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Summer/Fall 2005

CRITICAL RESOURCES FOR YOUR RESEARC

Minority Research Program Celebrates 20 Years

FROM THE DIRECTOR

RCMI—Celebrating 20 Years of Achievement

THIS ISSUE OF THE NCRR REPORTER commemorates the 20th anniversary of the Research Centers in Minority Institutions (RCMI) Program and the achievements of the RCMI scientists around the nation.

When Congress appropriated funds to create the RCMI program 20 years ago, it called attention to the disparities in the health status between minority and majority Americans. Today in the United States, infant mortality, diabetes, stroke, AIDS, heart disease, and a variety of cancers continue to claim a disproportionate toll on minority populations. However, as the articles that follow demonstrate, RCMI researchers have made critical contributions to addressing the health issues in minority populations. Examples of their efforts are seen in improved treatments for AIDS, heart failure, kidney disease, and many other areas of biomedical research.

In creating the program, the Congress also emphasized the important role that minority institutions have traditionally played in training professionals who provide health care to minority communities. Over the past two decades, RCMIs have maintained that tradition, training nearly 36 percent of the minority Ph.D.s in biomedical and behaviorial sciences and more than 30 percent of the minority M.D.s in the United States, as reported in FY 2003.

Numerous NIH Institutes and Centers have provided cofunding to RCMI activities, and these contributions also are recognized in the articles that follow. As with all research endeavors, collaboration is essential. We at NIH, and especially at NCRR, congratulate the RCMI researchers and administrators, and we look forward to their future achievements.

Barbara Alving, M.D.

Barbara Alving, M.D.
Acting Director, NCRR

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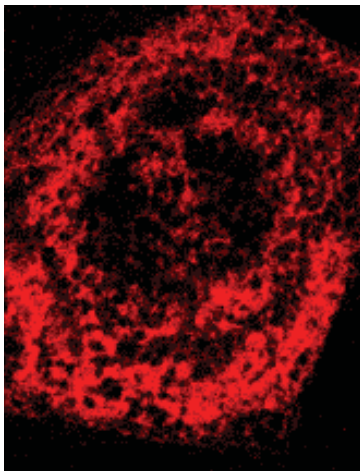
CRITICAL RESOURCES

SCIENCE ADVANCES



Research to Reality

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.

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On the Cover: Physician Keith Norris heads an effort to translate research findings into improved outcomes for patients susceptible to chronic kidney disease, which disproportionately affects minority populations. NCRR's Research Centers in Minority Institutions Program—now celebrating its 20th anniversary—strengthens this type of biomedical research at minority institutions nationwide.

PHOTO BY JOE TORENO

QUICK TAKES

New tools and updates from NCRR resources

Clinicians collected blood samples and medical information from women runners during a national fundraiser for breast cancer research. The samples will aid a large study of the genetics of breast cancer.

Breast Cancer Research Goes to the Races

When researchers at Indiana University School of Medicine were looking for volunteer participants for a clinical study of the genetic differences between women with and without breast cancer, they set up a booth at a pavilion near the local Komen Race for the Cure, a national event to raise funds for breast cancer research. The strategy paid off: The team collected 850 blood samples in one afternoon from women participating in the race. The effort succeeded thanks in part to the university's General Clinical Research Center (GCRC) staff, who helped take blood samples and gather data. GCRC laboratories now are performing DNA extraction and genotyping the samples to determine if breast cancer patients have unique variations in genes associated with the creation of new blood vessels.

Health Educators Travel to China

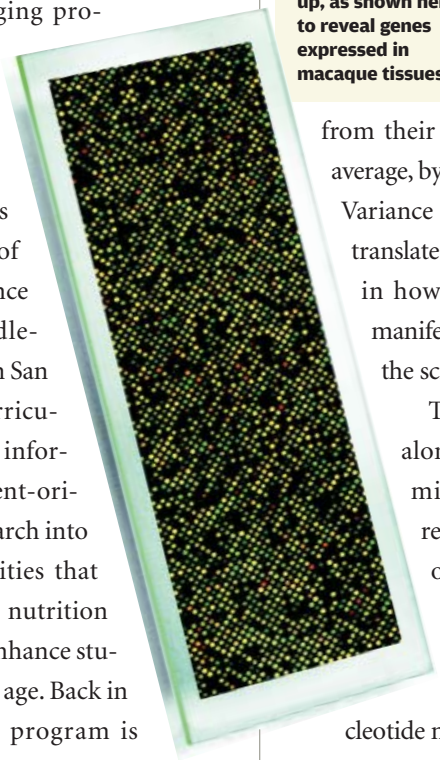
A successful NCRR-funded Science Education Partnership Award (SEPA) called Positively Aging, designed to teach middle-school students to make healthy lifestyle decisions, visited China earlier this year. At a three-day workshop at South Normal China University in Guangzhou, U.S. educators introduced more than 300 Chinese school teachers to this innovative, hands-on curriculum, which has been presented to hundreds of K-12 school teachers in the United States.

The Positively Aging program is developed and disseminated by an interdisciplinary team of scientists at the University of Texas Health Science Center and middle-school educators in San Antonio. The curriculum incorporates information from patient-oriented clinical research into educational activities that demonstrate how nutrition and exercise can enhance students' lives as they age. Back in South Texas, the program is continually used, evaluated, and updated at 14 schools that enroll primarily Hispanic students. All curricular materials are available on the Web at http://teachhealthk-12.uthscsa.edu.

Genomic Tools Aid Primate Studies

New genomic tools have begun to specify the genetic differences between humans and rhesus macaque monkeys, providing vital information for rhesus models of human disease, development, and behavior.

NCRR-supported researchers at Illumigen Biosciences, Inc., and the Washington National Primate Research Center (NPRC) in Seattle, along with their colleagues, have developed and sequenced more than 48,000 complementary DNA (cDNA) clones representing genes expressed, or turned on, in macaque tissues. An analysis of those sequences, published June 30 in *Genome Biology,* shows that macaque genes diverge from their human counterparts, on average, by 2.2 percent to 4.9 percent. Variance of that magnitude might translate into significant differences in how humans and macaques manifest and respond to disease, the scientists say.



Oligonucleotide probes on new rhesus microarrays will light up, as shown here, to reveal genes expressed in macaque tissues.

The macaque cDNAs—along with sequences determined by NCRR-funded researchers at the University of Nebraska Medical Center and the Oregon NPRC—also have been employed to construct oligonucleotide microarrays that greatly aid studies of gene expression (see *NCRR Reporter,* Spring 2005, pages 4-6). Further details on the macaque cDNAs and microarrays are available at www.macaque.org and http://rhesusgenechip.unomaha.edu. ■

PHOTO BY REBECCA L. FLETCHER, INDIANA UNIVERSITY SCHOOL OF MEDICINE (TOP LEFT); IMAGE COURTESY OF AGILENT TECHNOLOGIES (RIGHT)

Minority Research Program Celebrates 20 Productive Years

Collaborations enhance efforts to address health disparities.

