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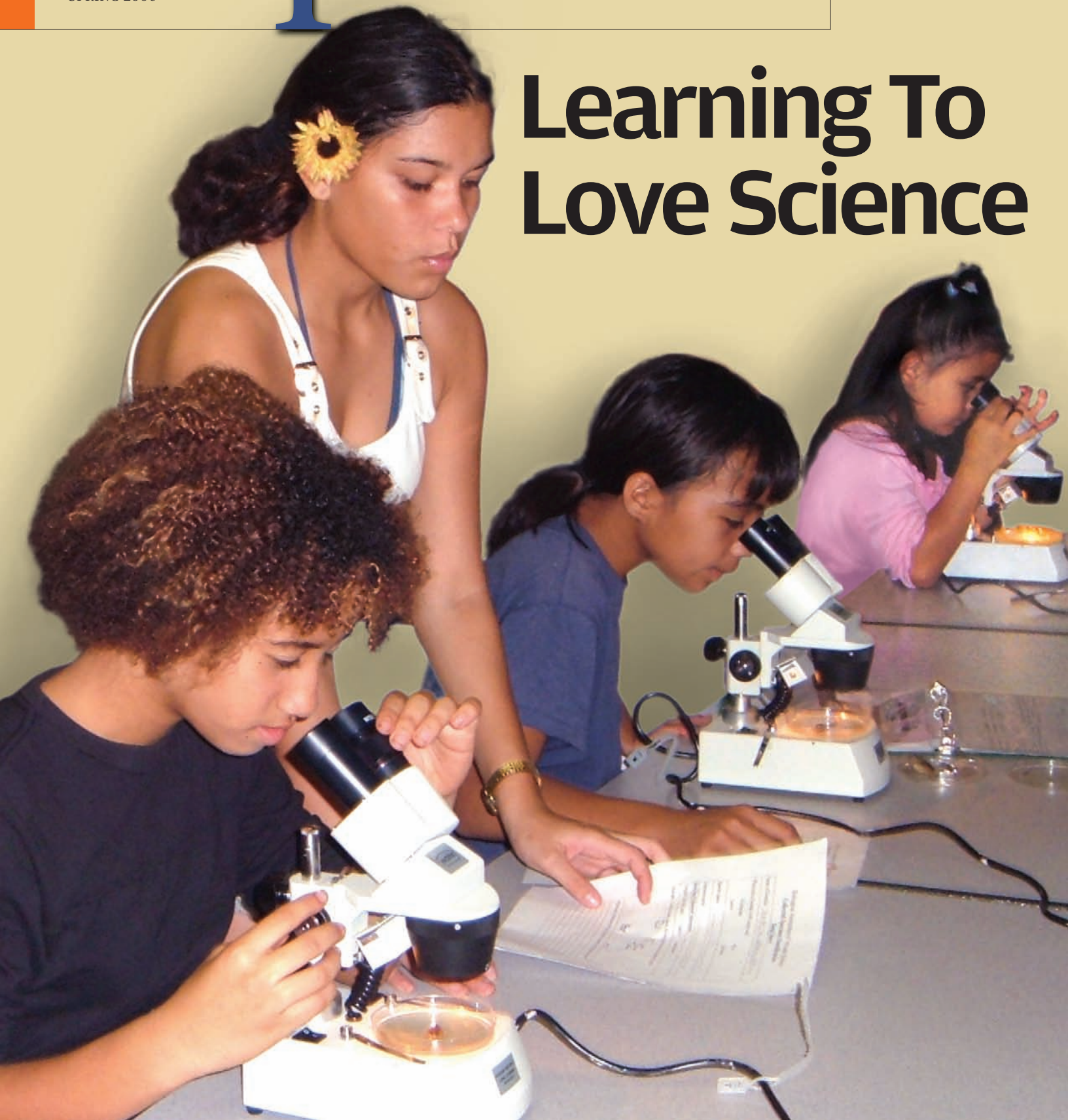
NCRR Reporter

Spring 2006

Critical Resources for Your Research

U.S. Department of Health and Human Services

Learning To Love Science



FROM THE DIRECTOR

Engaging Students and Informing the Public

To stimulate the public's curiosity about medical research and advances in medicine, NCRR has been funding innovative outreach projects through Science Education Partnership Awards (SEPA) for the past 15 years. By creating relationships among educators, museum curators, and medical researchers, SEPA encourages the development of hands-on, inquiry-based curricula that inform the participants about such timely issues as obesity, stem cells, and infectious diseases. In addition, SEPA provides professional development for teachers and mentoring opportunities for students K-12, which have proven to be integral to its success. Many SEPA projects are designed to engage underserved and/or minority populations to ensure that they have full opportunities to pursue careers in the health sciences.

For example, in this fiscal year, NCRR has provided almost $10 million to fund nine new SEPA projects in states ranging from California to New Jersey and Massachusetts to Mississippi. The grants will provide from two to five years of support and include such projects as partnerships between the University of Nebraska Medical Center and tribal schools in Nebraska and South Dakota to increase the number of Native Americans entering health careers. At the Yale University SEPA, K-12 students will learn about infectious diseases and their transmission by studying models of Lyme disease and West Nile virus. At the Children's Museum in Houston, participants will learn how to track their physical activity and nutrition and the role that both play in human health. The SEPA mentoring program developed at West Virginia University has been credited with increasing the percent of students who attend college and with ensuring their retention in college. Furthermore, nearly half of the SEPA students who have participated in the West Virginia program are earning health, science, or technology degrees.

To leverage the tremendous power of such projects, SEPA also provides support so that successful efforts can be widely disseminated. Curricula and other teaching aids are freely available through the Web at www.ncrrsepa.org.

Educating the public about what we do is a great challenge, but it's a vital task I hope you'll join us in undertaking. The future of biomedical research and the nation's health are at stake.

Barbara Alving, M.D.

