blood Diseases and Resources. She then became the NHLBI Deputy Director and Acting Director while also serving as the Director of the Women's Health Initiative (2002–2006). In 2005, Zerhouni tapped her to be the Acting Director of NCRR.

A Professor of Medicine at the Uniformed Services University of the Health Sciences in Bethesda, Alving is also a Master in the American College of Physicians. She currently serves the NIH Director as the official NIH liaison for the Centers for Medicare and Medicaid Services and is a member of the Advisory Board for Clinical Research at the NIH Clinical Center.

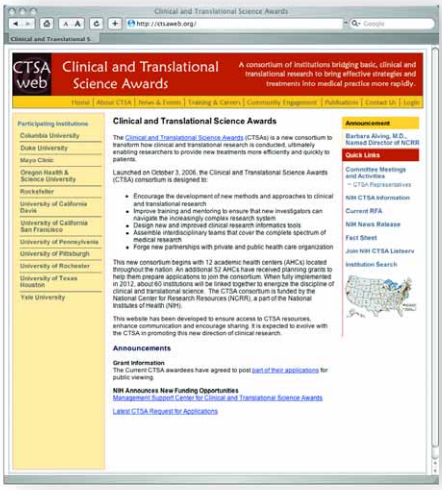
She is a recipient of the American Society of Hematology Award for outstanding service and also received a Commendable Service Award from the FDA for her work on hypotensive agents in albumin products. Her military honors include the U.S. Legion of Merit, awarded by the U.S. Army, for work that improved the care of soldiers in combat. She is a co-inventor on two patents, has edited three books, and has published more than 100 papers in the areas of thrombosis and hemostasis.

CTSA Web Site Launched

The recently unveiled Clinical and Translational Science Award (CTSA) program Web site (http://ctsaweb.org) features resources, news, and general information about the CTSA consortium. It aims to enhance communication and encourage sharing of resources provided by CTSA members.

The site includes detailed information on each CTSA, training activities sponsored by the CTSAs, publications, upcoming meetings, community engagement activities, and a fact sheet about the CTSAs. The site also links to the current CTSA Request for Applications, which was issued on March 22, 2007.

The CTSA consortium currently consists of 12 academic health centers around the nation, which are linked to energize clinical and translational science nationwide. In all, 60 institutions are expected to be part of the CTSA consortium by 2012. The CTSA initiative grew out of the NIH commitment to reengineer the clinical research enterprise, one of the key objectives of the NIH Roadmap for Medical Research.



■ **The newly launched CTSA Web site at http://ctsaweb.org.**

[CONTINUED FROM PAGE 13]

2007 Conferences Lineup

NCRR is sponsoring several conferences this year covering a broad range of topics, from the implementation of translational research in underserved communities, to the analysis of genes in the rhesus macaque, to the use of nonhuman primate models for developing AIDS treatments and embryonic stem cell lines. These conferences not only inform scientists of key developments in different areas of research, but they also serve to ensure that members of the NCRR community are aware of long-term goals and progress on different initiatives.

■ ■ ■

FOSTERING COLLABORATIVE COMMUNITY-BASED CLINICAL AND TRANSLATIONAL RESEARCH

May 15 and September 21, 2007

The May 15 workshop will identify key factors that prevent and enable effective academic-community research partnerships. Participants will develop and disseminate guidelines and best practices for conducting community-based clinical and translational research in minority and other medically underserved groups. Key areas of focus will include the development and maintenance of core research infrastructure to enable and encourage community participation, the development of research protocols that work effectively in community settings, and the establishment of community buy-in and trust to enhance recruitment and retention of research participants.

This one-day workshop will be held in the DoubleTree Hotel, Bethesda, Md., in conjunction with the 2007 National Research Conference (May 16–18) of the Agency for Healthcare Research and Quality's (AHRQ) Practice-Based Research Networks. A second regional workshop will be held in Los Angeles, Calif., on September 21. The two events are intended to develop specific recommendations to support the implementation of planned NCRR initiatives to enhance clinical and translational research in underserved communities. They will also help leverage related efforts of sister agencies, including AHRQ, the Health Resources and Services Administration, the U.S. Centers for Disease Control and Prevention, and the Indian Health Service.

Individuals interested in attending either workshop may contact Michael Sayre at sayrem@mail.nih.gov, Shelia McClure at mcclursh@mail.nih.gov, or Fred Taylor at taylorwf@mail.nih.gov.

