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NCRR Reporter

Summer 2007

Critical Resources for Your Research

U.S. Department of Health and Human Services

Forging a Path From Laboratory to Clinic

FROM THE DIRECTOR

Partnerships, Collaboration, and Connectivity Transform Clinical and Translational Science

With the upcoming announcement of the next round of Clinical and Translational Science Awards (CTSAs) in September, it is the ideal time to feature the training and research under way at the current CTSA sites. The articles that follow provide firsthand accounts of how CTSA support is enhancing investigators' skills by providing training in multidisciplinary and translational research, supplying new tools that transcend specific research areas, offering regulatory and patient recruitment assistance, and generally working to break down barriers from laboratory to clinic.

These examples are representative of numerous other efforts taking place in the CTSA institutions. The CTSA principal investigators and researchers are actively collaborating through steering committees focused on specific topic areas, such as informatics, training, translational research, community engagement, and oversight of pediatric involvement in all aspects of CTSA activity. In addition, consortium members have embraced partners that are both numerous and heterogeneous, including pharmaceutical companies, the Veterans' Administration hospitals, health maintenance organizations such as Kaiser Permanente, and state health agencies.

Future issues of the *NCRR Reporter* will focus on other CTSA sites and highlight additional features of the program, including progress on development of informatics systems that will provide interoperability and connectivity for conducting clinical and translational research while further enabling the CTSA sites to function as a consortium. Other highlights will include community engagement initiatives that bring together the CTSAs with underserved populations, grassroots and advocacy organizations, and public health professionals.

While NCRR is leading this effort, the CTSA program could not succeed without the assistance and cooperation of staff drawn from across the multiple Institutes and Centers of NIH. These individuals are helping us to guide and assist the consortium as it expands in both size and expertise. It is in this way—through multiple partnerships, collaboration, and connectivity—that CTSAs will transform clinical and translational research and apply new scientific advances to real-world practice.

Barbara Alving, M.D.

Barbara Alving, M.D.
Director, NCRR

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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.

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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: Cynthia McEvoy, M.D., associate professor of pediatrics at Oregon Health & Science University, tends to one of her patients (Diego, born on June 30, 2007) in the neonatal intensive care unit of the Doernbecher Children's Hospital in Portland, Oregon. McEvoy will be collaborating with colleague Daniel Marks, M.D., Ph.D., on a study to look at the effects of maternal nutrition on prenatal development. The study is an extension of research that Marks conducted in animals, supported through a pilot grant from NCRR's Clinical and Translational Science Award program.

PHOTO BY RICK RAPPAPORT PHOTOGRAPHY

Feeding the Pipeline of Clinical and Translational Researchers

To translate promising bench science into practices that improve health, researchers must have broad expertise at the intersection of the basic, clinical, and population sciences. NCRR's Clinical and Translational Science Awards (CTSAs) help institutions provide new and enhanced training programs that give researchers the skills they need for successful careers at these crossroads of science. Details of the programs vary, but the key, according to representatives of 2 of the first 12 programs to be funded, is to combine flexibility with rigor.

"People who come out of medical or graduate school are unusually valuable commodities," says Columbia University Medical Center (CUMC) faculty member Robert Winchester. "Let's invest a bit of time in individualizing the options to help applicants make informed choices about their careers."

Since receiving a CTSA in 2006, the university has unveiled a variety of programs aimed at enhancing skills in multidisciplinary and translational research. One example is a one-year certificate program in translational research for predoctoral students with requirements that vary according to each student's needs. Faculty advisors are on hand to discuss the types of courses and training needed by each applicant to achieve his or her career goals.

A key component of the CTSA is the K12 program that funds junior faculty members conducting research under the mentoring of an established translational researcher. All K12 scholars must complete a number of courses, with some needing to enroll in the master's program.

In addition, all CTSA trainees take part in weekly colloquia, which draw audiences with an array of skills. "We try to break down artificial barriers between divisions and disciplines," Winchester explains. "Sometimes the best research is done with other people; it can be catalytic." To further encourage cross-discipline interactions, the university is building a physical home for all CUMC students and postdocs interested in translational research. The spacious area will feature conference rooms, work centers, and sophisticated computer resources.

Across the country, the University of California, San Francisco (UCSF), is creating "a smorgasbord" of curriculum and approaches, according to Jeff Martin, who heads the training program there. In addition to a two-year comprehensive master's degree in clinical and translational research, UCSF offers a comprehensive one-year certificate program and an eight-week summer clinical research workshop. These programs address common deficiencies in M.D.- or Ph.D.-trained researchers, from expertise in epidemiology and biostatistics to knowledge of ethical and regulatory issues.

In addition to the existing programs, UCSF is developing a one-month course on designing clinical research, aimed primarily at clinical residents, "who heretofore have generally been forgotten in terms of induction and maintenance of research skills," Martin explains. The university also has plans to develop discrete tracks within the existing master's program in the two NIH-defined areas of translational research: 1) laboratory to human subjects and 2) evidence to clinical and public health practice.

This year alone, UCSF training programs support 30 master's students, 26 certificate candidates, and 132 summer workshop participants. Martin attributes this strong interest to a high level of rigor in the programs and an emphasis on practical application. "We want our scholars to understand the process of knowledge creation from start to finish with firsthand experience in all the steps along the way."

The CTSA Program supports similar clinical research initiatives at institutions across the country that will place budding translational and clinical scientists in the educational environments that lead to successful careers. ■

A STUDENT'S PERSPECTIVE

After graduating from UCSF's master's program in clinical and translational science, Ari Green, who also received his residency training at UCSF, is a faculty member at the university's Multiple Sclerosis Center. "Traditionally, clinician-scientists had to forge their own career paths, but many would repeat the same mistakes, and some would never gain adequate skills to answer clinical questions in a rigorous manner," Green says. He praises the UCSF program for giving him access to specialists across the university who could share their knowledge of the skills and resources needed to succeed in translational research.