Barbara Alving, M.D.
Acting Director, NCRR

INSIDE

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CRITICAL RESOURCES

SCIENCE ADVANCES

NCRR Reporter

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

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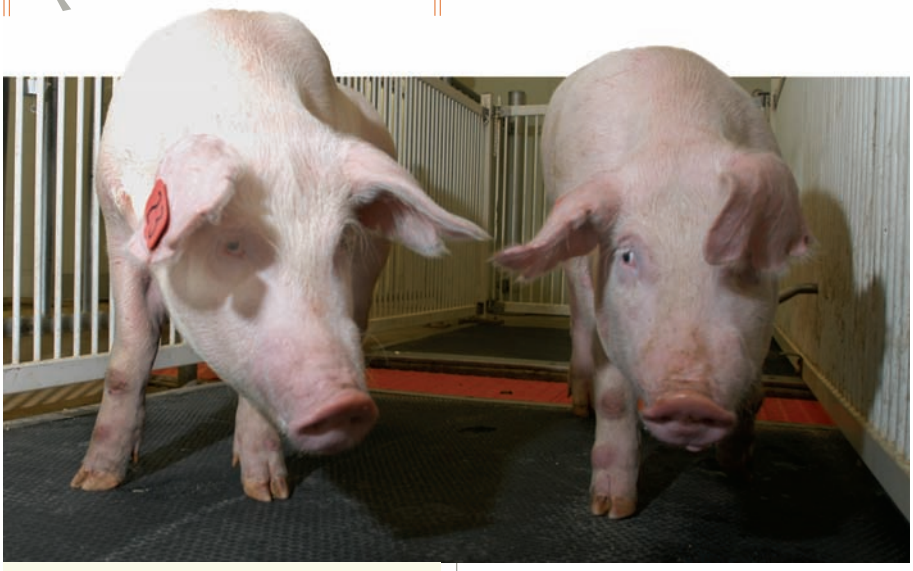
On the Cover: In the rural Hawaiian town of Hana, children and families engage in hands-on activities at a Family Science Night, designed to pique curiosity about health and research careers. This event is one of many innovative outreach efforts sponsored nationwide by NCRR's Science Education Partnership Awards.

PHOTO BY MARILYN LINK, UNIVERSITY OF HAWAII, JOHN A. BURNS SCHOOL OF MEDICINE

QUICK TAKES

New tools and updates from NCRR resources



Researchers report they have created pigs that produce healthier fatty acids.

Cloned Pigs Rich in Omega-3

Scientists at the NCRR-supported National Swine Research and Resource Center and their colleagues have succeeded in cloning pigs that produce healthier omega-3 fatty acids in their tissues and organs, according to a study published in the April 2006 issue of *Nature Biotechnology.*

Livestock cannot convert other fatty acids into omega-3 because they lack a *fat-1* gene, such as the one commonly found in the roundworm *C. elegans.* By inserting a modified version of this gene into fetal pig cells, the scientists were able to create cloned pig embryos that developed into animals with elevated levels of omega-3 fatty acids.

The cloned pigs contained roughly 8 percent of omega-3 and other healthy fatty acids, compared with less than 1 percent found in regular pigs. Scientists say the pigs could be used as models to study the importance of omega-3 fatty acids in prevention and treatment of coronary heart disease, immune-mediated disorders, and other clinical conditions. Additional research is needed to determine if these genetically altered pigs might also be safe for human consumption.

Key Psoriasis Gene Found

In the most extensive international study of a psoriasis gene to date, scientists at the University of Michigan have discovered a common genetic variation that makes people prone to developing the disease, which affects roughly 2 percent of the U.S. population and is characterized by itchy, red patches of skin.

The gene PSORS1, or psoriasis susceptibility 1, was identified in a clinical research study involving more than 2,700 individuals in which at least one family member had the disease. The study was assisted by the university's General Clinical Research Center, which has supported research on the genetics of psoriasis for more than a decade.

PSORS1 is the major gene, but not the only one, involved in the disease. People must inherit several psoriasis genes and be exposed to an environmental trigger, such as strep throat, to develop the condition.

Understanding the role of the PSORS1 gene may lead to developing new and more effective treatments for the disease. The study appears in the May 2006 issue of the *American Journal of Human Genetics.*

Tracking Avian Flu

Scientists in Alaska are on the lookout for the first signs of avian flu. Alaska's unique location—at the intersection of Asian and North American flyways—makes the state an ideal site for studying the virus in migratory birds.

Researchers at the University of Alaska have collected 4,500 samples from ducks, geese, and shorebirds in collaboration with federal and state agencies. So far only 30 samples have tested positive for various flu viruses, but none for avian flu of Asian origin. The work is funded in part by NCRR's IDeA Networks of Biomedical Research Excellence.

Virus surveillance in migratory birds will help scientists model how new viruses emerge and mutate. This, in turn, can help public health officials plan and implement public measures for future outbreaks. ■

On the lookout for avian flu, researchers collect a sample from a migratory goose in Alaska.

PHOTO BY STEVE MORSE, UNIVERSITY OF MISSOURI (TOP), PHOTO COURTESY OF HEATHER HUDSON, UNIVERSITY OF ALASKA FAIRBANKS (RIGHT)

Learning To Love Science

Innovative science education partnerships are changing the way we learn science.

BY AL STAROPOLI

Sometimes when science class ends, students complain. "They'd rather stay and tinker some more," says Mario Godoy-Gonzalez. His students are working intensely on *Click and Clone,* an Internet genetics activity developed at the University of Utah with NCRR support. Their mission is to create Mini-Mimi, a genetically identical clone of Mimi, a cartoonish virtual mouse.

"The activities are extremely cool. I like them because they get the students motivated," says Godoy-Gonzalez, who teaches high school science to 18 young adults, all of them Hispanic, in the small rural town of Royal City, Washington. "The activities show students relevant topics in science. And instead of just reading about science, students can do science."

Professional development sessions help high school science teacher Mario Godoy-Gonzalez learn the art of blending science and fun.