BY SCOTT J. BROWN

James Hildreth came home this summer—or as he puts it, as close to his Arkansas boyhood home as he could get and still do his AIDS research. Hildreth, an African American scientist, moved from Johns Hopkins University in Baltimore to Meharry Medical College in Nashville to direct the college's new NCRR-supported Center for Health Disparities Research in HIV. He joins Meharry at a historic time. NCRR's Research Centers in Minority Institutions (RCMI) Program, which supports research at Meharry and 17 other minority colleges and universities, celebrates its 20th anniversary this year.

Begun in 1985, the RCMI Program was developed by NIH to address health disparities between the nation's minority and majority populations, and it continues to spearhead that objective, says Sidney McNairy, the RCMI Program's first director. "Through the RCMI Program, NCRR has developed the critical infrastructure needed for minority institutions to be competitive and has laid the groundwork for collaborative, trans-NIH efforts to deal with health disparities," says McNairy, who today is director of NCRR's Division of Research Infrastructure, which administers the RCMI Program.

RCMI funding supports institutions in the United States and Puerto Rico that grant doctoral degrees in health-related fields and that have a 50 percent or greater enrollment of students from minority communities underrepresented in the biomedical sciences—African Americans, Hispanics, Native Americans, Alaskan Natives, Native Hawaiians, and Pacific Islanders. The program supports research infrastructure; funds research projects, many of which target diseases that disproportionately affect minority populations; and supports faculty development.

In collaboration with other NIH Institutes and Centers, NCRR has launched several important new initiatives at RCMI institutions. These collaborative efforts build upon the successes of the RCMI Program over the past two decades and position the program to further improve the health of the nation in the years ahead.

CENTERS TACKLE HEALTH DISPARITIES

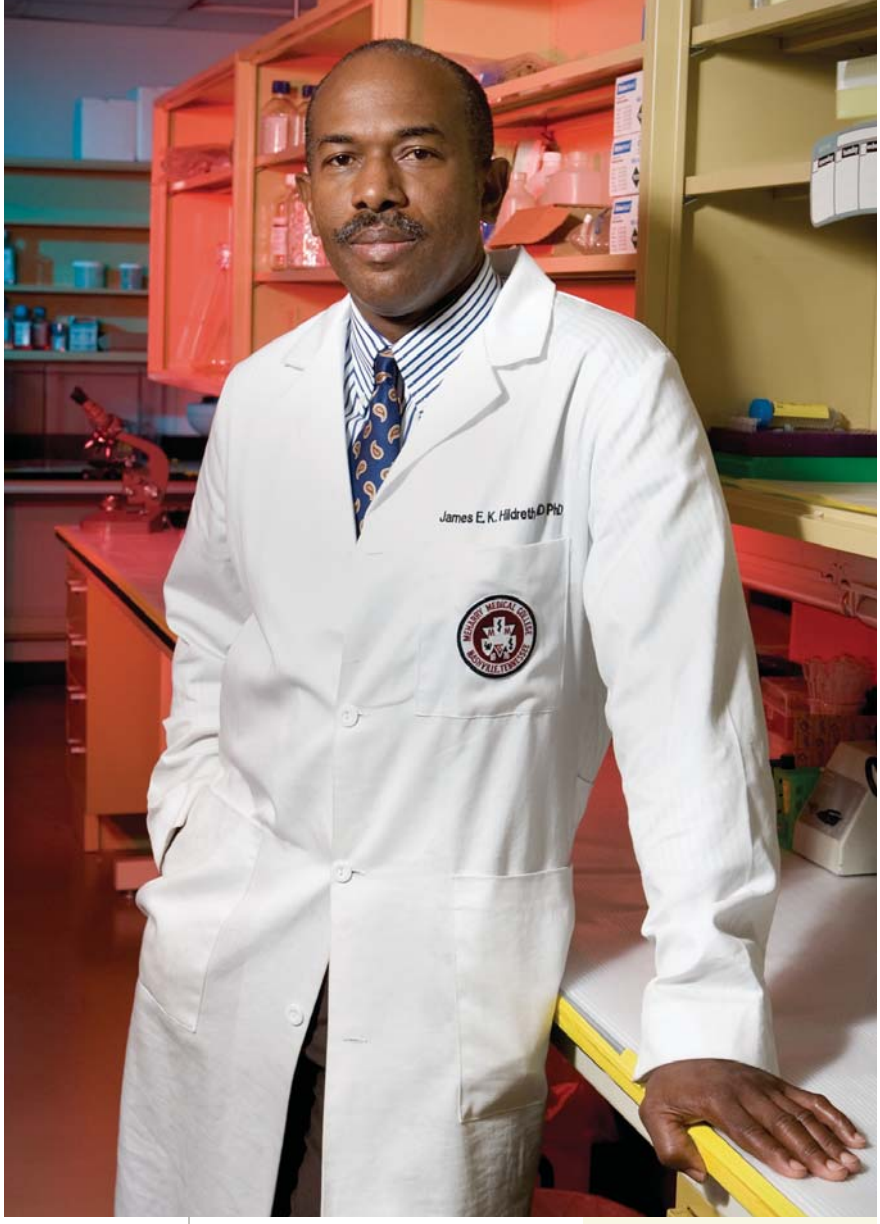
One of those collaborative efforts is what brought James Hildreth to Nashville. The Meharry Center for Health Disparities Research in HIV that he now directs is one of three Comprehensive Centers on Health Disparities (CCHDs) that NCRR established at RCMI institutions in 2003. The National Institute of Mental Health (NIMH) and the National Institute of Allergy and Infectious Diseases (NIAID) help NCRR support the Meharry CCHD. They also cofund another CCHD targeting HIV, run collectively in Puerto Rico by the University of Puerto Rico Medical Sciences Campus, the Ponce School of Medicine, and the Universidad Central del Caribe. A third CCHD, at Charles R. Drew University of Medicine and Science in Los Angeles, targets chronic kidney disease.

By forging collaborations among basic scientists, clinical investigators, and community health centers, the CCHDs strive

to quickly bring the results of their health disparities research into affected communities. Community health centers will play a crucial role in CCHD efforts to translate research findings into improved patient outcomes, because many individuals affected by health disparities receive care at those centers.

"We're taking a comprehensive approach, looking at the spectrum of chronic kidney disease, from basic molecular mechanisms to clinical studies to community-based approaches," says Keith Norris, director of the CCHD at Drew University. "We will take what we learn and try to transform that knowledge into effective health policy that will benefit all populations."

The Drew CCHD, located in a predominantly African American and Hispanic community, is in a prime position to target chronic kidney disease, which disproportionately affects minority populations. In collaboration with researchers at the University of California, Los Angeles, and the RAND Corporation, the Drew CCHD is working with communities to find ways to improve outcomes and better prevent kidney disease risk factors such as diabetes and hypertension.



James Hildreth heads efforts to reduce HIV infection and AIDS among African American women through research and community education programs.

The two CCHDs that address HIV and AIDS focus on specific minority populations hit particularly hard by the AIDS epidemic. Puerto Rico has always been among the top five U.S. jurisdictions in AIDS cases per capita, notes Carmen Zorrilla, who codirects the Puerto Rico Comprehensive Center for the Study of HIV Disparities. The CCHD has brought together all three accredited medical schools in Puerto Rico for the first time, says Zorrilla, enhancing their research infrastructure and capacity. "The center will encourage and support research that will develop culturally appropriate prevention and intervention programs targeted to the Puerto Rican population," she says. "It also will help the community of investigators in Puerto Rico to advance their career interests related to HIV and will establish a tradition of collaboration to benefit future generations of Puerto Rican researchers."

