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NCRR Reporter

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U.S. Department of Health and Human Services

Clinical and Translational Science

Speeding the translation of medical discovery into enhanced patient care

FROM THE DIRECTOR

Accelerating the Pace from Discovery to Clinical Practice

We are truly at a crossroads in medicine. The scientific advances of the past few years, particularly the completion of the Human Genome Project, dictate that we act now to encourage fundamental changes in how we carry out clinical research, and how we train the new generations of clinician scientists. As the nation's medical research agency, the NIH is taking a leadership role to ensure that the public's health is well served by these advances.

Two years ago, NIH Director Dr. Elias Zerhouni announced the NIH Roadmap for Medical Research—a set of strategic initiatives to accelerate the pace of medical discovery across all areas of science. One of the key areas of the Roadmap is the collective effort to re-engineer the clinical research enterprise. Based on input from the biomedical research community, we learned that a new way of doing clinical research and translational science is needed if we are to deliver new discoveries to patients.

With your help, we shaped the Clinical and Translational Science Awards (CTSAs) Program, which was announced last fall. We believe that CTSAs will give academic health centers and other research institutions more freedom to foster productive collaboration among experts in different fields, lower barriers among disciplines, and encourage creative approaches that will help us solve complex medical problems.

Our vision is to transform the nation's clinical research enterprise by achieving three main goals:

- *Innovative Research Programs:* To support the development of an academic home for innovative clinical and translational research programs at institutions nationwide, thereby providing integrated intellectual and physical resources that are more flexible and responsive to modern research needs.
- *Highly Trained Researchers:* To train a robust cadre of interdisciplinary researchers who have well-structured and well-recognized career pathways, and are well positioned to make the next breakthroughs in medical science.
- *Improved Patient Care:* All of this serves our ultimate goal—to improve health outcomes for patients with rare and common diseases by fostering collaborative relationships throughout communities and enhancing public trust in clinical and translational research.

The changes we have described will take place over a period of years; during this time we will work closely with our NIH colleagues and with the academic health centers, research institutions, and the public throughout the nation.

Barbara Alving, M.D.

Barbara Alving, M.D.
Acting Director, NCRR

INSIDE

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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.

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On the Cover: NIH's new initiative to enhance clinical and translational science includes support for "translational" resources and technologies that help to transform research findings into better medical care.

PHOTO BY PETER BECK/CORBIS

Clinical and Translational Science

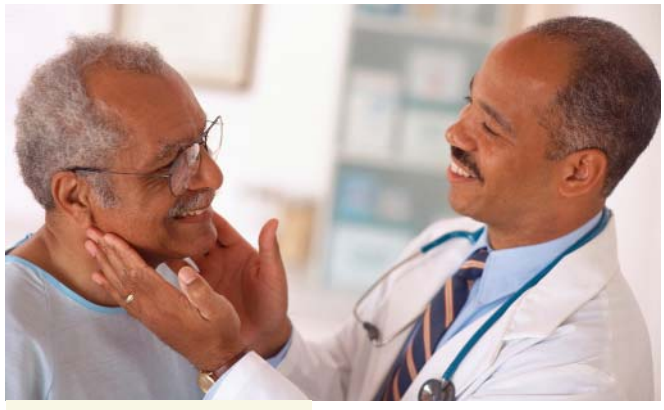
Speeding the translation of medical discovery into enhanced patient care.

BY VICTORIA L. CONTIE

Translating basic discoveries into improved medical care is a cornerstone of research funded by the National Institutes of Health (NIH). Yet scientists who conduct clinical and translational studies face multiple and complex challenges. Technological advances and increased regulatory demands have boosted the complexity and costs of clinical research, creating an increased need for expensive resources like bioinformatics, specialized research training, and staffing for patient recruitment and regulatory compliance. In addition, many physicians who conduct clinical and translational research are strained by dramatic increases in clinical-service demands and declining financial margins, which tend to divert time and attention away from health-related research. As a result, many institutions have difficulties recruiting and retaining a sufficient number of clinical and translational researchers.

To address these problems and accelerate the translation of basic discoveries into improved therapies and clinical practice, NIH in October 2005 launched a new program of institutional Clinical and Translational Science Awards (CTSAs). Through these awards, academic health centers across the country will create individualized academic "homes" for clinical and translational science. "The CTSA Program is designed to spur what will be a fundamental transformation of clinical and translational research in the United States," says NIH Director Elias A. Zerhouni, M.D. "Our goal is to make sure that new treatments and insights into disease can be captured more efficiently and delivered more quickly to patients."

The CTSAs, administered by NCRR on behalf of the NIH Roadmap for Medical Research, encourage institutions to propose new approaches to clinical and translational research, including new organizational models and training programs at graduate and post-graduate levels. The grants also will foster original research to develop clinical research methodologies in areas such as informatics, laboratory methods, technology, and community-based research.



The new Clinical and Translational Science Awards are designed to improve patient care by more rapidly bringing new treatments and discoveries to the clinic.

LISTENING TO THE SCIENTIFIC COMMUNITY

Like other NIH Roadmap initiatives, the CTSA addresses issues that are critical to the missions of all NIH components but are beyond the scope of any single NIH institute or center. The NIH Roadmap—launched in 2003 and created in consultation with hundreds of biomedical scientists—identified three fundamental, cross-cutting research themes that could have a significant impact on human health: new pathways to discovery, research teams of the future, and re-engineering the clinical research enterprise.