Forging a Path From Laboratory to Clinic

CTSA consortium accelerates the process of bringing research discoveries to patients. **BY LAURA BONETTA**

After administering two rounds of very intensive chemotherapy and radiation, followed each time by infusions of stem cells to help replace blood cells damaged during the course of treatment, Stephan Grupp and colleagues at Children's Hospital of Philadelphia can cure about half of their patients with neuroblastoma, one of the most common and deadly solid tumors among children. The success rate, much higher than that achieved by standard therapy without the stem cell infusions, "is better, but not nearly good enough yet," says Grupp.

To improve the outcome even further, he wanted to add another step to the therapy regimen by immunizing his patients against their cancer. Using a "cancer vaccine," Grupp could teach the patients' immune systems to seek out and destroy any remaining neuroblastoma cells, thus minimizing the chances of a relapse. But before embarking on this pioneering work, Grupp had to overcome one major obstacle: The immune systems of children who have undergone chemotherapy and radiation are severely weakened.

Grupp and colleagues, including Carl June at the University of Pennsylvania, tried "rescuing" the immune system by collecting blood cells from patients at the time of diagnosis and then coaxing the immune cells into dividing and multiplying outside the body. In a pilot clinical trial funded by the National Cancer Institute, the researchers transplanted the multiplied immune cells back into patients after they had received therapy. Preliminary data suggest that these transplanted cells are fully functional and allow a patient with a devastated immune system to mount an immune response to a vaccine.

To finish the current trial as quickly as possible and move on to testing the cancer vaccine, Grupp decided to enlist the help of a collaborating institution. That's when he came up against a mountain of administrative paperwork.

RECONFIGURING THE RESEARCH ENTERPRISE

Clinical trials, such as the one Grupp is conducting, are a critical step in translating scientific discoveries arising from laboratory, clinical, or population studies into practical applications that can improve human health. But researchers engaged in this "translational research" encounter numerous challenges on the path from bench-to-bedside testing. Unlike scientific research focused on a particular approach or discipline, translational research crosses boundaries between basic science and clinical applications, requiring intense interactions among investigators with diverse backgrounds and types of expertise and among members of both academic and industrial communities.

To strengthen and accelerate the process of bringing scientific discoveries to the community, the Clinical and Translational Science Award (CTSA) consortium, established by NCRR as part of the NIH Roadmap for Medical Research, strives to remove roadblocks and ease challenges in clinical and translational research. (See sidebar, "A Consortium for Transforming Clinical and Translational Research.")

■ Physician-scientist Stephan Grupp at the Children's Hospital of Philadelphia is testing a new therapy for neuroblastoma, a common and deadly cancer among children. Using resources provided through the Clinical and Translational Science Award at the University of Pennsylvania, Grupp was able to enlist the help of a collaborating institution to complete his study more rapidly.

For the most part, the current generation of clinical researchers could only draw on the resources of their own departments to carry out their work. "But as science has advanced, we need a set of tools and knowledge that transcends the structures of a typical clinical department," says Robert Califf, vice chancellor for clinical and translational research at Duke University Medical Center. "That is why NIH Director Elias Zerhouni decided we needed to provide a home for this kind of research." Califf, along with Lars Berglund, associate dean for clinical and translational research at the University of California, Davis, cochairs the CTSA consortium oversight committee.

The CTSA consortium, initiated in 2006 with 12 "homes" for clinical and translational research, is enhancing the nation's clinical research enterprise by encouraging and enabling transdisciplinary collaborations within and across research institutions, providing researchers with access to sophisticated technologies and expertise, offering assistance with regulatory and administrative tasks, and training the next generation of clinical and translational scientists.

Although the first 12 CTSAs are just starting to make the necessary facilities and programs available at their own institutions, many researchers are already realizing the impact that the new infrastructure will have on their current and future work.

SPEEDING THE DEVELOPMENT OF NEW THERAPIES

Through its CTSA, the University of Pennsylvania provided invaluable assistance to Grupp in negotiating an agreement to work on his neuroblastoma trial with colleagues at Dana-Farber Cancer Institute, considerably speeding up patient recruitment. "The collaboration will cut the length of the trial from eight to four months," explains Grupp.

Getting another entity involved in the trial was far from easy. "This is an Investigational New Drug (IND) study, and Penn holds the IND," says Grupp. "So we had to develop procedures for Dana-Farber to participate. We had to write new standard operating procedures that could be exported to a different site." The payoff is that when the trial is completed in fall 2007, Grupp will have a chance to move forward with testing his new cancer vaccine. And if he and investigators at Dana-Farber decide to collaborate to test the new therapy, the groundwork has already been laid. "We now have a clinical trial agreement between the two institutions," he says.

Researchers are often not trained in complying with all the regulations set in place to ensure patient safety, and even if they have the necessary know-how, they cannot afford the time and effort to get through all the associated paperwork. CTSAs focus on freeing up the intellectual and creative talents of clinical

PHOTO COURTESY OF CHILDREN'S HOSPITAL OF PHILADELPHIA

> The CTSAs help researchers deal with the complexities of human studies. —LARS BERGLUND, UNIVERSITY OF CALIFORNIA, DAVIS

and translational researchers by providing regulatory support, clinical research coordinators, technology transfer assistance, and project management. "The CTSAs help researchers deal with the complexities of human studies," says Berglund. "At our university, we have individuals who are trained to take care of regulations. With increased use, their experience increases, and they become better and faster at the task."

MOVING RESEARCH FROM THE LABORATORY BENCH TO PATIENTS

Another challenge faced by clinical and translational researchers is that their work calls for a broad set of skills and expertise that is rarely found in a single laboratory or department. "In the long run, the consortium will make translational and clinical research more economical and efficient by providing access to important skills and technologies currently limited to defined disciplinary areas or specific labs," explains Berglund.