Three pilot projects launched by the CCHD are testing various HIV prevention and intervention strategies relevant to Puerto Rican communities. One project is investigating ways to prevent another disease that disproportionately affects Puerto Ricans—hepatitis C virus infection, which often co-occurs with, and exacerbates, HIV infection. Another project is evaluating a rapid test for HIV diagnosis. The third project is addressing a purported link between feelings of stigmatization in people abused as children and poor adherence to HIV therapy.

The other AIDS-related CCHD, located at Meharry Medical College, focuses on African American women. "More than half of the new HIV/AIDS cases in the U.S. occur among African Americans, but if you consider women, the disparity is even more stark," says Hildreth, who serves as program director for Meharry's RCMI, in addition to directing the college's CCHD. Roughly two-thirds to three-quarters of new HIV cases in women occur among African Americans, he says.

The Meharry CCHD examines biological factors that may explain racial disparities in HIV infection. It also considers behavioral factors that put African Americans at higher risk for the disease. The CCHD plans to use community health organizations to

PHOTO COURTESY OF MEHARRY MEDICAL COLLEGE

educate the local African American population about HIV. Community organizations also will help recruit patients for CCHD clinical trials, which will test potential HIV vaccines and a possible anti-HIV microbicide, or "chemical condom." When applied as a vaginal cream, the microbicide may protect women from HIV infection.

"The RCMI at Meharry is going to be critical to our efforts," says Hildreth. The RCMI Clinical Research Center will provide statistical support and help enroll women for the clinical studies, he adds. CCHD activities also will be aided by the Center for Women's Health Research at Meharry, cofunded by the National Institute of Child Health and Human Development (NICHD) and NCRR.

A vital aspect of the CCHD, Hildreth says, is the training it provides to minority students and investigators. "The best and the brightest come in all hues and all ethnicities," he says. "The ultimate outcome of this is going to be that the pipeline of minority investigators—and even nonminority investigators—interested in health disparities will increase."

At the University of Puerto Rico Medical Sciences Campus, RCMI Director Emma Fernandez-Repollet and Associate Director José Conde oversee programs that address AIDS and other health disparities affecting Puerto Ricans.

DEVELOPING CULTURALLY COMPETENT CLINICAL RESEARCHERS

Another RCMI-related program addresses, even more directly, the need to increase the number of clinical investigators. In 2003, NCRR began administering the Clinical Research Education and Career Development (CRECD) awards program, which supports master's degree programs in clinical research. NCRR, in collaboration with seven other Institutes and Centers of NIH, awards CRECD grants to institutions that enroll 50 percent or greater minorities underrepresented in the biomedical sciences. The grants provide five years of funding to develop programs that train doctoral and

RCMI Research Advances Human Health

Since its inception 20 years ago, the Research Centers in Minority Institutions (RCMI) Program has tackled some of the nation's most difficult health issues. The stories that follow describe just a small sampling of the research conducted by RCMI-affiliated scientists who are making significant contributions to biomedical research and human health. In the area of cardiovascular disease, RCMI-supported scientists have helped to demonstrate the efficacy of a new heart failure medication for African Americans. Other RCMI-supported investigations aim to reverse paralysis in patients with spinal cord injuries. RCMI researchers also are tackling HIV infection, studying how HIV evolves resistance to antiretroviral therapy, and investigating an HIV protein that destroys immune-system cells.

These advances and others enabled by the RCMI Program illustrate the value of RCMIs and the minority institutions they support. In its 20th anniversary year, the RCMI Program looks forward to achieving many more biomedical advances in the years ahead.

Advancing Heart Failure Therapy for African Americans

The Food and Drug Administration recently approved use of the drug BiDil for African Americans with heart failure—the first time a drug has been approved for a particular racial group. The approval stemmed in part from results of the African-American Heart Failure Trial (A-HeFT), which examined the efficacy of BiDil among 1,050 African American patients with severe heart failure. RCMI Clinical Research Centers at Morehouse School of Medicine and Meharry Medical College were among 161 centers that studied A-HeFT participants.

In the study, the rate of death from any cause fell 43 percent among patients given

PHOTO BY JOSE JIMENEZ, UNIVERSITY OF PUERTO RICO MEDICAL SCIENCES CAMPUS

postdoctoral candidates in clinical research, with a focus on health disparity issues.

Five RCMI institutions currently have CRECD awards: the University of Puerto Rico, Medical Sciences Campus; Meharry Medical College; Charles R. Drew University of Medicine and Science; Morehouse School of Medicine in Atlanta; and the University of Hawaii at Manoa.

In 2002, almost one-third of minority students earning medical degrees, and 25 percent of those awarded doctorates in the biological sciences, received those degrees from RCMI-affiliated graduate and medical schools, notes NCRR's McNairy. "What better place to produce minority clinical investigators than at these institutions, which have in their grasp this talent pool, this untapped resource," he says.

The master's degree program in clinical research at the University of Hawaii illustrates the value of CRECD awards. The Hawaii program focuses on Asian, Pacific Islander, and Filipino populations in the state, whose health disparity issues include cardiovascular disease, asthma, diabetes, obesity, substance abuse, and oral health problems. "People think of Hawaii as a wonderful vacation paradise, but it is very resource poor in terms of the ability to deal with many health research issues," says Rosanne Harrigan, principal investigator of the program. "We feel very fortunate to have this CRECD program, and so do our students."

Minority institutions around the country hosted events to celebrate the RCMI Program's 20th anniversary. At a mini-symposium at Clark Atlanta University, participants examine a student poster dealing with prostate cancer in African Americans.

Through the master's program, students become culturally competent clinical researchers, leaders, and communicators, Harrigan says, able to effectively interact with people from diverse backgrounds. Students also learn to analyze clinical research literature, to answer clinical research questions with appropriate methodologies, to conduct ethically responsible

BiDil on top of standard therapy for heart failure. In addition, the rate of first hospitalization for heart failure was 33 percent lower among BiDil recipients than among patients given placebo plus standard treatment. Patients receiving BiDil also reported greater improvement in quality of life. (*New England Journal of Medicine* 351:2049-2057, 2004)

"Having a drug that significantly improves morbidity and mortality in African Americans with heart failure is a major breakthrough," says Theodore Addai, principal investigator for A-HeFT at Meharry Medical College. Addai notes that the prevalence of heart failure and the premature death rate from heart disease are high among African Americans compared to other racial groups.

BiDil actually consists of two drugs—hydralazine, an antihypertensive agent, and isosorbide dinitrate, used to treat angina. The two drugs act together to raise blood levels of nitric oxide, which helps ailing hearts. Some evidence indicates that the increased risk for heart failure among African Americans arises from a deficiency of nitric oxide.