MICHAEL KELLER/CORBIS

The latter served as the impetus for the CTSA Program. In ongoing forums and consultations, researchers and administrators described a need to transform clinical and translational science by creating a distinct discipline and an academic home at research institutions across the country.

In May 2005, an NIH-sponsored meeting brought together more than 300 members of the biomedical research community, who shared information about the frustrations and obstacles they encountered, as well as their optimism about the promise of translating basic discoveries into improved medical care. Participants generally agreed that a significant change was needed to enhance clinical and translational science. According to many attendees, institutional and programmatic boundaries had created fragmented research efforts, training programs, and resources that would be more effective if integrated.

at the May 2005 meeting. "Every place is different, so it's beneficial for institutions to have the flexibility to develop an organizational structure that's appropriate to their situation," Swain says.

The CTSAs were designed to support the full spectrum of clinical and translational science. Clinical research, as defined by the CTSA Program, includes studies and trials that involve human subjects. Translational research, however, has two key components. The first is the process of applying discoveries made in the laboratory, testing them in animals, and developing trials and studies for humans.

> "The CTSA Program was initiated to break existing barriers and, above all, to get people to work together to speed the delivery of improved health care to the public."

"The lack of centralized infrastructure has been a huge barrier to conducting clinical and translational research, which often requires expensive processes, facilities, and equipment," says Richard Rudick, a participant at the May 2005 meeting. Rudick is director of the Mellen Center for Multiple Sclerosis and chairman of the Division of Clinical Research at the Cleveland Clinic. "Another factor is that clinical and translational research requires a team approach, with multiple disciplines participating in the research endeavor. We have not had effective mechanisms for breaking down barriers between basic and clinical sciences to develop such research teams."

Comments such as these—gathered through multiple consultations with researchers and academic leaders—led NIH to launch the CTSA Program. "The development of the CTSAs truly came from listening to the research community," says NCRR Acting Director Barbara Alving. "We attempted to bring flexibility to the program by providing opportunities for institutions to design their own programs and develop a center, department, or institute of clinical and translational science."

This flexibility will be critical, says Judith Swain, director of the College of Integrated Life Sciences at the University of California, San Diego. She was among the many investigators who provided input

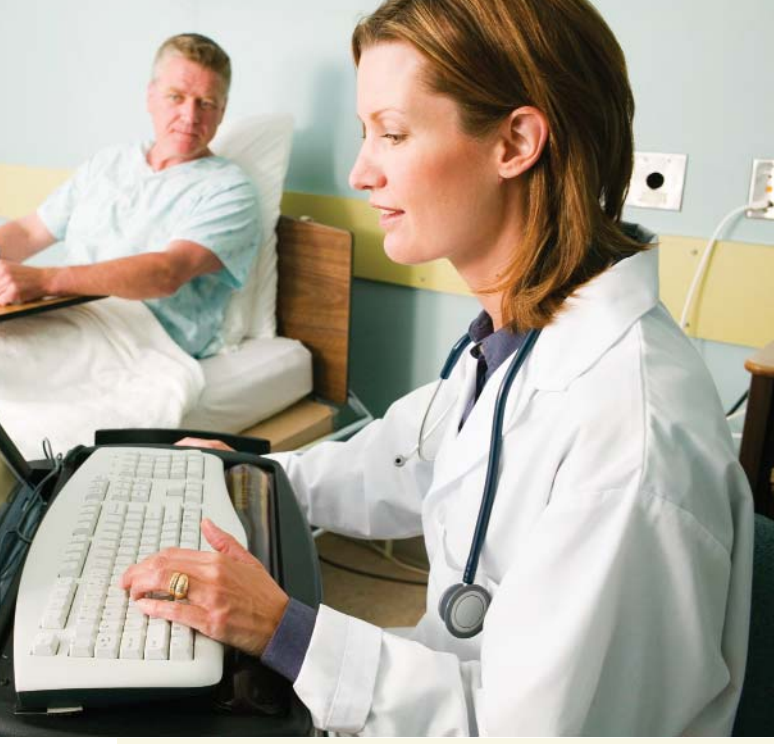
NIH Director Elias Zerhouni announced the creation of the new CTSA Program in October 2005. Developed with extensive input from the biomedical community, the program will create academic "homes" for clinical and translational science.

The second concerns research aimed at enhancing the adoption of best treatment practices into the medical community.

"The CTSA Program was initiated to break existing barriers and, above all, to get people to work together to speed the delivery of improved health care to the public," notes Anthony Hayward, director of NCRR's Division for Clinical Research Resources.

FORGING PARTNERSHIPS

As one aspect of working together, the CTSAs will create two-way synergies with local and regional communities, including the general population, community-based groups, and health-care providers. In one sense, the new academic homes will broaden the scope of their studies by collaborating with local communities. "An exciting aspect of the CTSA Program is its acknowledgment that academic health centers need to develop pipelines and partnerships with communities that reflect a diverse populace," says Gary Gibbons, director of the Cardiovascular Research Institute at Morehouse School of Medicine and a participant at the May 2005 meeting. "The CTSA Program recognizes that the medical school campus alone is not sufficient for conducting effective clinical and translational research. There must be links to



Biomedical informatics and computer-related technologies enchance the sharing of data across disciplines and across institutions, thus bringing diverse expertise and knowledge to bear on health-related problems.

communities to ensure that diverse populations, and clinical practitioners within those populations, are a part of addressing important health-related questions."