Institutions belonging to the CTSA consortium are establishing centralized facilities for specialized technologies, such as combinatorial chemistry and molecular therapies, imaging and informatics, as well as repositories of patients' samples. "These are institutional resources traditionally undersupported," says Califf. "All researchers can use them and have access to them more readily and at a lower cost than if they had to seek them out on their own."

In addition, CTSAs provide support for patient-oriented studies by providing access to patients and to trained medical personnel who can help researchers with medical evaluations, protocol design, review of clinical laboratory findings, and other competencies. This support is particularly critical to scientists in basic science departments, like Marc Flajolet at The Rockefeller University, who are not trained or do not have the resources to move important research findings to clinical applications.

In a study funded by the National Institute on Aging, Flajolet and supervisor Paul Greengard, director of The Rockefeller University Fisher Center for Alzheimer's Disease Research and a faculty member on the university's CTSA, reported that expression of high amounts of a particular enzyme increases the amount of amyloid beta, the rogue protein that accumulates within and around the brain cells of Alzheimer's disease patients.

■ Marc Flajolet, a researcher in the laboratory of Paul Greengard at The Rockefeller University, has identified a new set of compounds that can block the production of amyloid beta, a protein that accumulates in the brains of people with Alzheimer's disease.

On the other hand, inhibiting the activity of this enzyme—called casein kinase 1—reduces amyloid beta levels.

The results suggest that casein kinase 1 inhibitors could provide a new class of drugs for Alzheimer's patients. Such drugs are badly needed, because most current drugs being tested for Alzheimer's disease cause serious side effects in patients. The new compounds against casein kinase 1 might be safer because they use an entirely different mechanism.

Although the casein kinase 1 inhibitors look promising in the laboratory, more tests must be completed before they can be assessed in patients. For one thing, the compounds Flajolet

PHOTO BY GUY KLOPPENBURG, COURTESY OF THE FISHER CENTER FOR ALZHEIMER'S DISEASE RESEARCH

used in his study dissolve poorly in blood. He has, therefore, started to test similar molecules to find ones that are more soluble. Soluble compounds will then need to be tested in animal models of Alzheimer's disease to determine whether they improve symptoms.

But if these preclinical studies yield positive results, Flajolet might soon be in a position to test his compounds in clinical trials within the Rockefeller CTSA, which includes a hospital devoted exclusively to medical research. "We definitely have a lot of facilities here," says Flajolet. "We will do our best to take our findings through to studies in humans." The outcome may be a treatment for a disease that currently affects more than 5 million Americans; without effective treatments or cures, disease prevalence is expected to soar to 7.7 million people by 2030.

ENABLING PRECLINICAL STUDIES AND THEIR TRANSLATION TO PATIENTS

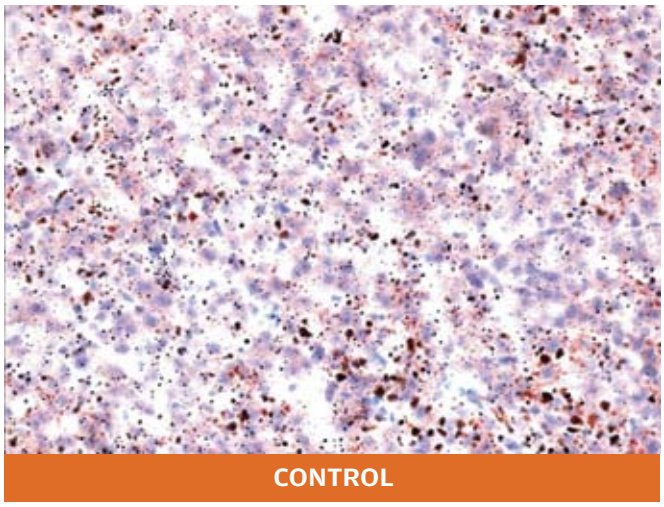
Whereas many clinical insights come from basic studies in the laboratory, others have their roots in observations in animal models. Daniel Marks of Oregon Health & Science University received a pilot grant from the university's CTSA to collaborate on a project initiated five years earlier by Kevin Grove at the NCRR-funded Oregon National Primate Research Center. "The pilot grant was so important, because I have not published in this field before," says Marks, whose medical training was in pediatrics. "It is hard to apply for an R01 grant if you have no publication record."

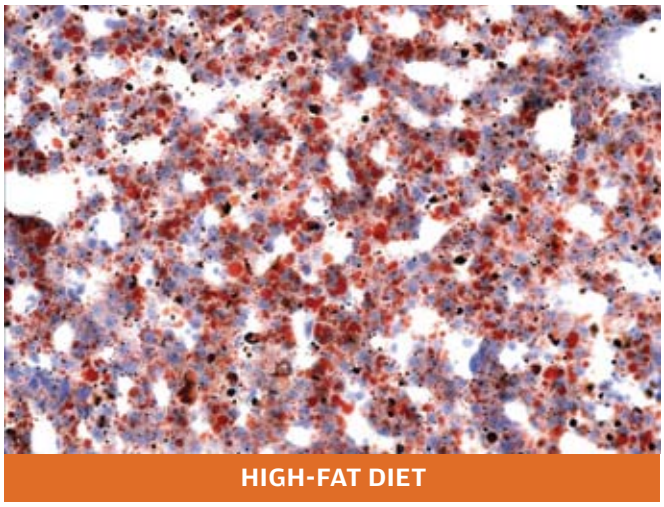
Grove had established a model of obesity in Japanese macaques by feeding them a diet consisting of 35 percent fat, the proportion of fat in the average U.S. diet. When given to pregnant monkeys, the diet invariably caused abnormalities in different organs in the developing fetuses. Marks documented an accumulation of fat in fetal liver cells associated with varying degrees of inflammation and scarring, a picture reminiscent of the liver disease typically observed in alcoholics. "To see this in the developing fetus is very alarming," says Marks. "If the results are confirmed in humans, they would have profound implications in light of the current obesity epidemic."