"The A-HeFT study represents a major advance in heart failure care," says Elizabeth Ofili, principal investigator for A-HeFT at Morehouse School of Medicine. "In addition to the outstanding recruitment and retention of high-risk African American patients—including 40 percent women—and the remarkable survival advantage, this trial has opened the door to testing therapies that potentially impact newly recognized disease mechanisms involving nitric oxide."

An A-HeFT substudy, called the Genetic Risk Assessment of Heart Failure in African Americans, is under way to determine how various genes might influence patient outcomes and responses to BiDil. Several A-HeFT sites, including the Clinical Research Centers at Morehouse and Meharry, are participating.

The genetic substudy is focusing on genes thought to be related to heart failure and to causes of heart failure such as hypertension. Using the vascular imaging laboratory at Morehouse's Clinical Research Center, Ofili and her colleagues recently found an association between a nitric-oxide-related gene and hypertension in African Americans (*Journal of the National Medical Association* 97:197-205, 2005). "Since these genes may be responsible for the benefits seen in the A-HeFT trial, we are working alongside researchers at the University of Pittsburgh Medical Center to analyze and generate new data for the A-HeFT genetic substudy," says Ofili.

Ofili and Addai [CONTINUED ON PAGE 8 ➤]

PHOTO COURTESY OF CLARK ATLANTA UNIVERSITY

> "We will take what we learn and try to transform that knowledge into effective health policy..."

research, and to carry out interdisciplinary investigations.

"The master's program provides the needed tools for junior faculty to understand, develop, implement, and interpret clinical research studies while simultaneously advancing their careers as budding clinical researchers," says David Easa, program director of the RCMI Clinical Research Center (CRC) at the University of Hawaii. "I consider the program an essential component of the CRC, needed to support clinical research career development at the university."

Students in the program visit communities affected by health disparities to learn about people's health concerns. These meetings make use of a Hawaiian practice called "talk story"—what mainlanders would call "shooting the breeze," says Harrigan. With community input, students develop research projects to tackle community health issues. Two of the students work directly in the community, spending half their time at community health centers. The university hopes these students will be the first of a new type of clinical researcher, based in the community rather than in hospitals.

In one project, the program's first graduate, who received her degree this summer, analyzed a large health insurance database to study adherence to treatment among children with attention deficit hyperactivity disorder. That condition puts children at risk for methamphetamine abuse, says Harrigan, a serious problem among Hawaiian youth. The student found low adherence in the community where she worked and identified factors that influence adherence. She will next work with the community to improve adherence, undertaking that project in a Ph.D. program in clinical research that the university has established based on its success with the CRECD master's program.

A LOOK AT NEUROSCIENCE AND STROKE

In addition to NCRR-administered initiatives like the CCHD program and the CRECD awards, RCMI institutions also contribute to programs that are cofunded by NCRR but administered by other NIH Institutes and Centers.

In 2000, for example, the National Institute of Neurological Disorders and Stroke (NINDS) launched the Specialized Neuroscience Research Programs (SNRPs) at Minority Institutions.

credit the RCMI Program for enabling their institutions' contributions to major trials like A-HeFT. "We're getting more and more research projects going through the Clinical Research Center," says Addai. "The RCMI Program has had an enormous impact." **—S.J.B.**

Unlocking the Secrets of Spinal Cord Injury

For 15 years, neuroscientist Marie Filbin has depended on the RCMI at Hunter College of the City University of New York for investigating the mechanisms that block regrowth of damaged nerve axons in the spinal cord. Her work is helping to identify new treatments that may restore function in patients paralyzed by spinal cord lesions.

Clinical trials of some of these therapies will probably begin within two years, says Filbin, director of Hunter's Specialized Neuroscience Research Program (SNRP) at Minority Institutions, cofunded by NCRR (see main article above). Filbin cautions, however, that progress will come gradually. "Initially, we would just like to see if we can get axons to grow short distances, so they can make connections that might allow, for example, bladder function to be restored," she says.

Marie Filbin investigates why nerve axons in the spinal cord fail to regrow after an injury. She is helping to develop new therapies that may one day restore function in patients paralyzed by spinal cord lesions.

More than a decade ago, Filbin and her colleagues discovered that a protein in the myelin sheath that covers axons, called myelin-associated glycoprotein (MAG), inhibits regrowth of damaged spinal cord axons. When MAG binds to a particular receptor complex on neurons, it triggers a cellular signaling pathway that inhibits axonal growth. Filbin's team recently found that part of this inhibitory pathway depends on cleavage of a portion of the receptor complex by enzymes called secretases. She plans to investigate whether drugs that block secretases can prevent inhibition by MAG and encourage axon regeneration in rats. (*Neuron* 46:849-855, 2005)

In other research, Filbin has shown that the drug rolipram spurs damaged spinal cord axons to regrow and improves motor function in rats with spinal cord injuries (see *NCRR Reporter,* Summer 2004, pages 12-13). Rolipram overcomes inhibition of

PHOTO COURTESY OF THE GENE CENTER, HUNTER COLLEGE, CITY UNIVERSITY OF NEW YORK

NINDS, NCRR, NIMH, and the National Center on Minority Health and Health Disparities (NCMHD) cofunded the first five years of the SNRPs. The programs cofunded by NCRR exist at eight minority institutions: the University of Puerto Rico; the Universidad Central del Caribe; Meharry Medical College; the University of Hawaii; Howard University in Washington, D.C.; the University of Texas at San Antonio; the University of Alaska at Fairbanks; and Hunter College in New York. All of these institutions—except the University of Alaska—have RCMIs. SNRPs support basic and clinical research programs in neuroscience, including studies of stroke, Parkinson's disease, Alzheimer's disease, and AIDS dementia.

David Easa says the master's program in clinical research at the University of Hawaii is essential to the careers of budding clinical investigators.

The problem of stroke also is being addressed by another initiative, the Stroke Prevention/Intervention Research Program (SPIRP). This NINDS program, cofunded by NCRR and the National Heart, Lung, and Blood Institute (NHLBI), was established in 2003 at Morehouse School of Medicine in Atlanta, an RCMI institution. SPIRP seeks to decrease the incidence of stroke in medically underserved populations and to establish stroke prevention and intervention programs. It also trains scientists to become stroke investigators.

Stroke has a particularly negative impact on African Americans. Data from the American Stroke Association reveal that deaths from stroke are roughly 40 percent greater among African Americans than among Caucasians, says NCRR's McNairy. Morehouse School of Medicine is the ideal location for SPIRP, he says, because Atlanta is the buckle of the "stroke belt"—a name given to the southeastern United States because of its high incidence of stroke.

"Through the years, we were seeing a marked disparity in stroke among minorities, but we seemed unable to do much about it," says Edgar Kenton, a clinical neurologist and director of SPIRP. "Now, with money going toward this kind of issue, it's going to make an enormous difference." Kenton says SPIRP seeks to prevent stroke by educating people about risk factors. The program also aims to minimize the medical consequences of stroke by improving medical interventions and patient rehabilitation. Various research centers at Morehouse support SPIRP activities, including the RCMI Clinical Research Center, he says.