In return for the community's participation, the CTSAs will help to deliver improved medical care to the entire population. "In its broadest definition, translational research includes bringing important discoveries back to the communities by disseminating new technologies and new advances into clinical practice," according to Gibbons.

Partnerships with foundations and industry also will be crucial to moving discoveries to the clinic. "The CTSAs provide a platform for integrating the interests and the resources of academic health centers, foundations, industrial partners, and communities," Gibbons adds. "The flexibility of the program creates an open door for these kinds of partnerships, allowing us to look for opportunities where we can leverage resources and have a shared set of objectives that complements NIH's mission of public health delivery."

BIOMEDICAL INFORMATICS

Information technologies and biomedical informatics also create new opportunities for forging partnerships by enabling the sharing of data across disciplines and across institutions. "We absolutely need innovation and new approaches for applying information technologies to the research process," Rudick says. "The challenge is, how do we deal with the massive amount of information that comes from gene sequencing, gene expression, proteomic data, and metabolomics on the one hand, and connect that to data from a particular patient?" In addition, issues related to workflow, usability, and interoperability with collaborating organizations must be addressed, along with the need for ensuring the privacy and confidentiality of human subjects.

The CTSA Program will support the development of such innovations at the institutional level and also will create a nationwide forum in which biomedical informatics directors from all CTSAs will collaborate to develop standards, best practices, and solutions to informatics-related problems.

A LOOK TO THE FUTURE

A key component of each CTSA will be the creation of one or more graduate degree-granting and postgraduate programs in clinical and translational science, which will provide an enriched environment for educating and retaining the next generation of clinical and translational researchers. Through the CTSA Program, investigators will be trained in diverse disciplines such as pediatrics, surgery, dentistry, nursing, and pharmacology. Institutions will have the freedom to create educational programs that best fit their organizational structures and institutional strengths.

"Previous attempts to address the problem through specific grants that fund clinical research training have fallen short, because they were all individual pieces," says Swain. "The CTSA Program is transforming, because it puts the training pieces together within a cohesive and overarching structure, an academic home."

NCRR's Hayward agrees that the creation of well-integrated homes for clinical and translational science will ultimately transform clinical research and medical care. "With the implementation and awarding of CTSAs," Hayward says, "we expect to see clinical and translational research develop as a distinct discipline. We expect to see new opportunities appear. And we want to see, above all, support for the interdisciplinary teams who will conduct the clinical and translational research of the future." ■

TO LEARN MORE:

- NIH plans to award four to seven CTSAs in fiscal year 2006, for a total of approximately $30 million. In addition, a one-time solicitation for CTSA planning grants will give institutions more time to prepare a CTSA application in the future. Approximately 50 planning grants, totaling about $11.5 million, are expected to be awarded this year. The initial round of CTSA applications are due to NIH by March 27, 2006.
- NIH expects to increase the number of awards annually and to have 60 CTSAs in place by 2012. Funding for the CTSAs will come from the redirection of existing resources, including funds from the NIH Roadmap budget and from existing clinical and translational programs.
- For more information about the CTSA Program, visit the CTSA Web site at www.ncrr.nih.gov/clinicaldiscipline.asp.

JIM CRAIGMYLE/CORBIS (TOP)

Preclinical Primate Studies Help Bring New Discoveries to Patients

Studies of nonhuman primates are an essential component of translational research, allowing scientists to evaluate potential medical interventions in a nonhuman model before testing proceeds in patients. Many of today's life-saving medical treatments—including polio vaccines, AIDS-fighting drugs, and heart surgery techniques—depended on preliminary evaluation in nonhuman primates.

To enable preclinical animal-based investigations, NCRR supports a nationwide network of eight highly specialized research facilities known as the National Primate Research Centers (NPRCs), which house and care for a variety of nonhuman primates that are important to biomedical research. Each NPRC has experienced staff and appropriate research environments for studying and developing nonhuman primate models of human health and disease. As the articles below illustrate, the NPRCs make essential contributions to preclinical studies of experimental therapies, diagnostic tests, and imaging agents.

Safeguarding New Organs

For thousands of people waiting for kidney transplants, learning they are on top of the list may be good news. Yet soon after transplantation, patients are given a drug regimen that suppresses the immune system to prevent organ rejection. Although immunosuppressants have considerably increased one-year survival rates, these drugs have numerous side effects, including eventual damage to the new kidneys.

Physicians Thomas Pearson and Christian Larsen and their colleagues at the Yerkes NPRC in Atlanta have helped develop a new drug to circumvent this problem. Early clinical trials suggest that the experimental drug, known as belatacept, may be as effective as cyclosporine, the mainstay in immunosuppressive therapy for the past 20 years.