To examine this question, Marks started collaborating with physicians at the neonatal intensive care unit of the university's affiliated hospital to examine the livers of human fetuses by ultrasound. "To set up a study like this, you must draft consent forms for the parents, in English and Spanish in this case, draft a procedure that details exactly what you want to do with the patient, the risks and benefits, how the data will be managed, how we will protect patient privacy, and so on," Marks elaborates. He is receiving invaluable assistance from his institution's CTSA in fulfilling these requirements.

TRAINING THE NEXT GENERATION OF TRANSLATIONAL SCIENTISTS

In addition to supporting Marks' research, Oregon Health & Science University's CTSA has provided training opportunities for a graduate student and medical student in his lab to become "card-carrying translational researchers," says Marks. The CTSA offers several courses through its Human Investigations Program to train health care professionals who want to make clinical research a substantial part of their long-term career goals.

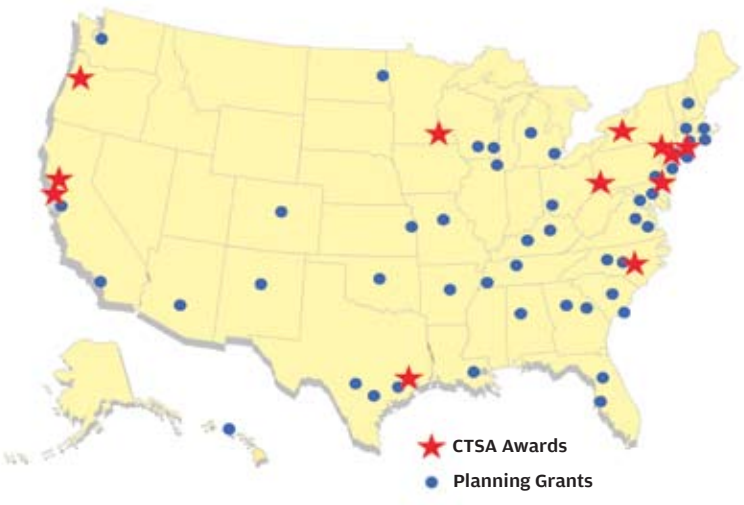




■ Daniel Marks and colleague Kevin Grove at the Oregon Health & Science University have been studying the effects of a high-fat diet on developing organs using a nonhuman primate animal model. These photographs show the livers of monkey fetuses whose mothers had been fed either a regular, low-fat diet (control) or a diet high in fat and calories. The livers were treated with a compound (oil-red O) that specifically stains fat deposits red. Many more fat deposits can be seen inside liver cells of fetuses in the high-fat diet group—a picture reminiscent of the fatty liver disease typically observed in alcoholics.

IMAGES COURTESY OF OREGON HEALTH & SCIENCE UNIVERSITY

> As science has advanced, we need a set of tools and knowledge that transcends the structures of a typical clinical department. —ROBERT CALIFF, DUKE UNIVERSITY MEDICAL CENTER



Twelve institutions participate in the CTSA consortium.
An additional 52 institutions have received planning grants to help them prepare applications to join the consortium.

Through this program, students can attend such courses as "Introduction to Clinical Research," "Clinical Research Design," and "Biostatistics and Protection of Human Subjects" as part of certificate, master's, and non-degree tracks. These courses provide training in clinical research from the initial trial design to data analysis and presentation, equipping students with the necessary expertise to pursue an independent career in this field.

Such training programs were established at Oregon and other CTSA institutions due to a realization that the scope of knowledge and expertise needed to be an effective translational or clinical scientist can no longer be acquired on the job as was done in the past (see "CTSAs in Focus," page 3). "We now offer different programs suited to different needs," says Berglund.

The three studies at Rockefeller, Oregon, and Penn span the continuum of clinical and translational research—from studies in the laboratory that may lead to new drugs, to animal models of disease that give important insights into human conditions, to new therapies tested in patients. They are just a few examples of the countless advances to be facilitated through the programs and resources established through the CTSA consortium.

As this initiative continues to expand with different CTSAs collaborating and sharing resources, it will help speed the course of translational and clinical research, ultimately benefiting the nation's health. "When we first got funded, I just wanted to focus on getting our own programs off the ground," says Berglund. "But the consortium has since become the most important part of our efforts. We are coming together at every level and really starting to work as a unit." ■

A CONSORTIUM FOR TRANSFORMING CLINICAL AND TRANSLATIONAL RESEARCH

The Clinical and Translational Science Awards (CTSAs) established a new consortium to transform how clinical and translational research is conducted, ultimately enabling researchers to provide new treatments to patients more efficiently and quickly. Launched on October 3, 2006, the consortium includes 12 academic health centers located throughout the nation. When fully implemented in 2012, about 60 institutions will be linked together. "Different CTSAs have different strengths," says Robert Califf, vice chancellor for clinical and translational research at Duke University Medical Center. "Our job is to create some common goals by sharing ideas and different expertise."

Representatives from all CTSAs meet several times a year to share experiences and establish best practices in a range of areas, including the following:

- Biostatistics and epidemiology
- Research design
- Communications
- Clinical research ethics and resources for research participants
- Participant and clinical interaction resources
- Regulatory knowledge
- Pediatrics
- Informatics
- Community engagement in clinical research
- Education and career development
- Institutional and national evaluation
- Translational research in traditional academic settings and in public-private partnerships
- Translational research

Information about the committees responsible for these areas and their activities is available at the consortium's Web site at http://ctsaweb.org.

From Brain Imaging to Chemical Probes

Grants enable advanced technologies.