SPIRP includes a community core that supports research rely-

axonal growth by increasing levels of cyclic adenosine monophosphate (cAMP) in the body. Rolipram treatment currently requires use of a spinal tissue graft at the lesion site to facilitate axonal growth. Filbin is working to optimize rolipram therapy to eliminate the need for invasive grafts.

Filbin also is reconstructing the signaling pathway triggered by cAMP. One part of this pathway boosts synthesis of molecules called polyamines, which overcome inhibition of neuronal growth. Filbin is now examining polyamine function in her rat model of spinal cord injury. (*Neuron* 44:609-621, 2004) **—S.J.B.**

The Evolution of HIV

Despite its ability to reduce death rates and complications of HIV infection, antiretroviral medication often leads to drug-resistant strains of HIV, which may be transmitted to the sexual partners of infected individuals. RCMI-supported researchers at the Ponce School of Medicine in Puerto Rico are investigating how antiretrovirals can influence the evolution of HIV and how this knowledge may ultimately help to enhance AIDS therapies. The scientists have found evidence that the body contains separate "compartments" of HIV infection and that drug-resistant mutations develop at different rates in different compartments.

Anil Kumar, associate director of the school's RCMI, and his colleagues analyzed HIV mutations in a small group of infected women who were taking highly active antiretroviral therapy (HAART), a cocktail of anti-HIV medications. The researchers searched for evidence of drug-resistant mutations in viral DNA extracted from [CONTINUED ON PAGE 10 ➤]

A technician prepares a sample for an AIDS-related research project at the Ponce School of Medicine.

PHOTO COURTESY OF PONCE SCHOOL OF MEDICINE

ing on community resources. One community project is examining whether lifestyle interventions can reduce stroke risk factors in African American families. Another project studies how stroke incidence varies by ZIP code in the Atlanta area in order to identify places most in need of stroke prevention efforts. A third project uses one of the nation's four Coverdell National Acute Stroke Registries. The registry, run by Emory University's department of neurology at Grady Memorial Hospital in Atlanta, collects data on patients admitted with acute stroke symptoms to hospitals across Georgia. The data are helping SPIRP researchers understand factors that contribute to stroke risk.

SPIRP also has a basic/translational science core, which aims to develop a neuroprotective agent that will protect brain tissue in stroke patients. Another project studies genetic markers that predispose individuals to stroke.

A FOCUS ON WOMEN'S HEALTH

Another RCMI-related initiative cofunded by NCRR is the Cooperative Reproductive Science Research Centers (CRSRCs) at Minority Institutions Program, established and administered by NICHD. CRSRCs support research critical to reproductive health. Each CRSRC collaborates with an NICHD reproductive science research program at a nonminority institution.

Since 2003, NICHD has supported CRSRCs at three RCMI institutions: Morehouse School of Medicine, Meharry Medical College, and Charles R. Drew University of Medicine and Science. NCRR cofunds the CRSRCs at Meharry and Drew. NCMHD and the NIH Office of Research on Women's Health also support the CRSRC program.

Valerie Montgomery Rice directs a clinical study of osteoporosis among African American women, a population prone to poor outcomes following osteoporosis-related hip fractures.

The CRSRC at Meharry, called the Cooperative Center for Research in Reproduction, addresses reproductive health issues that disproportionately affect African American women.

four types of samples: vaginal cells, vaginal secretions, peripheral blood cells, and cell-free plasma. The virus in vaginal tissues appeared to mutate and develop drug resis-tance at a slower pace than did HIV in blood cells, Kumar says. He suspects that the relative differences in drug concentrations in the bloodstream and the vagina are responsible for the different mutation rates. "Drug concentrations are highest in the blood, which opens the door to more rapid mutations and drug resistance," Kumar says.

Further analysis showed that cell-free viruses extracted from blood plasma and the vagina became drug-resistant much more rapidly than viruses from the cell-based samples. Viruses from the two cellular environments were shown to be genetically more similar to each other than to the cell-free viruses, says Kumar. "This suggests there is comparable evolution, and slower evolution, among cell-associated viruses," he adds.

Kumar credits the RCMI Program with providing crucial support to the medical school's ongoing investigations of HIV and other health-related issues. The RCMI provides direct research grants to investigators, funding for all of the school's research equipment, and support for faculty development, including visits from established investigators from the United States who collaborate with Ponce investigators. "Our researchers are continuously helped by the RCMI here at Ponce," Kumar says. (*Virology* 334:299-305, 2005) **—TINA ADLER**

HIV's Deadly Effect on Uninfected Cells

HIV infection is marked by destruction of the immune system's CD4+ T lymphocytes, or T cells, yet the virus itself infects less than 1 percent of T cells. Now a team of RCMI-supported researchers report that the uninfected, bystander T cells meet their untimely deaths because of a lethal protein, called Nef, released by the infected T cells.

When HIV-infected T cells produce Nef, the protein travels throughout the body embedded in the membranes of tiny vesicles released by the infected cells. These vesicles, called exosomes, normally carry immune molecules from the T cells to distant sites in the body. "The virus has piggybacked on these vesicles," says Vincent C. Bond, a molecular biologist at the Morehouse School of Medicine in Atlanta. Nef does its damage by latching onto T-cell CXCR4 receptors, triggering destruction of uninfected bystander cells.

PHOTO COURTESY OF MEHARRY MEDICAL COLLEGE

Researchers at Pennsylvania State University collaborate with the Meharry CRSRC by providing research expertise and recruiting Caucasian patients for clinical studies at the CRSRC. The studies examine differences in disease risk between African American and Caucasian women.

"The CRSRC program allows us to build our infrastructure for clinical research under the initial mentorship of a place like Penn State, which has a history of clinical research," says Valerie Montgomery Rice, director of Meharry's Center for Women's Health Research. "We can then begin to develop our basic science research into translational research and then into clinical-trial research, to get to the answers that will impact the well-being of women."

Health issues addressed by the Meharry CRSRC include treatment of uterine fibroids, polycystic ovary syndrome, and osteoporosis. The osteoporosis project, headed by Montgomery Rice, examines how circulating steroid hormones differ in African American and Caucasian women and how those hormones affect bone mineral density and bone architecture. All exams for the CRSRC clinical studies take place at the RCMI Clinical Research Center at Meharry, says Montgomery Rice. The RCMI Program will also provide mammography, ultrasound, and bone densitometry resources.

Whether tackling women's health, AIDS, stroke, or any of the other health issues that disproportionately affect minority communities, RCMI-associated researchers share a commitment to improve the health of all our nation's citizens—a goal they have steadfastly pursued for two decades.