Across the nation, thousands of children, teachers, and adults are learning about science through projects supported by NCRR's Science Education Partnership Awards (SEPA) Program. SEPA stimulates curiosity and encourages scientific investigation through hands-on activities.

Now in its 15th year, SEPA is implemented in more than 30 states, Puerto Rico, and five Native American communities and reaches tens of thousands of people every year. The Program's goal is to improve understanding of health and biomedical research by supporting projects that increase the scientific literacy of children, young adults, and the public at large. A better understanding of health and research issues allows people to make more informed decisions about lifestyle and medical care that can prevent disease and maintain health. The Program also contributes to the development of future scientists and clinical researchers by exposing young people to the excitement and value of scientific investigation.

SEPA projects come in a variety of styles, customized for each community. While one SEPA project may be led by a museum, another may be carried out in the classroom. "SEPA's public outreach through museums and science centers is fantastic, covering the basic and clinical research programs that NIH funds, as well as providing a community forum for discussing topics of high public interest, such as stem cell research," says

PHOTO COURTESY OF GENETIC SCIENCE LEARNING CENTER, UNIVERSITY OF UTAH

Utah high school student Katie Stokes gains understanding of genetics and cloning through an online activity called *Click and Clone*.

NCRR's Tony Beck, who oversees NCRR's SEPA Program. "In the classroom, SEPA is a phenomenal way to expose students and teachers to science and inquiry-based investigation."

Although every SEPA project is different, they all have one element in common: partnerships. In a Maryland SEPA project, universities partner with elementary schools in African American communities to educate children on health and fitness. In Hawaii, universities form local collaboratives to bring science to Native Hawaiians and other Pacific Islanders. And in Utah, a SEPA project works with Hispanic schools and the public at large through an Internet initiative. These are just a few of the 65 SEPA projects implemented nationwide.

> Now in its 15th year, SEPA is implemented in more than 30 states, Puerto Rico, and five Native American communities and reaches tens of thousands of people every year.

UTAH'S GENE GAMES

When geneticist Louisa Stark first launched the SEPA activities on the Utah Web site, she had no idea that *Click and Clone* would be such a hit. Stark directs the University of Utah's Genetic Science Learning Center, which is a powerhouse for spreading the word about genetics (http://gslc.genetics.utah.edu).

The SEPA project in Utah has relied strongly on the Internet to explore the intricacies behind genetics. The success of its Web site, visited by more than 150,000 people every week, may be explained by its highly visual design, similar to what teens see in video games and on TV. The site offers over 100 online activities, podcasts, virtual labs, interactive animations, and feature articles with topics ranging from cloning to stem cells to gene therapy.

The development of materials was driven partly by the need to fill a gap in educating students about genetics—a high-interest topic frequently on the front page of newspapers. "Teachers often told us that most genetics materials were too advanced or not hands on," says Stark. For Stark and her colleagues, based at a university with an outstanding record in genetics research,

PHOTO BY HARMONY STARR, GENETIC SCIENCE LEARNING CENTER, UNIVERSITY OF UTAH

developing educational materials became a natural choice. "More genes for genetic disorders have been discovered at the University of Utah than anywhere else in the world," she says.

Materials, however, are effective only if used. Thus, professional development remains one of the SEPA Program's core strategies. By teaching teachers, the center indirectly educates students on today's genetics developments. Through partnerships with school districts and teacher associations, about 1,500 middle school and high school teachers have been taught to use the center's SEPA materials.

> A better understanding of health and research issues allows people to make informed decisions about lifestyle and medical care that can prevent disease and maintain health.

Professional development helps build the confidence of teachers. "At first I was nervous teaching science, because I'm not a scientist," says Godoy-Gonzalez, who has used *Click and Clone* and other activities with his students. "But the support has been magnificent. I feel like I have a backup team of scientists helping me."

Teachers who do not attend the instructional workshops can still download any of the 51 hands-on activities available at the site. "Some activities get 500 downloads every day, consistently," says Stark. All activities are free of charge.

One online module was expanded into a full-size museum exhibit, called *Stem Cells and You*. The exhibit was developed in collaboration with Utah's Museum of Natural History to support a public outreach component of the NIH Roadmap for Medical Research. This traveling exhibit explores the science, medical applications, and social and ethical issues related to stem cell use and is currently touring museums around the country.

In the future, Stark plans to enhance the Web site to communicate the importance of research to the public. "We would like individuals to understand more about genetic tests, the benefits of participating in clinical trials, and ultimately the new genetic treatments that could help them and their loved ones," she adds.

MARYLAND'S BRAIN FITNESS

How much science goes into running up the stairs? Apparently a lot, if you ask kinesiology professor Cathy Ennis. She and her colleagues at the University of Maryland, College Park, have developed a unique SEPA project that explores the science behind exercise. "Be Active Kids! (BAK!) is a set of curricular materials that uses physical education to teach students science," says Ennis. What makes BAK! unique is its integration of physical education with reading, science, and math. The project reaches about 3,000 children in grades 3 to 5 every year. BAK! is implemented in partnership with Prince George's County Public Schools, which serve a student population that is roughly 75 percent African American (http://www.hhp.umd.edu/BeActiveKids).

Through the materials, three fictional characters—Flex Coolbody, Dr. Love's Healthy Heart, and Mickey's Mighty Muscles—guide students in learning about their flexibility, target heart rate, and strength training. At the beginning of the semester-long project, students are given their own science journals. As the project progresses, they become junior scientists by jotting down data, completing tables, and drawing graphs in their journals related to the exercises they perform.

Fourth graders in Hawaii learn about the bones of the human body as they help to solve "Medical Mysteries" during a classroom activity.