Looking at a photograph or tapping fingers to a tune sends signals to certain areas of the brain, increasing blood flow to those regions. Changes in blood flow and, more precisely, in the amount of oxygen, can be detected by functional magnetic resonance imaging (fMRI), an increasingly popular technique for probing the working human brain. John Gore, director of the Vanderbilt University Institute of Imaging Science in Nashville and world-renowned expert in the technology, has used fMRI to determine which parts of the brain "light up" when, for example, schizophrenic patients experience hallucinations or alcoholics have cravings.

■ John Gore, director of Nashville's Vanderbilt University Institute of Imaging Science, received a $2 million award to support the purchase of a 7-tesla human magnetic resonance imaging and spectroscopy system. It provides the highest magnetic imaging available for humans and is one of only several such instruments in the country.

Whereas fMRI gives insights into how the brain functions, another sophisticated technology tells researchers about the activities of tiny molecules. Nuclear magnetic resonance (NMR) spectroscopy exploits the magnetic properties of atomic nuclei to provide three-dimensional molecular structures. Maurizio Pellecchia of the Burnham Institute for Medical Research in La Jolla, Calif., has taken NMR spectroscopy to a new level by using it to study how proteins interact with one another and with other molecules. The information suggests how interactions among different molecules in the body generate signals necessary for biological processes and functions.

Both Gore's and Pellecchia's pioneering research recently got a boost through NCRR's High-End Instrumentation (HEI) Grant Program. Established in 2002, the HEI Program helps researchers purchase expensive equipment, such as imaging systems, high-end microscopes, supercomputers, and spectrometers, by providing anywhere from $750,000 to $2 million toward the cost. To date, NCRR has awarded 101 HEI grants and 2 supplements totaling $155.8 million. The most recent round of 14 awards, including those to Gore and Pellecchia, was announced in June. "Researchers can ask questions they could not ask before. They can do amazing experiments only possible with the new equipment," says Marjorie Tingle, director of the HEI Program. "The new instruments have much higher resolution and unsurpassed sensitivity."

Indeed, thanks in part to $2 million in support from NCRR, Gore's Vanderbilt University Institute of Imaging Science now houses a 7-tesla (7T) MRI scanner—the largest and most powerful MRI instrument currently available. Because of its greater magnetic strength, the new 35-ton scanner offers a more sensitive measure of changes in brain activity. It also provides higher resolution, giving researchers even more detailed pictures of the brain. Thus researchers can get a better idea of which areas of the brain are involved in complex behaviors or diseases.

PHOTO BY DANA JOHNSON, COURTESY OF VANDERBILT UNIVERSITY MEDICAL CENTER

The new 7T MRI scanner is bolstering the work of about 30 Vanderbilt researchers studying developmental disorders, learning disabilities, and psychiatric disorders such as schizophrenia, pathological gambling, and depression. In addition, through grants from NIH's National Institute of Biomedical Imaging and Bioengineering, the imaging institute provides training to graduate students, postdoctoral fellows, and medical residents in state-of-the-art imaging techniques. "We are training more than 50 people in imaging science," says Gore. "This new instrument will be a major flagship for a lot of their work."

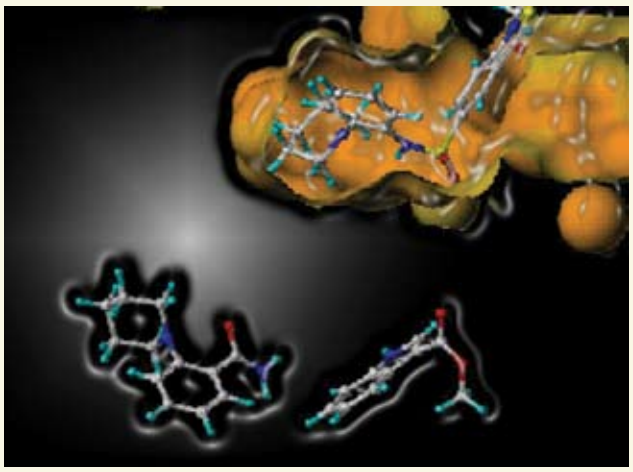
The new scanner will also serve the Meharry-Vanderbilt Alliance for Research Training in Neuroscience, a partnership that grew out of a broader, formal alliance, created in 1998 between Meharry Medical College—a historically black institution in Nashville—and Vanderbilt University Medical Center to foster collaboration on biomedical research, research training, and clinical care. Recent fMRI work within this Alliance has focused on identifying which brain circuits are active in chronic alcoholics and drug addicts during various stages of rehabilitation to understand the neuronal bases of these conditions.

Pellecchia's NMR instrument is also having a far-reaching impact on the work of researchers throughout the country. His group has pioneered using information collected by NMR spectroscopy to design small molecules, called chemical probes, to disrupt interactions among proteins. Doing so may reveal the importance of a particular interaction or pathway to disease and also give researchers a starting point for drug development.

Pellecchia and colleagues recently used the technique to identify chemical probes for the protein Bid, a molecule that causes neuronal cell death and is a suspected player in brain injury and neurological disorders, such as amyotrophic lateral sclerosis, also known as Lou Gehrig's disease.

Traditional drug discovery techniques often look for "downstream" targets of a protein—for example, in the case of an enzyme, the molecules the enzyme modifies. But because Bid is not an enzyme, it is not easily amenable to such approaches. Pellecchia used NMR spectroscopy to understand the structure of Bid and, in particular, the part of the protein that interacts with other molecules. He then used this information to design several chemical probes that stick to Bid, preventing it from finding its "partners." By preventing these interactions from occurring, the chemical probes also prevented Bid from inducing neuronal cell death. After further optimization, these chemical probes will be tested in animal models for their potential use in preventing nerve cell damage due to brain injury and other conditions.