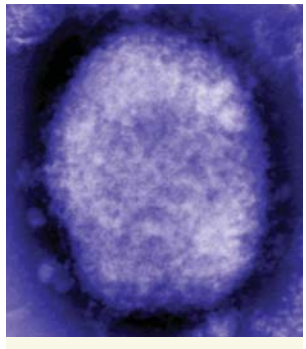
In preclinical studies conducted on nonhuman primates, Pearson and his colleagues found that belatacept effectively reduces the rate of rejection of transplanted kidneys. "The expertise and experience of the Yerkes research staff, as well as the physical facility and resources, greatly augmented the development of belatacept," says Pearson. Belatacept works by attenuating the immune system's activation of T cells that would attack the new kidney.

Pearson's preclinical findings laid an important foundation for evaluating the drug in humans. Recent Phase II clinical trials involving 218 kidney transplant patients found that acute rejection and infection frequency were similar whether patients received cyclosporine or belatacept. Those receiving belatacept, however, showed better kidney function than the group receiving cyclosporine. Also, one year after transplantation, kidney damage known as chronic allograft nephropathy was present in only 20 percent of patients receiving belatacept, compared with 44 percent of cyclosporine patients. "We are hopeful that Phase III trials will show similar results," says Pearson. If it reaches the market, belatacept could lead to improved long-term transplant and patient survival, he adds. (*American Journal of Transplantation* 5:443-453, 2005; *New England Journal of Medicine* 353:770-781, 2005)

—AL STAROPOLI

Diagnostic Tests for Highly Infectious Agents

Scientists at the Oregon NPRC developed a novel series of tests that show evidence of being more sensitive and accurate in diagnosing human monkeypox infections than current tests approved by the U.S. Centers for Disease Control and Prevention (CDC). The studies may lead to improved diagnoses, therapies, and preventive measures for monkeypox and other sometimes-deadly agents that might proliferate in a natural outbreak or a bioterror attack.



The monkeypox virus, shown here, can be deadly to humans. Diagnostic technologies and therapies developed for monkeypox might also apply to smallpox and related viruses.

JOHN KAPRIELIAN, COURTESY OF CDC/PHOTO RESEARCHERS, INC.

NPRC researchers Mark Slifka and Matt Lewis traveled to

Wisconsin to examine more than 40 individuals who had been exposed to the monkeypox virus, a close relative of the smallpox virus. In 2003, dozens of people in the Midwest had been exposed to pet prairie dogs infected with monkeypox, and 72 cases of human infections were later reported to the CDC.

The Oregon researchers used a unique series of diagnostic tests to confirm previously unverified human infections. The diagnostic series also identified an additional three individuals whose infections had been undiagnosed because they lacked obvious symptoms. These three people, having been vaccinated against smallpox more than a decade before, were fully protected against monkeypox disease.

Slifka notes that the biocontainment level-3 laboratory associated with the Oregon NPRC is one of the few in the country with the appropriate safeguards, expertise, and authorization to conduct experiments with monkeypox. "Our studies would not have been possible without access to the NPRC or the resources of the General Clinical Research Center, where some blood analyses were performed," Slifka says. "While this research primarily focused on monkeypox, this same technology could also be used to better detect a smallpox outbreak." Although smallpox no longer exists in nature, having been eradicated through effective worldwide vaccine programs, the virus is still considered a significant bioterror threat.

The technology and diagnostic platform developed through these experiments has now been licensed to an Oregon Health and Science University spin-off company, Najít Technologies, which specializes in developing effective diagnostics and antibody-based therapies against potential bioterrorism agents, as well as other rare and neglected diseases. (*Nature Medicine* 11:1005-1011, 2005) **—VICTORIA L. CONTIE**

Imaging Agent Aids Neurological Diagnoses

A novel brain-imaging agent first conceived more than a decade ago promises to allow early diagnosis of human neurological disorders and is now being evaluated in Phase II and III clinical trials. In the 1990s, Bertha Madras of the New England NPRC helped to create the new agent, called altropane, and demonstrated its clinical potential by using it to diagnose neurological abnormalities in monkeys.

Injected into the body, altropane binds to the dopamine transporter (DAT), a molecule that is produced exclusively by dopamine-containing cells in the brain, cells that are depleted in Parkinson's disease and are implicated in other neurological disorders. With certain types of brain-imaging scans, radiolabeled altropane reveals the amount and location of DAT molecules in the brain. Because DAT molecules reside almost exclusively on dopamine-producing cells, altropane neuroimaging reveals the density, location, and possibly the function of dopamine-producing neurons.

In human studies, the imaging agent known as altropane reveals differences in the brains of a healthy volunteer (top) and in patients with moderate (middle) and severe (bottom) Parkinson's disease.

Working with collaborators David Elmaleh and Alan Fischman at the Massachusetts General Hospital, Madras demonstrated in monkeys that altropane accumulates rapidly and selectively in brain regions rich in dopamine neurons. They also found that altropane could detect a loss of DAT sites—due to a depletion of dopamine-producing neurons—in monkeys that had a neurological condition analogous to Parkinson's disease in humans. Parkinson's symptoms arise from a progressive loss of dopamine neurons. Once the preclinical studies demonstrated a severe reduction of dopamine neurons in Parkinsonian monkeys, the clinical trials at the Massachusetts General Hospital followed shortly thereafter. An initial clinical study by the team showed that altropane allowed scientists to distinguish between people with and without Parkinson's disease, based on a marked reduction of DAT in the Parkinson's patients. A multicenter Phase III trial of altropane neuroimaging is currently evaluating the technique's ability to distinguish Parkinsonian from non-Parkinsonian tremors.