But the curriculum goes beyond exercise to also encourage a healthy lifestyle. As part of the project, students are asked to choose a snack from a list that includes fruit, milk, a candy bar, soda, chips, a carrot stick, and french fries. They are then given the calorie counts for each snack and learn that it takes approximately 22 steps to use up one calorie. With this information, the children perform some quick calculations. Among oohs and aahs, students learn that it takes only 100 steps to use up the calories in a carrot but more than 6,000 steps for the candy bar. "Students begin to learn that there is a direct and immediate consequence to their decisions," says Ennis.

BAK!'s innovative approach is a welcome sign as the nation struggles to reduce obesity. During Family Science Night, up to 200 parents and siblings also participate in health and fitness events. The project will soon be expanding from the 15 schools it currently serves to 150 schools in Prince George's County, Maryland.

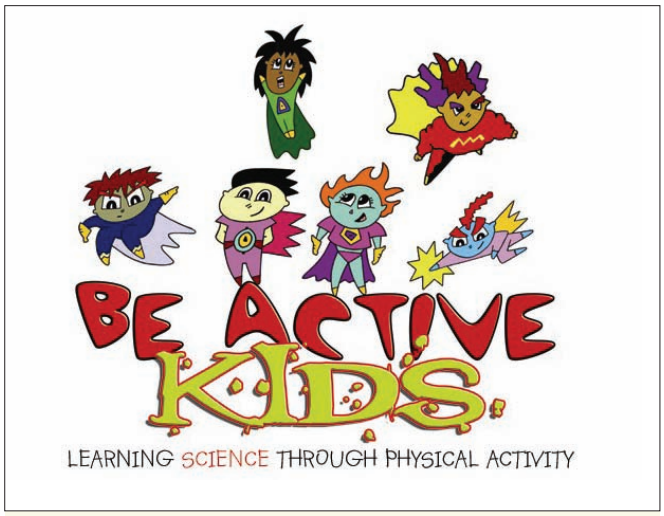
HAWAII'S NEXT WAVE

Planes and boats are part of the daily life of the SEPA staff in Hawaii. In a state of islands, this type of commute is typical. Hawaii is highly rural, with some islands being fairly distant or having small populations. Family physician Kelley Withy, who directs the SEPA project in Hawaii, sees the islands' geographical barriers in a positive light. "Remote communities are often the ones that need the project most, because they are exposed to less opportunities," she says.

In Hawaii, the SEPA project strives to guide students toward institutions offering degrees in health science. The lack of role models can make this challenging, though. Some islands completely lack not only a hospital but also, at times, a resident doctor. To counteract this, Hawaii's SEPA project piques the interest of young adults, families, and teachers by hosting a free Family Science Night in collaboration with local schools, community organizations, and the Bishop Museum.

In one station, students can become "doctor detectives," determining a patient's breath flow, heart rate, and body temperature and then matching them to a list of specific diagnoses. At other stations, students and parents can chat with health career professionals and learn more about careers, starting salaries, job outlooks, and health education projects in Hawaii. In all, more than 2,000 people have attended Family Science Night in rural communities throughout the islands.

Family Science Night is one of several strategies to interest, recruit, and encourage students to pursue health careers. Following Family Science Night, SEPA recruiters capitalize on students' enthusiasm by visiting the community's classrooms. Often accompanied by Hawaii health professionals, recruiters discuss health careers in depth.



Flex Coolbody, Mickey's Mighty Muscles, and other fun characters guide Maryland elementary students in learning the science behind physical education.

Seeing recent college graduates motivates many students to apply for a three-day summer program, during which high school students gear up to attend the University of Hawaii. To many students, some of whom have never left their home islands, this can be a life-changing experience. They live in the university's dorms and work with faculty to learn about health careers through hands-on activities. Students perform hearing tests, intubate mannequins, examine X-ray equipment, and participate in other educational endeavors.

But activities do not end with the summer project. SEPA of Hawaii works year-round by making staff available to answer questions via phone, e-mail, or personal classroom visits. Over the years, the project has become the glue between communities and institutions of higher learning, building a bridge between students and health careers. As with all SEPA projects, success depends on dynamic partnerships among universities, public schools, museums, or community centers. "We couldn't do half of what we do without our partnerships," says Withy.

TO LEARN MORE:

- The SEPA Program supports the creation of innovative partnerships between biomedical and clinical researchers, teachers and schools, museums, and other organizations. SEPA grants provide from two to five years of support. Domestic organizations with a scientific and/or educational mission are eligible to submit applications. To learn more or apply for SEPA funding, visit www.ncrr.nih.gov/clinical/cr_sepa.asp.
- Details on all 65 SEPA projects currently implemented across the nation, information on teacher and curricular materials, and links to SEPA project Web sites can be found at www.ncrrsepa.org.

PHOTO COURTESY OF BISHOP MUSEUM (OPPOSITE)

Cracking the Genetics of Disease

We are all created equal. Or perhaps 99.99 percent equal, at least genetically speaking. The other 0.01 percent variation is what can make the difference between health and disease. Scientists at the Broad Institute, an MIT-Harvard collaboration, are stepping up their analyses to identify the genetic variations that determine our susceptibility to common disorders such as heart attack, diabetes, autoimmune diseases, and hypertension. The emphasis on common disorders and study of multiple genetic variations marks an advance from the 1990s, when single genes that cause severe disease, such as cystic fibrosis, were first identified.

Now, scientists can compare the vast majority of genetic variation carried in sequences of healthy and ill individuals. In practice this approach, called whole-genome genotyping, is feasible for the first time ever. The process identifies the genotype at hundreds of thousands of positions across the genome. "There is tremendous advantage in terms of cost and efficiency to using these whole genome genotyping approaches," says geneticist Stacey Gabriel, director of the Center for Genotyping and Analysis at the Broad Institute. In contrast, attempting to compare complete DNA sequences between individuals would be entirely cost prohibitive. Comparing one gene at a time for variations also would be a slow process, considering that humans have 30,000 genes. To further complicate matters, susceptibility to most common diseases is determined by a multitude of genes. Identifying the best treatment for common diseases will likely require knowledge of the predisposing genes.