"As the new millennium progresses, the RCMI Program continues to strive toward improving the nation's health in a country increasingly unwilling and unable to accept health disparities between racial and ethnic groups," says NCRR's McNairy. We are becoming "a nation of one-thirds," he notes: One-third Caucasian, one-third African American, and one-third Hispanic and other minorities. The RCMIs will play a special role in that new, transformed nation, he says, and they eagerly await the challenge. ■

TO LEARN MORE

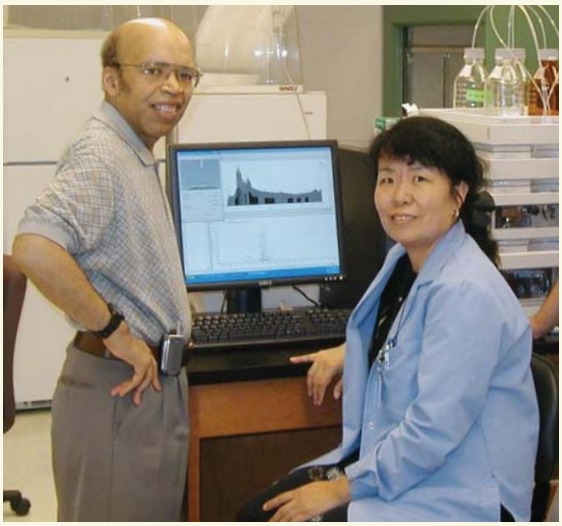
The initiatives described in this article take place at institutions of higher learning across the United States and in Puerto Rico that host NCRR-supported Research Centers in Minority Institutions (RCMIs). Further information on the following initiatives is available on the Web:

- Specialized Neuroscience Research Programs (SNRPs) at Minority Institutions: www.ninds.nih.gov/funding/minorities_and_disabilities.htm
- Stroke Prevention/Intervention Research Program (SPIRP): www.ncrr.nih.gov/resinfra/spirp.asp
- Cooperative Reproductive Science Research Centers (CRSRCs) at Minority Institutions: www.nichd.nih.gov/about/cpr/rs/crrcmi.htm

For additional information on the RCMI Program, visit www.ncrr.nih.gov/resinfra/ri_rcmi.asp.

When Bond's team exposed T cells to soluble Nef, the cells underwent cell death, or apoptosis. Nef concentrations corresponded with the rate of apoptosis in the laboratory dish, but it is not yet known whether the concentration of Nef in a patient's blood is related to health status.

■ *Research by Vincent Bond and colleagues, including Ming Bo Huang (right), suggests that HIV kills more cells by triggering cell death in bystander lymphocytes than by infecting cells directly.*



The Morehouse researchers were able to thwart Nef-induced apoptosis by treating the T cells with protein kinase inhibitors. This suggests that kinases, which occur naturally in the body, also may contribute to Nef-related apoptosis. Bond suggests that the body's own immune defenses against HIV fail in part because Nef antibodies target the wrong part of the deadly protein.

Funding from the Morehouse RCMI, which Bond directs, has enabled the research leading to these recent discoveries. In addition to supporting many Morehouse investigators, the RCMI has paid for practically all of the school's major research equipment, says Bond.

Bond and his colleagues hope their studies will aid development of a vaccine or drug therapy that blocks the effects of the critical portion of the Nef protein that triggers apoptosis. "Most existing HIV medications target the virus or some aspect of the viral life cycle," says Bond. However, some drugs, specifically protease inhibitors, also appear to block Nef from inducing apoptosis. "We're saying, to put it bluntly, the Nef protein and not viral infection causes AIDS," says Bond. (*Journal of Virology,* 78:11084-11096, 2004) **—T.A.**

PHOTO COURTESY OF MOREHOUSE SCHOOL OF MEDICINE

Estrogen in a New Kind of Bind

Newly discovered estrogen receptor sheds light on cancer and its treatment.

BY MARGIE PATLAK

Estrogen is a paradoxical hormone—essential to women's health but also implicated in several forms of cancer. Now the discovery of a new type of estrogen receptor provides further clues to the complex functioning of estrogen and may even lead to improved therapies for breast cancer and other estrogen-related disorders. Studies of the new receptor also may help to explain why patients do not always respond as expected to "anti-estrogen" drugs like tamoxifen.

"Our findings open up a whole new area in estrogen biology that requires a re-evaluation of some of the assumptions made in the past," says Eric Prossnitz, a professor of cell biology and physiology at the University of New Mexico Health Sciences Center in Albuquerque. Using state-of-the-art instruments and technologies funded by NCRR, Prossnitz and his colleagues showed that the protein known as GPR30 functions as a novel estrogen receptor that triggers distinctive signaling pathways.

Estrogen receptors are of particular interest because the hormone is thought to fuel a number of cancers, including breast, ovarian, uterine, and possibly prostate cancer. When selecting appropriate therapies for breast cancer patients, physicians first determine whether the tumor cells are positive or negative for estrogen receptors. Receptor-positive tumors often are treated with compounds—like tamoxifen—that block estrogen from binding to its receptors, thereby hindering tumor growth. Tamoxifen has been shown to slash the risk of breast cancer recurrence by 30 percent to 50 percent in some—but not all—women whose tumor cells are positive for estrogen receptors. The newly discovered estrogen receptor may help to explain why some receptor-responsive tumors appear unaffected by the drug.

Prossnitz and his colleagues found that GPR30 responds to tamoxifen differently than the other two estrogen receptors known in humans. Specifically, tamoxifen essentially pulls the trigger of the GPR30 receptor rather than blocking its actions. Therefore, the growth of a breast tumor that has both standard estrogen receptors and GPR30 might not be stopped as effectively by tamoxifen as tumor cells that have only the standard receptors.

The discovery of the new estrogen receptor builds on the hunt for new receptors that began in earnest in the 1990s. Much of that search focused on finding G protein-coupled receptors (GPCRs), a large family of receptors that help to regulate most physiological processes in the body. "Regardless of the disease you are looking at, there's probably a GPCR that plays an important role," says Prossnitz.

In the late 1990s, four independent research groups reported that they had discovered a new GPCR—GPR30—the function of which remained a mystery. Other scientists later found that cultured breast cancer cells that had GPR30 but lacked standard estrogen receptors tended to react biochemically to estrogen. This suggested that the mysterious GPR30 might bind to estrogen.

To explore this possibility, Prossnitz and his colleagues created a fluorescent version of GPR30 and then used a confocal fluorescence microscope to see where the receptor

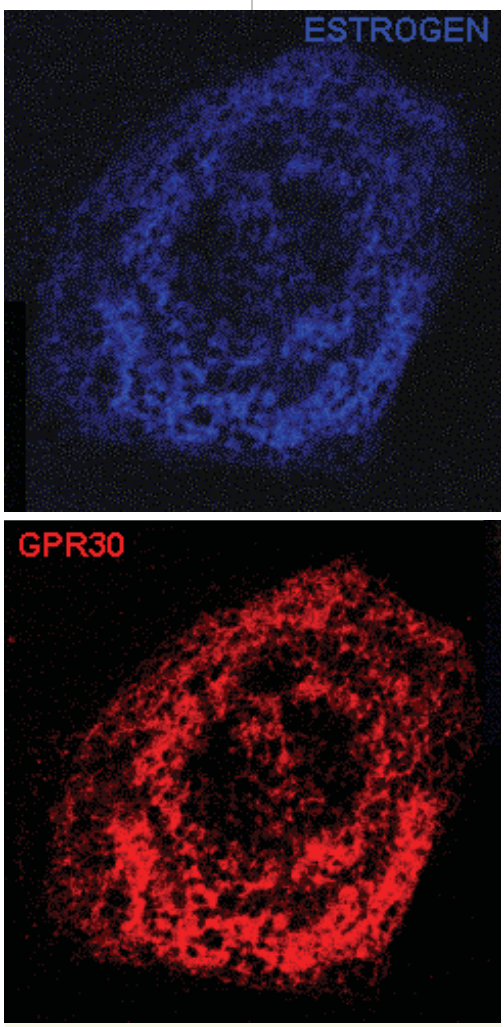
appeared as a brilliant color in cultured cells. The scientists then added, to the same cells, stains for various cellular components, such as the mitochondria, the outer cell membrane, the nuclear membrane, and a tubular network known as the endoplasmic reticulum.