Altropane also may help to diagnose attention deficit hyperactivity disorder (ADHD), which is characterized by excess DAT in the brain (*Biological Psychiatry* 57:1293-1300, 2005). The team used altropane to detect an increase in DAT density in six adult ADHD patients. A larger study of altropane as a diagnostic agent for ADHD is underway. **—SCOTT J. BROWN**

Daring To Take Risks and Reap the Rewards

Innovative high-risk projects offer potential for health-related breakthroughs.

Medical advances often originate with a flash of creativity and a tolerance for risk. Recognizing that the safe bet is not always the best path when pursuing scientific knowledge, NCRR funds Exploratory/Developmental Research Projects, known as R21 grants, to give scientists the freedom to pursue innovative, high-risk scientific ideas, methods, or technologies that may ultimately lead to significant health-related payoffs. For instance, neuroscientist Paul Thompson depended on R21 funding to develop sophisticated computational tools for imaging and analyzing how diseases or adverse events affect the brain. A different R21 grant allowed geneticist Carl Pinkert to create a unique animal model for studying mitochondria disease, which has broad implications for human health.

NIH created the R21 funding mechanism to provide up to two years of support for the early and conceptual stages of innovative research projects. NCRR funds R21 grants in two broad categories: biomedical technology and comparative medicine.

At the University of California, Los Angeles, Thompson and his colleagues developed a novel computational framework that effectively stretches, contorts, and changes the geometry of highly detailed three-dimensional brain images obtained via magnetic resonance imaging (MRI). These manipulations allow scientists to overlap and meld multiple brain images, collected over time or from multiple individuals, and enable comparisons between normal and dysfunctional brains. To date, the images have clearly revealed the changes wrought by Alzheimer's disease, methamphetamine abuse, schizophrenia, and AIDS. "With R21 funding, we developed new mathematical methods for understanding the effects of disease," says Thompson, an associate professor of neurology. "These images are really snapshots of a disease spreading over time."

In Alzheimer's disease, for example, MRIs collected every six months showed the brain's outer layer, or cortex, becoming thinner as the condition progressed. Because the new methods can detect even the tiniest brain changes as neurodegenerative processes begin, patients may benefit from earlier diagnosis and treatment.

Other studies used MRI scans to compare the brains of methamphetamine users to healthy adults. The drug users showed specific patterns of tissue loss in areas that control craving, emotion, and reward. Those brain regions may lose up to 10 percent of their tissue over time, a finding that may explain a user's quest for increasingly higher doses to maintain a high. Methamphetamine also eats away at the hippocampal regions that control learning and memory, impairing both.

The mathematical algorithms developed with R21 funding also are shedding light on human immunodeficiency virus (HIV) infections. Although many studies have examined the pathogenesis, transmission, and treatment of AIDS, scientists know surprisingly little about how HIV, the AIDS-causing virus, affects the brain. "Part of the problem is that most imaging techniques are not quite sensitive enough yet," Thompson says. But with the new brain-mapping algorithms, Thompson and his colleagues were able to detect subtle differences between uninfected and HIV-positive individuals, revealing destruction of brain regions that control motor, language, and sensory functions. "This helps to explain the slowed reflexes and disruption of balance and gait that often affect people with early AIDS," says Thompson.

"Some of the current mathematical work is to find features in images that can gauge the impact of disease and response to therapy," Thompson adds. "For instance, the scans can test a new drug's ability to penetrate the brain during clinical trials." By mapping a series of brain images after a patient

Innovative brain-mapping techniques allow scientists to detect subtle disease-associated brain changes, including percentages of brain tissue loss, represented by different colors, in AIDS patients.