To increase the availability of genotyping for medical researchers, NCRR awarded a five-year, $14 million grant to develop the Center for Genotyping and Analysis in 2004. "The Broad Institute is clearly a leader in genotyping analysis because of their previous experience with other large-scale projects that have analyzed variation in the human genome," says Anthony Hayward, director of NCRR's Division for Clinical Research Resources.

The center has developed a strategic approach by looking only at the most common type of mutation in the genome, the single nucleotide polymorphism (SNP), or "snip." A SNP is the mutation of a single DNA base (A, T, C, or G) along the genome.

Stacey Gabriel and her team at the Broad Institute collaborate with disease consortia for multiple sclerosis, lupus, and type 1 diabetes to determine links between genetics and disease.

In essence, SNPs are genetic markers that crop up roughly every 300 bases. SNPs need to be thought of as the genetic basis for our individuality—not so much "mutations" as the variability that makes each of us unique. However, certain combinations of SNPs predispose individuals to disease. Scientists estimate that there are 10 million locations where SNPs can occur.

At the Center for Genotyping and Analysis, scientists are examining SNPs in hundreds of thousands of different combinations along the genome. To accomplish this effectively, the center utilizes state-of-the-art technology, including gene chips that can map, or genotype, up to 500,000 SNPs at a time in predetermined genome sections.

Preliminary results of these scans help researchers decide if they should look more closely at selected genes or move on and analyze another combination of SNPs. The idea is to cast a wide net and then focus in on specific SNP combinations. By using targeted genotyping, researchers can develop comparisons between healthy and diseased populations more rapidly and cost-effectively.

Currently, the center is working with several consortia—focusing on multiple sclerosis, lupus, type 1 diabetes, cancer and bipolar disorder—to examine thousands of genetic samples for each disease. "These studies will wrap up in the next two years," says Gabriel. "What we will know about these diseases two years from now will be totally changed." Understanding gene mutations also may help to develop new drugs and diagnostic strategies for the future.

PHOTO COURTESY OF BROAD INSTITUTE

Researchers can now take advantage of the laboratory's facilities to genotype their samples at a reduced cost through a new program that accepts applications twice yearly. "We offer the ability to manage and analyze data for whole-genome scans, which are in great demand and currently predominate in our work," says Gabriel. Interested scientists can submit their human or animal DNA for SNP analysis. "It has been great to be selected by NCRR to help other people do the kinds of studies that we're already doing. It's really about leveraging what is already there," Gabriel adds. **—AL STAROPOLI**

TO GAIN ACCESS: Researchers can apply for subsidized genotyping by filling out an application found on the Center for Genotyping and Analysis Web site at www.broad.mit.edu/genotyping/upload.html. Applications are accepted twice yearly. The next round of applications is due in June 2006.

A Measure of Age

Don Ingram pinches the skin on his forearm and wonders what happened to its elasticity. Now in his 50s, he has studied aging at the National Institute on Aging for nearly 30 years. "I'm now hitting full stride in my productive adult life. Why is it that we must lose that vigor?" says Ingram. Interestingly enough, some people reach their 60s in very poor physical and mental condition, while others in their 80s are still healthy and clearheaded. This is because chronological age is not the same as biological age. Scientists believe that biological changes in the body, rather than years of life, could be better predictors of health and potential life span. These changes can be measured through biomarkers such as glucose, blood cell count, cholesterol, and insulin.

Biological data gathered over decades from older primates, like the one shown here, could help researchers better understand the aging process in humans.

The National Institute on Aging and the NCRR-funded Wisconsin National Primate Research Center (NPRC) have announced the debut of an online biomarker database for aging research, the Internet Primate Aging Database, or iPAD. The iPAD contains tens of thousands of biomarker data such as cholesterol, body weight, hemoglobin, and 33 others, collected over the life spans of numerous primates. "Each of these biomarkers may affect aging in a different way," says Wendy Newton, research specialist at the NPRC. Understanding how biomarkers function may help explain the connection between biology and aging, she adds. The iPAD has already spurred several papers published in peer-reviewed journals.

Using data retrieved from iPAD, Ingram and colleagues examined various biomarkers in an aging population of 345 healthy rhesus monkeys. Their study concluded that age does indeed influence biomarkers. In particular, lymphocytes, white blood cells that identify and attack viruses, showed a marked change. "Just when we begin needing them as we get older, their numbers go down," says Ingram. By monitoring biomarkers in primates, which generally have much shorter life spans than humans, scientists can evalaute whether interventions such as exercise, diet, hormones, pharmaceuticals, or dietary additives can slow the rate of aging.

The iPAD allows researchers to perform detailed data queries by gender, age, site, diet type, primate species, or a specific biomarker. Statistical query results can be downloaded into a spreadsheet for further manipulation or presented in table form along with mean, standard deviation, standard error, and total number of data points. This powerful database will soon incorporate graphing functions and other add-ons. Previously available only on CD-ROM, the database is now available to researchers, free of charge, on the Web.

"Because the aging process is remarkably similar in humans and nonhuman primates," says Ingram, "clinical investigators could benefit from a preliminary analysis of iPAD data before developing human studies." This could provide scientists with valuable insights as they begin to establish protocols for aging research. **—AL STAROPOLI**

TO GAIN ACCESS: The iPAD is supported by the National Institute on Aging and the Wisconsin National Primate Research Center, one of eight NCRR-funded primate research centers nationwide. To access iPAD, request a user name and password at http://iPAD.primate.wisc.edu. With more than 500,000 data points from 17 different nonhuman primate species, users can view biomarker data that spans an animal's lifetime. Researchers interested in becoming part of this interdisciplinary, collaborative effort can contribute their primate data by contacting the iPAD system administrator, Wendy Newton, at wnewton@primate.wisc.edu.