When the researchers compared the location of fluorescent GPR30 with that of the specific stains, they were surprised to discover that GPR30 congregates in the membrane of the endoplasmic reticulum, inside the cell. In contrast, other known GPCRs inhabit the outer cell membrane, where they can bind to compounds incapable of traversing the membrane. Because GPR30 lodges within the cell, the receptor must bind to a compound—like estrogen—that can pass through the cell's outer membrane.

To confirm that GPR30 binds to estrogen, the researchers created a fluorescent version of the hormone and added it to the cultured cells. The resulting fluorescent pattern was identical to that seen when fluorescent GPR30 was added alone to the cells, suggesting that estrogen must bind to GPR30 (see images at right).

Key to this research was the laser-scanning confocal fluorescence microscope purchased with an NCRR Shared Instrumentation Grant (SIG). (For more information about the SIG Program, see the *NCRR Reporter,* Fall 2004, pages 8-9.) "A standard fluorescence microscope, which visualizes the entire thickness of the cell, has trouble distinguishing two structures in the cell that are piled atop one another," Prossnitz says. "A mitochondrion might be above the endoplasmic reticulum, but you can't distinguish the two."

It is impossible to cut thin slices of living cells to examine under the microscope, but a laser-scanning confocal fluorescence microscope uses optical techniques to create visual "slices" through a cell. Because the microscope collects light only from a very thin layer of the cell, everything above and below that layer is ignored. "It allowed us to get very high spatial resolution images, especially when using multiple colors as we did. We could look at the very precise location of these colors in the cell," says Prossnitz.



New Mexico researchers used fluorescent stains in a breast cancer cell to show that estrogen (blue) appears in the same location as GPR30 (red). This strongly suggests that GPR30 binds to estrogen.

Additional NCRR funding, to create a Center of Biomedical Research Excellence (COBRE) at the University of New Mexico Health Sciences Center, enabled the purchase of more cutting-edge instruments for flow cytometry and microscopy, which Prossnitz and his colleagues used daily for their investigations. (For more information about COBRE, see the *NCRR Reporter,* Winter 2004, pages 4-7). "Without the NCRR funding, it would have been very difficult to do our research," Prossnitz says.

Once they established that GPR30 binds to estrogen, Prossnitz and his colleagues showed that the binding triggered a unique series of biochemical pathways that differed from the effects seen when estrogen binds to traditional estrogen receptors. These novel pathways also are triggered when tamoxifen binds to GPR30. The researchers then looked at a few cultured breast cancer cell lines and found that the more aggressive cancers tended to have more GPR30 receptors than the less aggressive ones.

"But much work has to be done to figure out precisely where GPR30 fits into the estrogen picture," Prossnitz says. "Our findings suggest that the signaling mechanisms used by estrogen are more complicated than previously expected and that, to fully understand how estrogen mediates its effects, we must cast a wider net and consider new estrogen receptors when we study estrogen and disease." Many of those studies are already underway in Prossnitz's lab, including research aimed at finding which tissues and cancers have GPR30 and what compounds selectively inhibit the receptor. ■

The research described in this article is supported in part by funding from NCRR, the National Institute of Allergy and Infectious Diseases, the National Institute of Biomedical Imaging and Bioengineering, the National Cancer Institute, and the National Science Foundation.

ADDITIONAL READING

■ Revankar, C. M., Cimino, D. F., Sklar, L. A., et al., A transmembrane intracellular estrogen receptor mediates rapid cell signaling. *Science* 307:1625-1630, 2005.

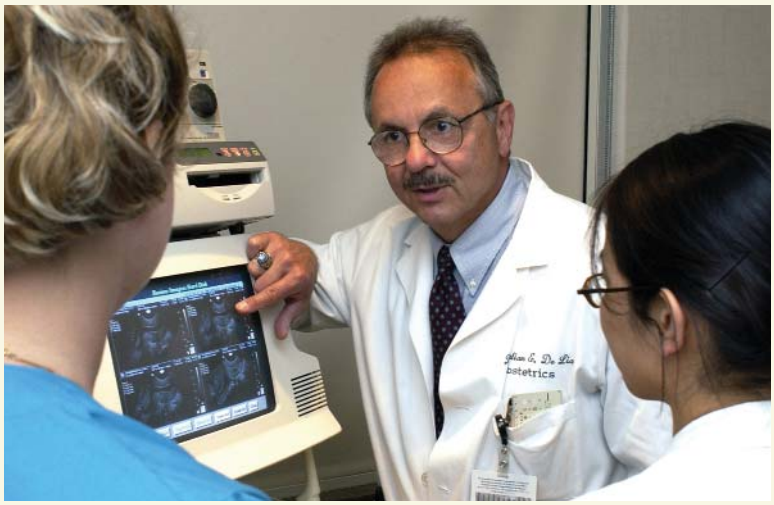
IMAGES COURTESY OF ERIC PROSSNITZ, UNIVERSITY OF NEW MEXICO

Birthing Twins—and Technologies

An experimental surgery moves out of the laboratory and into medical practice.

Some twins have a difficult time with sharing, even before they leave the womb. Unfortunately, the results can be tragic for those with the rare condition known as twin-to-twin transfusion syndrome (TTTS). The circulatory systems of TTTS twins become connected, with one twin—the recipient—draining the other twin of nutrients. Among many complications, the recipient produces too much amniotic fluid, which a physician must regularly remove to prevent premature birth. Even with this precaution, at least 40 percent of TTTS twins die, and head scans of surviving newborns show that 14 percent to 18 percent may have neurological consequences. Without treatment, the fetal mortality rate is 80 percent or more.

To improve the odds, Julian E. De Lia pioneered a procedure called fetoscopic laser occlusion of chorioangiopagous vessels (FLOC). By inserting a fiber-optic scope into the amniotic cavity, the surgeon can examine the placental vessels and then seal off those connecting the twins. Amniotic fluid may still need to be drained during the pregnancy, but the fetus' risk of neurological impairment declines.



Julian De Lia discusses an ultrasound image from a pregnant patient whose twins' circulatory systems are connected, a condition called twin-to-twin transfusion syndrome.

De Lia began seeking a treatment for TTTS after encountering his first patient with the condition in the 1980s. His department chairman at the University of Utah School of Medicine was encouraging physicians to seek opportunities for making medical advances and, coincidentally, a laser laboratory at the university was looking for applications for lasers.

After initial animal studies, De Lia and his team were ready to evaluate FLOC in the clinic and so turned to the NCRR-supported General Clinical Research Centers (GCRCs), first at the University of Utah and then at the Medical College of Wisconsin, where De Lia is currently an associate professor of clinical medicine. "There was no format set up for that sort of clinical research other than the GCRC," he says. "The staff at the GCRC had the expertise we needed to monitor and care for these patients."