One of the limitations of using NMR spectroscopy is that typically the technique can be used on only one sample at a time. In addition, the amount of sample needed for a single experiment can be substantial, depending on the instrument's signal-to-noise ratio, or its ability to distinguish a true signal from background noise. With the $1.45 million HEI grant, Pellecchia was able to purchase a 700-MHz NMR instrument with an accessory that generates a substantially higher signal-to-noise ratio, reducing the amount of sample needed for a study. The new instrument also comes with an automated sample changer, allowing it to test multiple samples automatically, greatly increasing the speed and efficiency of experiments.

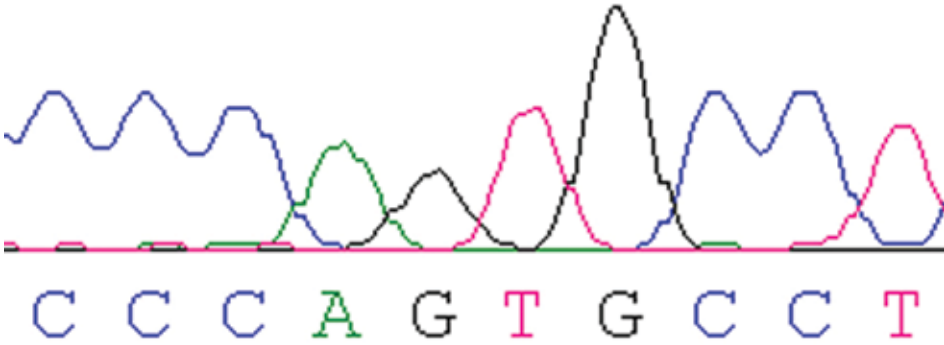


■ Scientists at the Burnham Institute for Medical Research in La Jolla, Calif., are using nuclear magnetic resonance spectroscopy to probe interactions between small molecules and proteins as a first step in identifying potential drug targets. New instruments, supported by an NCRR High-End Instrumentation grant, will allow more researchers to benefit from the technology.

The new NMR instrument will support several multidisciplinary projects by Burnham Institute investigators focused on infectious diseases and signal transduction in cancer cells. It also will serve, in part, the San Diego Center for Chemical Genomics, as part of an NIH Roadmap Network to accelerate medical discoveries. All NIH-funded researchers can collaborate with members of the Network to identify small molecules that act in their favorite pathway. As Pellecchia points out, the San Diego Center for Chemical Genomics is the only center in the Network that will use NMR spectroscopy. "We are proud of that fact," he says. "And we are thrilled we've been awarded an additional instrument to support research in this area."

—FRANCES MCFARLAND HORNE

IMAGE COURTESY OF BURNHAM INSTITUTE FOR MEDICAL RESEARCH



Genetic Resources for the Rhesus Macaque

Genetic tools will enhance studies with a widely used animal model. **BY LAURA BONETTA**

The human genome project, along with a variety of new genetic tools and technologies, sparked a flurry of research aimed at understanding how variations in the genetic code affect human health. Similar accomplishments using the rhesus macaque would greatly enhance the value of this animal model, according to participants at the workshop "Improving Genetic Resources for the Rhesus Macaque," held on the NIH campus in May 2007.

"NCRR has had a long-standing interest in the development of genetic tools for the rhesus," says John Harding, director of primate resources at NCRR, who organized the workshop. "We expect that the refinement of available genetic tools will greatly enhance the ability of researchers funded by many of the NIH Institutes and Centers to make fundamental discoveries related to human health using the rhesus."

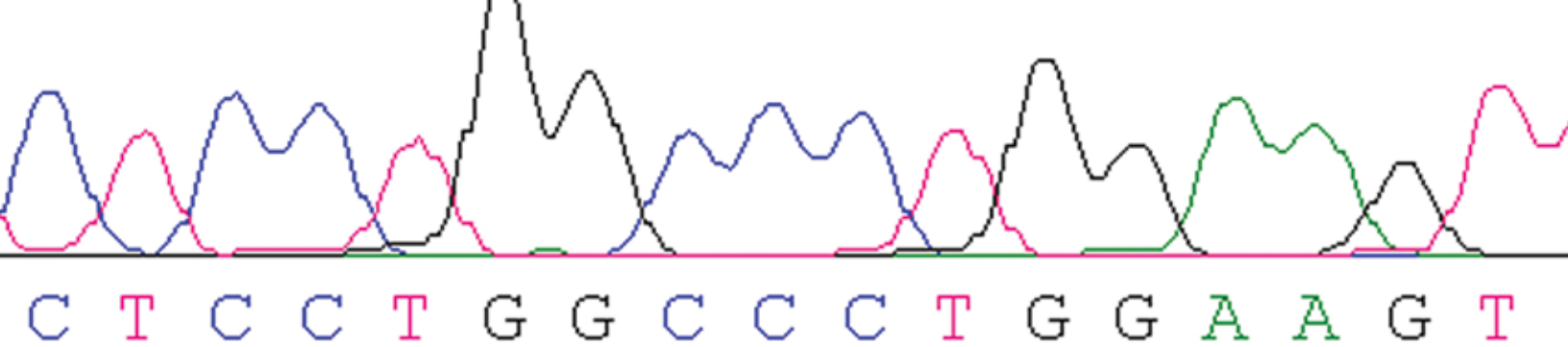
ENHANCING TRANSLATIONAL RESEARCH

Because the rhesus macaque (*Macaca mulatta*) and humans shared a common ancestor only 25 million years ago, they have similar brain function, physiology, and susceptibility to infectious diseases. Indeed, the rhesus macaque—one of the few animals to develop AIDS-like symptoms when infected with the monkey counterpart of HIV—is by far the best model for studying AIDS and testing candidate vaccines. In neuroscience, the rhesus macaque has been extensively used to study brain development and carry out studies of alcoholism and drug addiction and of neurological diseases, such as Alzheimer's. More recently, studies using the rhesus macaque have yielded important insights into metabolic syndromes, such as diabetes and obesity.