PHOTO BY J. LENON, WISCONSIN NATIONAL PRIMATE RESEARCH CENTER

High-End Technologies for High-Powered Research

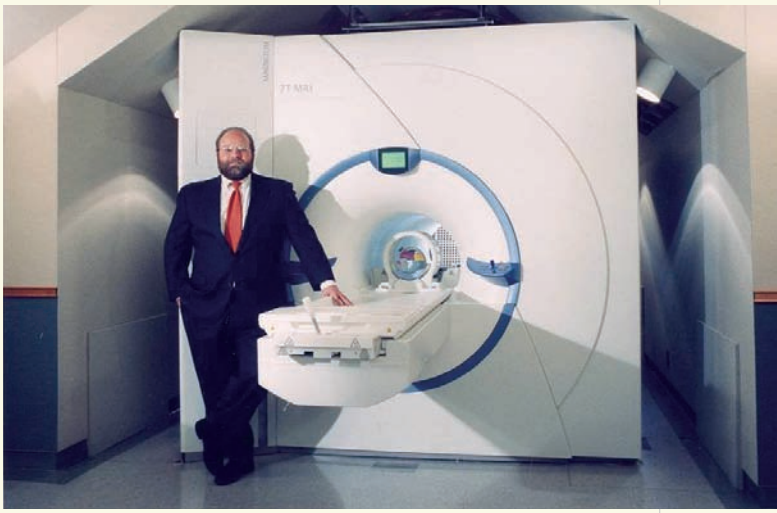
Grants for high-end instruments give a boost to imaging studies, and more.

Imagine having to deliver a 33-ton package in the middle of Manhattan, containing a magnet so powerful that it could draw every metal object in a three-mile radius. It happened two years ago, when New York University (NYU) School of Medicine became home to one of the world's most powerful magnetic resonance imaging (MRI) machines. Around the same time, another large device, one that churns out radioactive elements, was delivered to the opposite coast, at the University of Washington in Seattle.

Both machines came with hefty price tags, paid in part by a new class of NCRR grants for High-End Instrumentation (HEI). NCRR has long been supporting the purchase of instruments costing up to $500,000 through its Shared Instrumentation Grant (SIG) Program (see *NCRR Reporter*, Fall 2004, pages 8-9). But many devices used in biomedical research are much more expensive. "We were getting applications for the maximum amount of the SIG award, but the total cost of the instrument was well over $1 million," says Marjorie Tingle, who oversees the HEI and SIG Programs for NCRR's Division of Biomedical Technology. "We realized there was a need for high-end instrumentation that was not being met." And this realization proved to be correct. In 2002, the first year the HEI grants were made available for instruments costing more than $750,000, NCRR received close to 100 applications.

Joseph Helpern was among the successful applicants. As director of NYU's Center for Biomedical Imaging, Helpern received a $2 million HEI grant to purchase a new MRI machine. MRI allows researchers to visualize almost every tissue in the body. When undergoing an MRI scan, the patient lies inside a large, cylinder-shaped magnet as waves—thousands of times stronger than the Earth's magnetic field—are sent through the body, forcing the nuclei of atoms to wobble. A scanner records the nuclei's movement, and a computer then turns this information into a three-dimensional picture.

A unique aspect of the NYU machine is the strength of its magnet, which measures at 7 tesla, nearly 5 times as powerful as the 1.5-tesla MRI systems used routinely at most medical centers. "It is equivalent to having built a new telescope to look into space. You can see things that you never saw before," Helpern says.



Joseph Helpern used HEI funding to purchase a robust MRI system, nearly 5 times more powerful than most clinical MRI machines. This high-end instrument will aid studies of Alzheimer's disease, breast cancer, and other conditions.

Although other 7-tesla MRI systems are used for clinical research, these scanners are limited, for technical reasons, to imaging the head. But Helpern worked closely with Siemens Medical Solutions in Erlangen, Germany, to create an instrument that could image the entire human body. Initially, the idea was met with some skepticism. "It took a lot of conference calls and discussions with engineers, but we did it," says Helpern. "This is an example of a unique cooperation between a private institute, a vendor, and the National Institutes of Health."

Another challenge for Helpern was to figure out how to house the massive instrument at NYU. For starters, he designed a 420-ton, octagon-shaped steel shield for it. In addition, the university built a 14-foot-high concrete bed to support the instrument and to protect it from vibrations. Once the MRI was put in place and thoroughly tested, Helpern's team and several collaborators began gathering breathtaking images of different parts of the human body. In one project, Helpern is trying to develop methods to detect the telltale signs of Alzheimer's disease and other disorders that affect the brain.

PHOTO BY RENÉ PEREZ, NEW YORK UNIVERSITY SCHOOL OF MEDICINE

"Other NYU researchers have embarked on a series of breast-imaging studies, with spectacular results," says Helpern. "The possible applications of this machine are endless."

Another type of imaging, positron emission tomography (PET), relies on the detection of positrons, tiny particles emitted from radioactive substances. An instrument called a cyclotron makes short-lived isotopes—such as carbon-11, with a half-life of 20 minutes, or fluorine-18, with a half-life of 110 minutes—which are then used to synthesize different compounds. Once administered to a patient, these radioactive compounds, or tracers, yield chemical information about various tissues. Because the isotopes are short-lived, they need to be manufactured onsite.

The University of Washington has had a thriving PET imaging program for 19 years. But to obtain radioisotopes for PET research, imaging groups originally had to purchase time on a cyclotron belonging to a different university department. In 2002, however, "life got much better," says Kenneth A. Krohn, who heads the university's Cancer Imaging program project. Krohn received a $2 million HEI grant to purchase a cyclotron dedicated to imaging research. "We can now make more radioactive compounds for more studies, with more collaborators, and we can use more complicated protocols," he says. "Since installing the new machine, the center's productivity and the number of investigators using our tracers has increased by about fourfold."