Since those initial studies, De Lia and others have continued to develop and enhance this surgical procedure, now a more accepted treatment option for TTTS. Clinical trials comparing FLOC and amnioreduction have had mixed results, but a recent European study of 142 women was stopped early when twins in the laser group fared better than those treated with amnioreduction alone. The study, published last year in the *New England Journal of Medicine,* showed that the laser group had a higher likelihood of survival of at least one twin to six months of age and fewer abnormalities on neuroimaging.

Another multicenter trial comparing the two therapies was recently completed with support from the National Institute of Child Health and Human Development, and the results are now being evaluated. "It is important for doctors and patients to understand that, although laser surgery is an advance for treating TTTS, the best role for laser is far from clear," says principal investigator Timothy Crombleholme, a surgeon at Cincinnati Children's Hospital Medical Center. "What we struggle with every day with these patients is determining under what circumstances is one approach better."

De Lia and others are working to improve laser treatments and to identify alternative TTTS therapies. Recently, De Lia's team discovered that most TTTS mothers are anemic and malnourished themselves, probably due to the stresses of the pregnancy, which complicates the twins' conditions.

—TINA ADLER

PHOTO BY PAUL RAMSEY

Young Scientists Recognized by White House

Two NCRR-supported scientists were among the 58 recipients of the Presidential Early Career Awards for Scientists and Engineers (PECASE) granted by the White House during a June 13, 2005, ceremony on Capitol Hill. The PECASE is the highest honor bestowed by the U.S. government on young scientists whose work shows exceptional promise.

Derrick Brazill, assistant professor of biology at City University of New York's Hunter College, received the award for his work in understanding cell communication. Brazill examines how certain signaling molecules secreted by cells help to coordinate cell growth and differentiation into new cell types. Primary funding for his research comes from the National Institute of General Medical Sciences and the National Science Foundation, with additional support from NCRR's Research Centers in Minority Institutions Program. "NCRR helped supply some of my start-up funds, which allowed me to buy equipment and get my lab up and running when I first got to Hunter," says Brazill.

Catherine Gordon, another PECASE recipient, is director of the bone health center at Children's Hospital in Boston.


DERRICK BRAZILL


CATHERINE GORDON

Gordon studies how nutrition and other lifestyle variables influence bone development in adults and young women. She receives primary funding from the National Institute of Child Health and Human Development and also has benefited from an NCRR clinical research training grant. "The NCRR grant opened a lot of doors for me and prepared me to continue my career as a clinical investigator," says Gordon. ■

Nearly $18 Million Awarded for Instrumentation

NCRR has awarded one-time grants to 11 research institutions around the country to support the acquisition of scientific instruments that cost between $750,000 and $2 million each. High-End Instrumentation (HEI) grants provide researchers with access to advanced instrumentation—including imaging systems, high-resolution mass spectrometers, electron microscopes, and supercomputers—that might otherwise be too costly to obtain. "The faster we can place these new technologies in the hands of as many NIH investigators as possible, the more rapidly we can transfer this new knowledge to patient treatments and cures," says NCRR Acting Director Barbara Alving. The HEI Program is cost-effective because purchased equipment must be shared by at least three NIH-supported scientists. Further information on the program, including a list of this year's awardees, is available at www.nih.gov/news/pr/jul2005/ncrr-12.htm. ■

New NAS Members Used NCRR Resources

Among the 72 new members elected to the National Academy of Sciences in May are seven, listed below, whose research benefited significantly from NCRR-funded resources. Election to the academy is considered one of the highest honors that can be bestowed on a scientist or engineer.

Axel T. Brünger, Stanford University. For his studies of the cell's complex protein machinery, Brünger relies on resources of the Stanford Synchrotron Radiation Laboratory's Structural Molecular Biology Program, cofunded by NCRR. Other NCRR-supported resources used by Brünger include the Macromolecular Diffraction Biotechnology Resource at Cornell University.

Michael J. Donoghue, Peabody Museum of Natural History, Yale University. Donoghue used a Science Education Partnership Award from NCRR to add new health-related materials and curricula to an elementary and middle school science education program at the Yale Peabody Museum. The enhanced program now addresses the relationship between biodiversity and human health.

Nancy G. Kanwisher, Massachusetts Institute of Technology. Kanwisher uses the NCRR-supported Center for Functional Neuroimaging Technologies at Massachusetts General Hospital to examine how the human brain responds to visual tasks and stimuli. Her research contributes to the brain morphometry portion of NCRR's Biomedical Informatics Research Network.

Michael Karin, University of California, San Diego (UCSD) School of Medicine. Karin has relied on the NCRR-supported National Center for Microscopy and Imaging Research at UCSD to study molecular pathways in inflammation, cancer, and cellular differentiation. Karin's bio-

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molecular studies also have benefited from other NCRR-supported resources, including the Resource for Biocomputing, Visualization, and Informatics at the University of California, San Francisco.

Tom A. Rapoport, Harvard Medical School. Rapoport has depended on the NCRR-supported Undulator Resource for Structural Biology at Cornell University to study the structures of proteins involved in transporting molecules across cell membranes. The NCRR-supported Center for *C. elegans* Anatomy at Albert Einstein College of Medicine also has aided his membrane protein research.

Christine E. Seidman, Harvard Medical School. Seidman's research on the molecular basis of cardiomyopathy has relied on X-ray diffraction resources of the NCRR-supported Biophysics Collaborative Access Team (BioCAT) at the Illinois Institute of Technology. Her research on the genetic underpinnings of congenital heart disease has made use of additional NCRR-supported resources, including the General Clinical Research Center at Children's Hospital, Boston.

Edward I. Solomon, Stanford University. Solomon has relied on resources of the Stanford Synchrotron Radiation Laboratory's Structural Molecular Biology Program, cofunded by NCRR, to study the structures and functions of metal-containing protein molecules involved in a variety of physiological processes. ■

New Laboratory To Focus on Vaccine Research

In the new $5.6 million Center for Immunobiology and Vaccine Development (CIVD) at the Children's Hospital and Research Center in Oakland, California, scientists are conducting research to produce more effective vaccines for childhood diseases such as meningitis. The CIVD, which opened earlier this year, received a $2 million construction grant from NCRR. Specialized shared facilities include a DNA clean room and a biological safety level 3 facility, which allow researchers to handle infectious agents under safe conditions.

Scientist Jo Anne Welsch conducts immunological research in the new CIVD lab.

PHOTO COURTESY OF CHILDREN'S HOSPITAL AND RESEARCH CENTER AT OAKLAND

The center operates on the premise that understanding how the immune system fundamentally works will permit scientists to design new vaccines and to improve existing ones. "We want to understand how the immune system develops in humans. For example, why do adults develop antibodies when injected with some pathogens while babies do not?" says senior scientist Alex Lucas.

The CIVD's interactive laboratories house molecular, cellular, and clinical studies all under one roof. The center's interdisciplinary approach to immunobiology is especially important for addressing today's rapidly evolving infectious agents, such as those that cause AIDS and SARS. ■

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