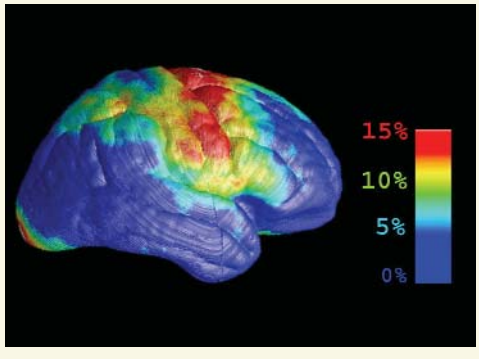


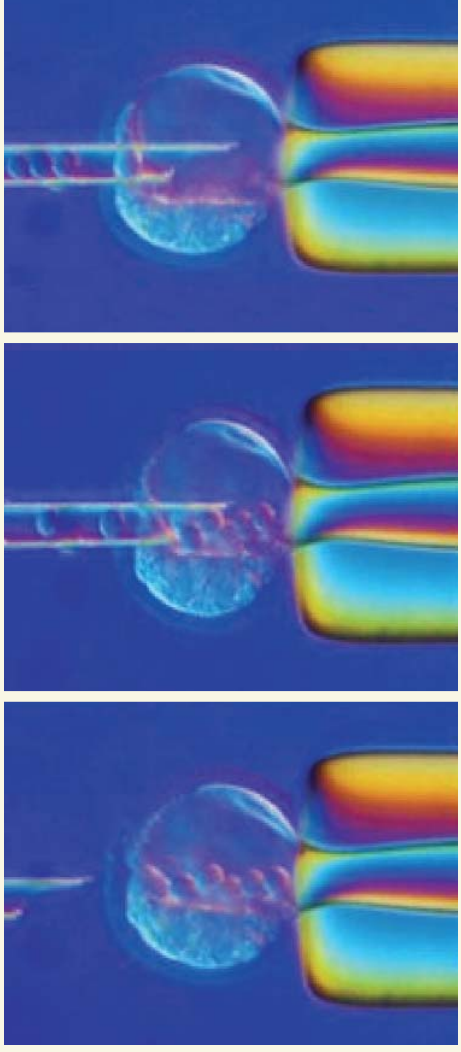
IMAGE COURTESY OF THE LABORATORY OF NEURO IMAGING, UNIVERSITY OF CALIFORNIA, LOS ANGELES

receives a drug, clinicians can more rapidly track the effectiveness of a medication. "A lot of the modeling work we've done for the R21 project was demonstrating that these new computational tools might be better than other techniques that are currently used. And when they aren't better, we go back to the drawing board."

Going back to the drawing board can be the standard operating procedure for exploratory research projects, says Carl Pinkert, a professor of pathology and laboratory medicine at the University of Rochester Medical Center in New York. His proposed R21 project—to create methods for producing transgenic mouse models that would enhance understanding of human mitochondrial disorders—was deemed high-risk in part because no such models had yet been made, despite concerted efforts by several research groups. Still, such models were recognized as highly desirable.

"Every living cell contains hundreds to thousands of mitochondria," says Pinkert. These organelles are the cell's major energy source for life processes. Mitochondria are so critical, Pinkert adds, "that if they become functionally impaired, they are implicated in a long list of diseases, from lethal neonatal deficiencies to causal relationships associated with neurodegeneration and aging." (For more information on human mitochondrial disorders, see the *NCRR Reporter*, Winter 2005, pages 12-13.)

For decades, scientists have had the ability to create genetically engineered mice by altering the DNA within the nucleus of a fertilized mouse egg. The nucleus presents a comparatively simple, one-target site for genetic manipulation. In contrast, modifying the DNA that is housed within each cell's thousands of mitochondria—known as mitochondrial DNA, or mtDNA—has long presented a technological hurdle. The tiny double-stranded, circular mtDNA and genes are distinct from the DNA found in the chromosomes of the nucleus, so conventional genetics tools and techniques do not apply. Pinkert knew that unique technologies and methods must be developed to engineer new mouse models for studying mitochondrial disorders.



Researchers used R21 funding to develop a technique for genetically engineering mice with "transplanted" mitochondria. A multicelled mouse embryo (central sphere in all three images) is injected (from the left) with embryonic stem cells that contain mitochondria from another mouse species. A micropipette (at right in all three images) holds the embryo in place during the injection. The altered mouse embryo is then transplanted into a female mouse for further development and birthing.

R21 funding allowed Pinkert, with his colleague Ian Trounce in Australia, to conduct experiments that led to the first viable mice genetically engineered to contain mitochondria from another species. Starting with embryonic stem cells from the domestic mouse, the scientists destroyed the mitochondria within and then reconstituted the cells with mitochondria from other species. The altered stem cells were then added to more than 1,000 multicelled mouse embryos. Female mice born with cross-species mtDNA were bred and produced six "germline" offspring (from four separate lineages) that contained only the introduced mitochondria—in effect, "transplanted" mitochondria—from another species. Only two of the six transmitochondrial offspring were females, and one lived to generate a line now used in developmental and neurodegenerative research.

The study was essentially a proof-of-principle that led to further refinement of the approach and additional mitochondrial experimentation by Pinkert and other research teams. "Without the R21, the early work fundamental to developing these animal models would have been put on a back burner," Pinkert says. A few laboratories have since produced several mouse populations that harbor specific mutations or modified mtDNA. "The R21 was crucial in doing this. It was high risk, innovative at the time, and it still has a number of hurdles to address," Pinkert adds. "But now we have models that we can evaluate, providing a critical advance for medical research."

—SHARON GIDDINGS

APPLY FOR FUNDING: NCRR, along with other NIH components, awards investigator-initiated Exploratory/Developmental Research Grants (R21s) to provide up to two years of funding for the early and conceptual stages of innovative, high-risk projects that may offer a significant payoff for biomedical science. In some cases, a Phase II Exploratory Development Grant (R33) can provide interim funding until an investigator-initiated Research Project Grant (R01) can be secured. Applications are now being accepted for novel projects to enhance animal stem cell research (http://grants.nih.gov/grants/guide/pa-files/PA-04-125.html). For the NIH Program Announcement related to R21 funding, visit http://grants1.nih.gov/grants/guide/pa-files/PA-03-107.html.