■ *Kenneth Krohn prepares to create radioactive tracers in a state-of-the-art cyclotron acquired through an HEI grant. The tracers are used primarily for cancer imaging in patients.*

PHOTO COURTESY OF UNIVERSITY OF WASHINGTON

PET imaging is primarily used to study cancer. With short-lived isotopes, a researcher can use different tracers in a single imaging session to measure multiple tumor properties at once. "Tomorrow we are going to study a woman with a sarcoma in her shoulder, and we will obtain images using three different tracers," says Krohn. "Carbon-11-labeled thymidine will measure the rate of DNA synthesis in the tumor; fluorine-18-labeled fluoromisonidazole will measure the degree of hypoxia, or lack of oxygen, in the tumor, since tumors that are hypoxic respond poorly to radiation therapy; and carbon-11-labeled verapamil will measure multidrug resistance, another indicator of the response to therapy." A study like this, typical of several done each day at the center, can be completed in about two-and-a-half hours. This technology is critically important for selecting the right treatment for each patient.

Although the cyclotron is primarily used for cancer research, the instrument also is used for other purposes. For example, the NCRR-funded Washington National Primate Research Center makes use of the short-lived tracers for studies on primate models of disease. A major focus of Krohn's research is the development of new tracers. He recently synthesized fluorine-18-labeled annexin V to detect cells undergoing programmed cell death in a rat model of cancer. With further evaluation, the tracer might become a useful tool for detecting a patient's clinical response to cancer therapy.

The researchers acknowledge the importance of the HEI program for their work. "The cyclotron would have been too expensive for us to buy," says Krohn. "It cost $1.7 million, plus $1 million to prepare the site for installation." Helpern concurs. "The HEI is a very significant program," he says, speaking from experience. Sixteen years ago, Helpern's group received a $400,000 SIG from NCRR to build the world's first 3-tesla MRI system specifically for human brain research. "Now the 3-tesla system is exploding in popularity," he says.

—LAURA BONETTA

APPLY FOR FUNDING: Applicants for High-End Instrumentation (HEI) grants may request up to $2 million to cover the purchase of a major piece of equipment, including mass spectrometers, electron microscopes, supercomputers, and more. Institutions are expected to provide support for the associated infrastructure. Grants are available to domestic public and nonprofit health professional schools, other academic institutions, hospitals, health departments, and research organizations. To be eligible, the application must identify three or more NIH-funded investigators who will use the instrument. Applicants are encouraged to contact NCRR program staff at HEI@mail.nih.gov before applying for a grant. Additional information about HEI grants is available at http://www.ncrr.nih.gov/biotech/btheinstr.asp.

Darwin Prockop and his colleagues study how adult human stem cells might exert a therapeutic influence on neighboring cells, helping to repair dysfunctional cells in damaged tissues.

Unlocking the Mysteries of Stem Cells

Scientists explore the therapeutic mechanisms of adult stem cells.

BY SANDRA J. ACKERMAN

Several years ago, Darwin Prockop of Tulane University and a group of medical students set out to solve a mystery that might have been dubbed the Case of the Disappearing Stem Cells. Their findings, to date, have led to two ground-breaking papers and a handful of new insights into one of nature's essential tools for repairing damaged tissues. In fact, clinical studies based on Prockop's animal research may ultimately help to improve the treatment of cardiac, bone, and neurodegenerative disorders, and possibly some forms of cancer.

Scientists first observed the mysterious disappearance of stem cells while testing experimental therapies for animal models of inherited or acquired diseases. In some cases, infusion of healthy adult stem cells significantly improved an animal's condition. But even when the treatment was clearly effective, the stem cells themselves soon became virtually undetectable.

"The tissues got better," says Prockop, director of Tulane's Center for Gene Therapy, "but we couldn't find many of the cells afterward." For example, in a mouse model of myocardial infarction, or heart attack, Prockop's research team injected half a million mesenchymal stem cells, or MSCs. Derived from bone marrow, MSCs can differentiate, or mature, into almost any tissue in the body except blood cells. MSC infusion spurred the repair of muscle tissue in the heart, helping the animals to regain a stronger and faster heartbeat. Yet, seven weeks after the infusion, the scientists found fewer than five MSCs in the entire heart muscle.

As the principal investigator of the NCRR-supported Adult Mesenchymal Stem Cell Resource, Prockop is thoroughly knowledgeable about these cells. He oversees their preparation, testing, and distribution to scientists all over the world (see box).

Prockop found his way to stem cells through collagen, the fibrous protein that is the principal source of strength for bone and other tough tissues of the body. With research that continued over decades, first at the National Institutes of Health and later at the University of Pennsylvania and the Robert Wood Johnson Medical School in New Jersey, Prockop and his colleagues defined the unusual pathway by which cells synthesize collagen.

The investigators then isolated the human genes for collagen, along with a series of mutations that interfere with either the normal production or the normal function of collagen. These mutations cause a rare and sometimes disabling disorder known as brittle bone disease, or osteogenesis imperfecta. Children with severe forms of the disease die before or shortly after birth. Children with milder forms easily fracture their bones and often stop growing altogether.

Prockop's group provided critical preclinical data to colleagues Edwin Horwitz and Malcolm Brenner at St. Jude Children's Research Hospital. Studies published by Horwitz and Brenner in 1999 and 2001 describe clinical research in which normal MSCs were given to a small number of children with severe osteogenesis imperfecta. Each young patient received first a bone marrow transplant from a healthy sibling, then an infusion of MSCs from the same individual. Because the patient's immune system had already been "replaced" with cells from a

PHOTO COURTESY OF TULANE UNIVERSITY HEALTH SCIENCES CENTER

healthy sister or brother, scientists expected that the new stem cells would not be rejected by the patient. Within a few months, children who received the stem cell infusions began to grow rapidly, and 80 percent were able to sit up unassisted for the first time in their lives. These encouraging results raise the prospect of new and more effective treatments not only for osteogenesis imperfecta but also for other bone disorders, including osteoporosis.