During the past several years, NCRR-funded researchers have developed a variety of genetic tools, such as genetic maps and DNA microarrays, that can now be used in combination with the genome sequence to learn more about the genetic underpinnings of various conditions. Is there a particular combination of genes, for example, that enhances the response to a vaccine? Or are there particular genetic variations that render monkeys more prone to developing diabetes? Finding answers to these questions will be facilitated by the development of more refined genetic tools and resources.

THE RHESUS MACAQUE GENOME

The sequencing of the rhesus macaque genome was funded by the National Human Genome Research Institute and performed at the Baylor College of Medicine Human Genome Sequencing Center in Houston, Texas; the Genome Sequencing Center at Washington University in St. Louis, Mo.; and the J. Craig Venter Institute in Rockville, Md. It was based on the DNA from an Indian-origin, female rhesus macaque housed at the NCRR-funded Southwest National Primate Research Center (NPRC) in San Antonio, Texas. The California, Oregon, and Yerkes NPRCs, also supported by NCRR, contributed additional biological samples used in the study. "The project was greatly



assisted by NCRR," says Richard Gibbs, professor of molecular and human genetics at Baylor College of Medicine and lead author for the April 13, 2007, *Science* article reporting the draft sequence.

WHAT COMES NEXT?

Taking advantage of the draft human genome sequence, the International HapMap Project, initiated in 2002, has identified millions of single nucleotide polymorphisms (SNPs), or single-letter variations among the genomes of different individuals. The availability of a great number of SNPs, more or less evenly spaced across the genome, allows researchers to find ones that are associated with a particular trait. Because of the structure of the genome, SNPs serve as signposts, highlighting nearby genes that may contribute to that trait.

A SNP mapping project for the rhesus macaque would allow researchers to carry out similar genome-wide association studies in this species. In some cases, it may be easier to identify SNPs associated with a human disease or condition using a controlled population of laboratory animals rather than human beings; in other instances, DNA regions identified to contain interesting genes in human studies could be further interrogated in the rhesus macaque.

MORE AND MORE SNPS

As part of the rhesus macaque genome project, researchers already found several thousand SNPs in this species, but they want to identify many more. Elaine Mardis, associate professor of genetics and molecular microbiology at Washington University, has began searching for common SNPs in the genomes of eight Chinese and eight Indian macaques. She is using a new sequencing technology, developed by the company Solexa, that can rapidly and inexpensively produce tens of millions of random genomic DNA sequences from each animal.

NCRR-supported scientists Robert Norgren, at the University of Nebraska Medical Center in Omaha, and Betsy Ferguson, at the Oregon NPRC, are looking for SNPs within specific genes involved in the immune, nervous, and reproductive systems or in aging—in other words, genes that may be of particular interest to biomedical researchers. They are taking advantage of the published rhesus macaque genome sequence to identify variations within genes among 24 Indian and Chinese animals. "We expect to deliver 70,000 gene-based SNPs in total, with about seven SNPs per gene on average," Norgren says.

Newly identified SNPs are deposited in public electronic repositories, including a new database called Monkey SNP (http://monkeysnp.ohsu.edu/snp) developed by Ferguson and Christopher Dubay at the Oregon NPRC. "We came to develop the database by necessity," Ferguson explains. "We had many research projects limited by either the absence of SNPs or by the difficulty in retrieving SNP data from other public databases. I cannot tell you how many people call me up who want to know if I can find a SNP for them for a candidate gene."

MORE DETAILED SEQUENCES

The draft sequence for the macaque genome is enabling the identification of common SNPs and the determination of their locations. But for some regions of the genome, finding genetic variations will require much more detailed and precise sequence data. This is because, although these regions contain families of genes that are similar to one another in sequence, their sequences vary considerably among different individuals within a species and from species to species.

Daniel Geraghty at the Fred Hutchinson Cancer Research Center in Seattle is focusing on one such region: the major histocompatibility complex (MHC), a gene-dense region that plays an important role in the immune system, in autoimmunity, and in reproductive success. By obtaining detailed sequence data for various MHC-region genes, Geraghty is developing a resource for identifying variations that, for example, slow the progression of AIDS or bode well for a vaccine response.

These studies are just a sprinkling of the activities NCRR grantees and other researchers are pursuing as they develop genetic tools for the rhesus macaque. Expanding such efforts will enable all researchers to take full advantage of this important animal model in translational research studies. ■

To learn more about NCRR's National Primate Research Centers, visit www.ncrr.nih.gov/comparative_medicine/resource_directory/primates.asp.

Five Members Appointed to NCRR Advisory Council

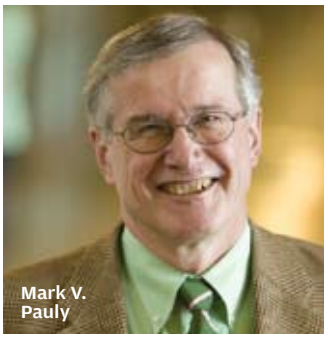
The National Advisory Research Resources Council advises NCRR on policies and programs and performs second-level peer review of grant applications. Five distinguished researchers and health administrators were recently appointed as new council members.


Nancy J. Brown

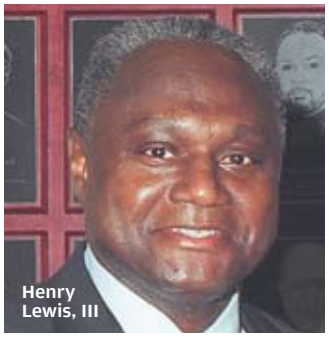
Nancy J. Brown, Robert H. Williams Professor of medicine and pharmacology and associate dean for clinical and translational scientist development in the School of Medicine, Vanderbilt University. Brown is nationally known for her research on blood pressure regulation. She is a founder and former director of the Master of Science in Clinical Investigation program and was recently recognized for her commitment to promoting research among young physicians.