■ ■ ■

IMPROVING GENETIC RESOURCES FOR THE RHESUS MACAQUE

May 23, 2007
Natcher Conference Center, Building 45
NIH Campus, Bethesda, Md.

This workshop will identify enhanced genetic resources for optimizing the use of the rhesus macaque as a model animal in biomedical and translational research. In particular, participants will define the resolution, approach, and resources needed to generate a single nucleotide polymorphism (SNP) map of the rhesus macaque genome.

The workshop was conceived, in part, during the 2006 NCRR-sponsored "Genetic Tools for Optimizing the Use of Rhesus Macaques for Translational Research" workshop in which participants identified the development of an SNP map for the rhesus as a major goal. Grantees funded by NCRR have so far identified SNPs that distinguish between macaques of Chinese and Indian origin. In addition, as part of the project to sequence the rhesus genome, scientists at the Human Genome Sequencing Center, Baylor College of Medicine, have identified several thousand SNPs from a subset of the rhesus genomic sequence.

Individuals interested in attending the workshop may contact Jack Harding at hardingj@mail.nih.gov.

■ ■ ■

THE 25TH ANNUAL SYMPOSIUM FOR NONHUMAN PRIMATE MODELS FOR AIDS

September 10–13, 2007
Monterey Conference Center
Monterey, Calif.

This symposium will serve as a scientific forum for disseminating and exchanging the new research findings, ideas, and directions of an international group of scientists whose research focuses on the study of experimental immunodeficiency virus infections. These include human immunodeficiency virus (HIV), simian immunodeficiency virus (SIV), and recombinant SIV/HIV in nonhuman primate models. The knowledge gained from nonhuman primate studies will help scientists better understand how HIV and SIV cause disease and will facilitate the development of new methods for the treatment, control, and prevention of AIDS in human populations.

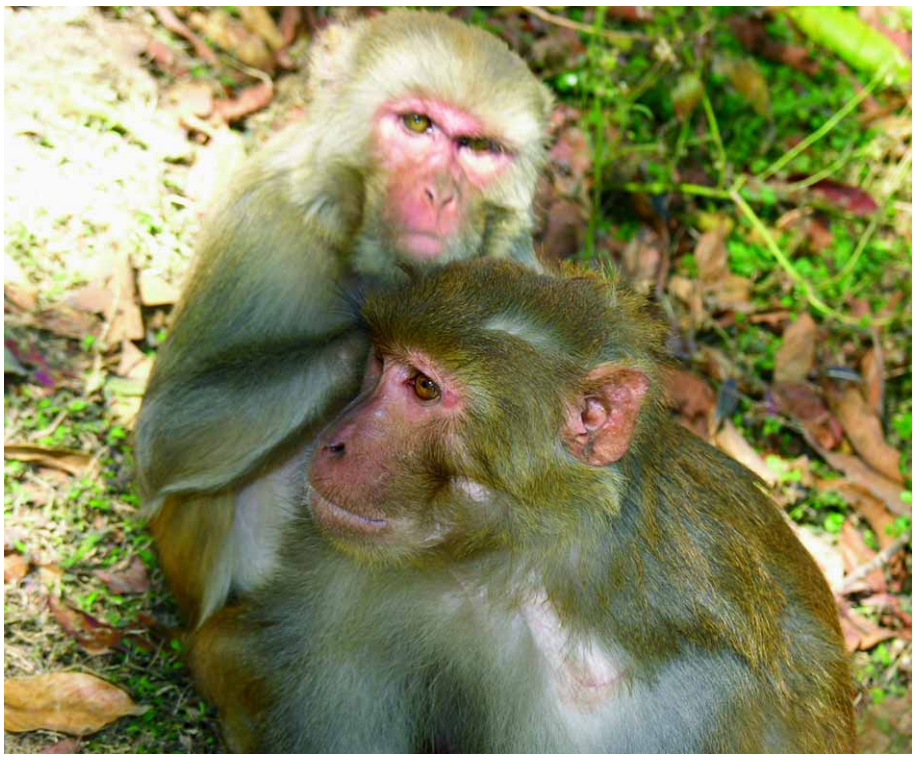
Previous meetings of the Annual Symposium have had a significant impact on understanding viral pathogenesis in primate models and the development of AIDS drugs and potential vaccines. This year's meeting will focus on the biology of primate lentivirus infection and the use of nonhuman primate models for the study of viral pathogenesis, vaccines, and therapeutic approaches against primate lentivirus infection and disease; primate genomics; viral agents associated with simian acquired immunodeficiency syndrome; and the mechanisms of natural resistance to endemic primate lentiviral infection in several primate species.