IMAGES COURTESY OF CARL PINKERT, UNIVERSITY OF ROCHESTER MEDICAL CENTER

Ahead of the Curve

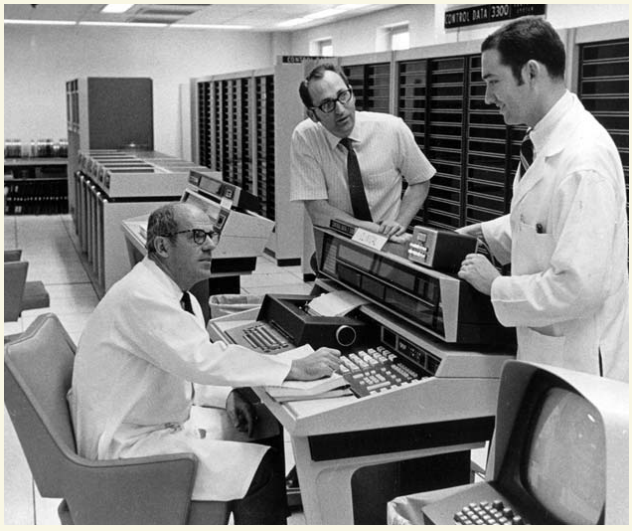
Pioneering the use of information technology in patient care.

Although information technology is now common in many hospitals and biomedical laboratories, in the 1950s only a small number of researchers imagined its enormous potential. In 1967, supported by NCRR, physician Homer Warner led a seminal effort that created one of the first bioinformatics systems. This work has influenced patient care, increased safety, and produced cost-effective service in hospitals around the nation. Today, NCRR continues its support of clinical bioinformatics as an integral component of the new Clinical and Translational Science Awards.

Clinical application of bioinformatics began in earnest when the University of Utah installed a state-of-the-art computer in the early 1960s. Back then, Warner became intrigued by the possibility of using this new technology with patients at the Latter-day Saints (LDS) Hospital. It wasn't long before he gained access to the giant machine and began writing programs to study coronary blood flow. Because the computer was only available at night, he set a cot beside it to sleep while the computer slowly crunched numbers.

One of the central questions in his mind was how to obtain around-the-clock physiological information from post-operative cardiac patients. Warner resolved this problem by inserting catheters into patients' arteries. When connected through a computer, the apparatus calculated stroke volume, heart rate, cardiac output, and blood pressure on demand. Resulting data were displayed on the screen of an oscilloscope, and three small lights alerted nurses of abnormal vital signs that could lead to complications. This was one of the first uses of computers for preemptive patient monitoring, a concept now propagated through nearly every intensive care unit.

By the late 1960s, Warner obtained an NCRR grant to develop a computer facility for the medical community. Through this award he acquired one of the first Control Data 3200 computers. "The CD 3200 was an amazing machine for its time," says Warner. "There was a total of 64K in the whole machine and it filled a 20-by-20-foot room, which required under-floor air conditioning." Nonetheless, it was lightning



Physician Homer Warner (seated) consults with colleagues Alan Pryor (center) and Reed Gardner in 1970—in the early days of hospital information technology.

fast for its time, with an ability to perform 800 calculations every second. The system placed LDS Hospital ahead of the curve. "We had visitors coming from all over the world to see our system," adds Warner.

As computer systems advanced, so did Warner's ideas. In the 1970s, using the CD 3200 computer, he developed a hospital information system named HELP (Health Evaluation through Logical Processing), which collected extensive patient data. The system eventually grew to incorporate information from various parts of the hospital—laboratory results, pharmacy prescriptions, nursing care plans, surgery schedules, and accounting—thus creating one of the first integrated clinical systems. This integrative approach to organizing and storing patient information gave health professionals access to the totality of records in one system, which supported their decision making.

In the late 1980s, HELP benefited thousands of patients. At LDS Hospital, automated prescription of antibiotics to surgical patients decreased the rate of adverse drug events by 30 percent and halved the cost of antibiotics per patient. In addition, in-hospital mortality dropped significantly. Almost 40 years later, Warner's initial technology gamble paid off handsomely by demonstrating how it could not only improve lives, but also save them.

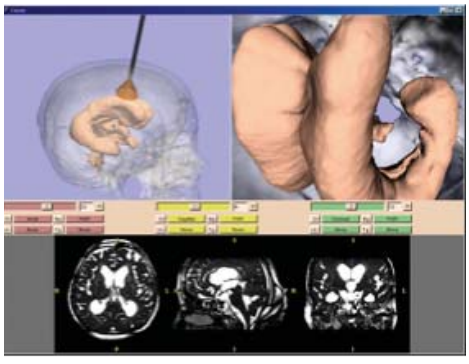
—AL STAROPOLI

PHOTO COURTESY OF LDS HOSPITAL

NCRR Funds New National Technology Centers

Evolving technologies allow scientists to peer into the most hidden reaches of the human body. NCRR continues to support development of such technologies by funding two national centers focused on imaging and carbohydrate biochemistry.

Brigham and Women's Hospital of Boston will receive $15 million over five years to establish a national Image Guided Therapy Center. This unique resource will allow physicians to see deep beneath the skin during surgical procedures through imaging techniques such as CT scanning, ultrasound, and endoscopy. The technology will allow surgeons to navigate instruments inside the body through small incisions, thereby reducing bleeding and infection. The National Cancer Institute and the National Institute of Biomedical Imaging and Bioengineering cofund this award.



Software combines multiple medical images, allowing surgeons to navigate minute tools during delicate brain surgery.