Valerie Copie

Valerie Copie, associate professor of biochemistry at Montana State University. Copie's investigations focus on the connection between a protein's three-dimensional architecture and its biological function(s), the mechanism by which atomic structures and internal dynamics modulate biochemical activity, and the significance of conserved amino acid residues in protein families. Her approach involves multidimensional, heteronuclear, solution nuclear magnetic resonance (NMR) spectroscopy along with complementary biophysical techniques.


Mark V. Pauly

Henry Lewis, III, professor and director of research programs in the College of Pharmacy at Florida A&M University (FAMU). Lewis has previously served as dean of the College of Pharmacy at both FAMU and Texas Southern University and was interim president of FAMU. He also has been on the national advisory council of the National Institute of General Medical Sciences and was an NIH extramural associate. Lewis is currently the principal investigator for the Research Centers in Minority Institutions at FAMU. His area of research is sickle cell anemia.


Henry Lewis, III

Mark V. Pauly, Bendheim Professor of health care systems, business and public policy, and insurance and risk management, Wharton School of the University of Pennsylvania, and professor of economics, College of Arts and Sciences. Pauly was a commissioner on the Physician Payment Review Commission and is an active member of the Institute of Medicine. He was previously on the faculty of Northwestern University. Pauly has studied how health insurance coverage affects the use of various types of medical services and has been investigating ways to reduce the number of uninsured through tax credits and the appropriate design for Medicare in a budget-constrained environment.


Janet L. Smith

Janet L. Smith, Margaret J. Hunter Collegiate Professor of life sciences and professor of biological chemistry at the University of Michigan. Smith's research focuses on understanding biological processes by determining the structures of key proteins. In particular, her work examines the structures of proteins from infectious pathogens, including the RNA viruses that cause West Nile, yellow fever, and dengue, and those involved in biosynthetic pathways for the polyketide family of secondary metabolites.

Rubenstein Receives Prestigious Award

Arthur H. Rubenstein, executive vice president of the University of Pennsylvania for the Health System and dean of

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the University of Pennsylvania School of Medicine, received the 2007 Academic Health Centers Leadership Award from the Clinical Research Forum, an organization consisting of the nation's leading academic health centers, for "his lifetime of leadership in academic clinical research." In October 2006, the University of Pennsylvania, along with the Children's Hospital of Philadelphia, received a $68 million Clinical and Translational Science Award (CTSA) from NCRR. Prior to the CTSA, the university was home to an NCRR-funded General Clinical Research Center headed by Rubenstein.

Rubenstein has led the development of an aggressive scientific program to advance clinical and translational research at the University of Pennsylvania. The new Institute for Translational Medicine and Therapeutics, supported through the CTSA Program, is an interdisciplinary alliance, also involving the Wistar Institute, the University of the Sciences in Philadelphia, and eight other schools at Penn.

An internationally prominent endocrinologist, Rubenstein is recognized for his clinical expertise and groundbreaking research in diabetes. He has served as president of the Association of Professors of Medicine, the Association of American Physicians, and the Central Society for Clinical Research and has been chairman of both the American Board of Internal Medicine and the National Diabetes Advisory Board. Over the years, he has received several grants and awards from NCRR.

NIH Funds Repository for Knockout Mouse Project

NIH has awarded $4.8 million to the University of California, Davis, and Children's Hospital Oakland Research Institute to establish and maintain a repository of up to 8,500 strains of mice in which certain genes have been made inoperable, or "knocked out."

The grant is the final component of the NIH Knockout Mouse Project (KOMP), a trans-NIH initiative designed to increase the availability of genetically altered mice and related materials. The more than $50 million KOMP created the mouse embryonic stem cell lines—the types of cells that give rise to knockout mice—in which 8,500 different genes were knocked out.

The newly established repository will make knockout mice available to researchers as live mouse lines, embryonic stem cell clones, frozen embryos, and sperm. Researchers then will be able to study the mice to develop better models of many human diseases.

NCRR, the National Human Genome Research Institute, and the National Institute of Allergy and Infectious Diseases have funded the four-year grant to establish and operate the new repository. Previous KOMP awards established a data coordination center to track knockout mouse production and supported efforts to improve methods for creating knockout lines.

Information on the new repository and KOMP is available at www.komp.org.

Network Connects Investigators at Minority Institutions

NCRR will initially provide $9.5 million over three years to launch a network connecting researchers based at minority institutions and other collaborating institutions throughout the United States who are focused on studying and treating diseases that disproportionately affect minority populations.

The network will provide the necessary infrastructure and resources for facilitating multicenter, collaborative research that applies discoveries generated in the laboratory to clinical trials, as well as developing common practices in disease prevention and intervention in local communities. In particular, by providing informatics tools for analyzing and managing clinical research data, recruiting for clinical trials, and sharing information with patients, the network will enable researchers to collaborate more efficiently with each other and their communities.

The effort will be coordinated by Keith Norris, an expert in kidney disease at Charles R. Drew University in Los Angeles, Calif. In addition to Drew, participating institutions include Morehouse School of Medicine, Atlanta, Ga.; University of Hawaii, Honolulu, Hawaii; University of Puerto Rico Medical Sciences Campus, San Juan, Puerto Rico; Meharry Medical College, Nashville, Tenn.; Hunter College, City University of New York, N.Y., and Howard University, Washington, D.C. Jackson State University, Jackson, Miss., will be the site of the Data and Technology Coordinating Center for the network.

These institutions are part of NCRR's Research Centers in Minority Institutions program, which aims to enhance the research capacity and infrastructure at minority colleges and universities that offer doctorates in health and health-related sciences. ■

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