Scientists interested in attending the meeting should visit www.cnprc.ucdavis.edu/NHPM2007.

DEVELOPMENT AND USE OF NONHUMAN PRIMATE EMBRYONIC STEM CELL LINES
Fall/Winter 2007

The workshop will review the status of derivation, availability, and characterization of nonhuman primate embryonic stem cells (NHP ESCs) and define their potential uses, specifically in regard to translational research. Another goal will be to provide advice to NIH administrators on new initiatives needed to fully realize the potential of NHP ESCs to help advance the goals of regenerative medicine. Participants will include researchers with experience in NHP ESC derivation and experts in the areas of human ESC research and regenerative medicine.

Individuals interested in attending the workshop may contact Jack Harding at hardingj@mail.nih.gov.



The effort to sequence the rhesus macaque genome was supported by several NCRR-funded National Primate Research Centers.

Genome of the Rhesus Macaque Unveiled

Scientists had already laid bare the complete genetic codes of humans and chimpanzees. They have now added a third primate to the list of sequenced genomes: the rhesus macaque or, by its Latin name, *Macaca mulatta.* This old-world monkey is the nonhuman primate most widely used in biomedical studies focusing on major diseases, such as AIDS and diabetes. Its genome sequence is reported in the April 13, 2007, issue of *Science* magazine.

The sequencing, funded by NIH's National Human Genome Research Institute, was performed at the Baylor College of Medicine Human Genome Sequencing Center in Houston, Texas; the Genome Sequencing Center at Washington University in St. Louis, Missouri; and the J. Craig Venter Institute in Rockville, Maryland.

It was based on the DNA from a single individual—a female rhesus macaque housed at the NCRR-funded National Primate Research Center (NPRC) at the Southwest Foundation for Biomedical Research in San Antonio, Texas. The California, Oregon, and Yerkes NPRCs, also funded by NCRR, contributed additional biological samples used in the study.

The human genome was sequenced in 2001. With the sequencing of the chimpanzee *(Pan troglodytes)* genome in 2005, scientists were able to investigate which genes humans share with this close relative, from which they diverged about 6 million years ago. Macaques are more distant in the evolutionary timescale, as they are believed to have diverged from humans 25 million years ago.

But this distance is actually useful for studying evolution. By comparing rhesus macaque and human DNA, which are about 7 percent different from one another, scientists can see which genes have been conserved in primates over time and which ones have not. Compared to the human genome, the chimp genome is only about 1.5 percent different.

The *Science* article describes about 200 genes that probably play a key part in determining differences among primate species, including genes involved in hair formation, immune response, membrane-protein generation, and sperm-egg fusion. Also, researchers found some intriguing examples where a normal form of a macaque gene looks like a diseased human gene.

PHOTO BY RANDALL C. KYES / UNIVERSITY OF WASHINGTON

Now Available by e-Mail

NCRR Reporter
Critical Resources for Your Research

National Center for Research Resources
NATIONAL INSTITUTES OF HEALTH

Stay informed with a FREE subscription to the NCRR Reporter

Sign up now to receive NCRR's quarterly *NCRR Reporter* magazine—direct to your inbox! The new electronic edition of the magazine links to the full content of the print *Reporter* and to additional Web-exclusive news.

You'll find timely articles about:

- Research tools and resources that might aid your scientific investigations
- Significant biomedical advances and their potential impact on human health
- New funding opportunities and profiles of grantees
- Late-breaking news from NCRR

It's easy to subscribe:

Sign up to receive the electronic edition of the *NCRR Reporter* at www.ncrr.nih.gov/e-Reporter

To request a free subscription to the print magazine, contact info@ncrr.nih.gov

---

U.S. Department of Health and Human Services
National Institutes of Health
National Center for Research Resources
One Democracy Plaza, 9th Floor
6701 Democracy Blvd. MSC 4874
Bethesda, MD 20892-4874

Official Business
Penalty for Private Use, $300

Presorted Standard
U.S. Postage Paid
DHHS/NIH/RR
Permit No. G-818