Indiana University in Bloomington will receive $3.2 million over three years to launch the National Center for Glycomics and Glycoproteomics, which will study sugars, but not the ones in foods. These are complex signaling molecules found throughout our bodies, and they are critical for reproduction, growth and development, and our ability to fight infection. The center will create and share new tools to unravel the structures of these molecules and how they work. Scientists will use these to study both basic biology and diseases from cancer to alcoholism. ■

Grants Enhance Research Facilities

Ten institutions nationwide received awards totaling $30 million from NCRR's Research Facilities Improvement Program. The grants will allow construction of new laboratory space and upgrades to research-imaging facilities, among other improvements. "These investments in research facilities are vital to our nation's ability to conduct cutting-edge biomedical research, including efforts to address AIDS, cancer, Alzheimer's disease, diabetes, and many other major illnesses," says Barbara Alving, NCRR's acting director.

Students learn about the cardiovascular system at Maryland Science Center in Baltimore.

The awards will fund construction for several new facilities, including a behavioral research center at the University of North Dakota; a women's cancer laboratory at the University of California, Irvine; and a center for human genetics at the University of Pennsylvania. ■

Bringing Science to the Public

Whether learning about the genome, transmission of Lyme disease, or diabetes, pre-college students across the country will be immersed in science as part of a series of awards to encourage research careers and increase science literacy.

Through the Science Education Partnership Awards (SEPA) Program, NCRR has awarded nearly $23 million toward the funding of 21 science education projects in 2005. SEPA projects aim to generate enthusiasm about health and science research by exposing pre-college students, their families, and the public to science through a variety of activities. "By giving students the chance to participate in hands-on, inquiry-based research projects, we hope to demystify science and make it more accessible," says Barbara Alving, acting director of NCRR.

SEPA grants provide from two to five years of support for implementing projects in partnership with educators, researchers, or community groups. SEPA grants sponsor projects at health science centers, universities, K-12 schools, science museums, and community organizations across the country. For more information, visit www.ncrrsepa.org. ■

[CONTINUED ON BACK COVER ➤]

PHOTO COURTESY OF BRIGHAM AND WOMEN'S HOSPITAL (LEFT)
PHOTO COURTESY OF MARYLAND SCIENCE CENTER (TOP RIGHT)

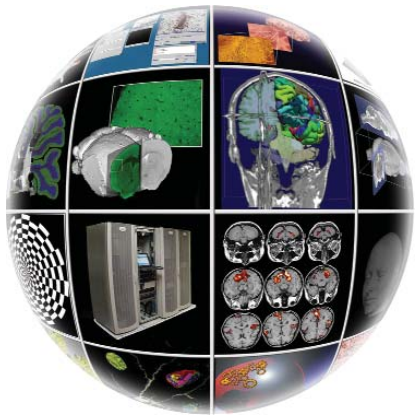
[CONTINUED FROM PAGE 11]

Neuroimaging Tools and Data Available on Web

A roving band of five unnamed researcher participants—who traveled across the country to nine different sites to have their brains examined via MRI—has contributed to a first-of-its-kind neuroimaging dataset that will help scientists to standardize and calibrate imaging data for multisite studies for years to come. The dataset, known as the Function BIRN Phase I Traveling Subjects Dataset, is the latest of more than two dozen open-source data and software tools made available to scientists worldwide by the Biomedical Informatics Research Network (BIRN).

Created in 2001 with NCRR support, BIRN is a national consortium of 28 research institutions and 37 research groups dedicated to creating a usable cyberinfrastructure that shares and integrates data, expertise, and unique technologies from multiple disciplines and research institutions thereby enabling collaborations that address complex health-related problems. (For more information, see the *NCRR Reporter*, Fall 2003, pages 5-7.) Initial efforts focus on neuroimaging data, but the tools and technologies developed by BIRN will ultimately be applicable to other disciplines.

Calibration across sites is important, because brain scans from a single individual can appear surprisingly dissimilar when collected using different MRI instruments and methodologies. "In fact, we found there is more variation between sites than there is between subjects," says Steven Potkin, professor of psychiatry at the University of California, Irvine, and head of a series of BIRN projects related to functional imaging. "Unless this can be corrected, there is no point in doing a multisite imaging study."



The Biomedical Informatics Research Network has developed open-source neuroimaging tools and datasets available to researchers around the world as they investigate the causes and potential therapies for Alzheimer's disease, schizophrenia, and other brain-related disorders.

IMAGE COURTESY OF THE BIRN COORDINATING CENTER, UNIVERSITY OF CALIFORNIA, SAN DIEGO

The Phase I study of five subjects allowed the Function BIRN research teams to develop techniques that greatly reduce intersite variability, thus laying a solid foundation for Phase II, which will interpret functional neuroimaging datasets from more than 200 subjects examined at MRI facilities nationwide.

Other datasets and tools available for download at the BIRN Web site include data analysis software for correcting image distortions, software for de-indentifying MRI images, data management tools for large and diverse clinical neuroimaging research projects, and several datasets related to the mouse brain. On the horizon is a new BIRN project that will focus on neuroimaging of nonhuman primates. To learn more about BIRN's open-source software and data, visit http://nbirn.net/Resources/Downloads/. ■

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