Prockop arrived at Tulane in the summer of 2000, accompanied by more than a dozen scientists who had already spent several years preparing and studying adult MSCs. The NCRR resource opened shortly thereafter, and the search for the disappearing stem cells was under way. The group published one possible solution to the mystery in the *Proceedings of the National Academy of Sciences* (*PNAS*) in December 2005. When MSCs are implanted in the brain of a mouse, the scientists found, the cells did not proliferate but rather stimulated the proliferation of neighboring neural stem cells, which are found in small numbers in the adult brain. The researchers suggest that the MSCs stimulated neural stem cell production by secreting chemical signals known as chemokines and cytokines. The new neural stem cells then dispersed throughout the brain and began to differentiate into several types of mature neural cells in normal fashion, although few of the original MSCs survived.

The Tulane research team presented another possible solution in January 2006, again in *PNAS*. This time the scientists made an unexpected discovery while studying the cellular mitochondria, known as "the powerhouse of the cell" because they supply the energy needed for normal cellular functions. In culture, the scientists demonstrated, the mitochondria of MSCs can actually move or transfer themselves, or their DNA, into cells with malfunctioning mitochondria. By giving their own mitochondria to other cells, the MSCs can help to repair the effects of serious maladies such as heart disease, spinal cord injury, or stroke.

Alternative explanations for disappearing stem cells may still be forthcoming, as Prockop and his collaborators continue to pursue their investigations. Meanwhile, the Adult Mesenchymal Stem Cell Resource provides researchers worldwide with the means to pursue their own lines of inquiry.

The stem cell resource receives some funding from HCA Healthcare Corporation and the Louisiana Gene Therapy Research Consortium, yet the essential agency at the outset was the NCRR, Prockop says, because its support offered his group the time and the equipment they needed. The stem cell center continues looking for more ways to serve the research community. "This is an important service being provided to the scientific community by Tulane and by NCRR," Prockop says. "These cells offer significant potential for biomedical research that will define the basic biology of adult stem and progenitor cells and the possible use of these cells for treating a large number of human diseases."

The research described in this article is supported in part by NCRR; the National Heart, Lung, and Blood Institute; and the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

About the Adult Stem Cell Resource

NCRR established the Adult Mesenchymal Stem Cell Resource in 2003 to open up a bottleneck that had hindered progress in the promising field of stem cell research—that is, scientists lacked a reliable, standardized, and fully characterized source of adult stem cells. Each shipment from the Tulane-based resource lists the characteristics of the enclosed stem cells. Because the resource staff consistently maintains cell characteristics from one batch to another, researchers can compare results over time or among various studies.

The resource's stem cell distribution system fills a unique niche in the international scientific community, says Brian Butcher, associate director of the resource and a research professor of medicine at Tulane. Indeed, the original grant application to create the stem cell resource received 164 letters of support from researchers worldwide, Butcher says. The resource offers adult rat, mouse, and human mesenchymal stem cells for in vitro or animal studies. Administering these cells to patients or using them for commercial purposes is prohibited.

The cells are supplied frozen in liquid nitrogen in small vials, with approximately 1 million cells per vial. Each shipment includes a second vial as a backup. The current fee of $150 can sometimes be waived in cases of hardship.

For more information, or to place an order, scientists should contact Roxanne Reger at msc@tulane.edu or visit the Web site at www.som.tulane.edu/gene_therapy/distribute.shtml.

Shining a Light on Diabetes

For patients living with severe type 1 diabetes, a life free from insulin injections could be sweet news. Clinical research studies show that some patients no longer need insulin injections, nor experience episodes of dangerously low blood sugar, after receiving islets obtained from a healthy pancreas. But monitoring the survival of these transplanted islets—a step critical to success—has often been challenging.

Now cell biologist Anna Moore and her colleagues at Harvard Medical School are proposing an intriguing method to track the viability of transplanted islets in this experimental technique. By labeling them with microscopic nanoparticles of iron in the laboratory prior to injection, the researchers were able to spot transplanted islets in living mice through the use of magnetic resonance imaging (MRI). "We have turned the light on diabetes, by being able to follow these cells," says Moore.

Currently, how many islets survive transplantation is estimated by measuring levels of either glucose or insulin in the blood. But insulin and glucose levels fluctuate in response to eating and exercise and may be affected by stress and illness.

By labeling islets with iron nanoparticles, the researchers were able to use MRI to spot transplanted islets in living mice.

A more precise alternative would be to biopsy the tissue and count the islets, an invasive procedure. Moore's approach sidesteps these tests by tagging the cells directly, making them distinct from other cells and readily identifiable when the mouse is placed within an MRI machine. "We now have the power to see islets in vivo," she says.

Moore injected the labeled islets into the space between the mouse kidney and its thin tissue surface, and then tracked them through MRI scans as they restored normal insulin levels in diabetic mice. She found that labeling of the islets neither caused toxicity nor kept them from producing insulin.

This original approach may one day benefit patients who have type 1 diabetes. By using labeled islets and performing periodic MRI scans after transplantation, physicians might be able to quickly determine if islets are dying and whether additional transplants are needed.

Cell biologist Anna Moore prepares insulin-producing islets for transplantation into diabetic mice.

Critical to Moore's research was the ability to obtain purified human islets from several NCRR-supported Islet Cell Resource (ICR) Centers. Originally established to produce and distribute clinical-grade islets for human transplantation, the ICRs have expanded their scope of responsibility to also provide human islets for basic laboratory and preclinical investigations like Moore's, that advance research in diabetes. "Our studies depend on having access to these islets," says Moore. "We wouldn't be able to do the job without them." (*Nature Medicine* 12:144-148, 2006) **—AL STAROPOLI**

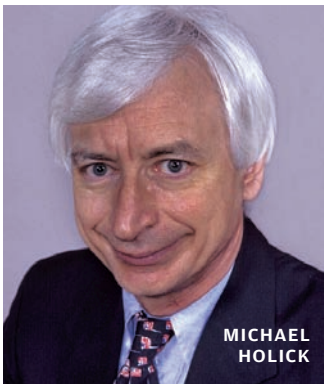
NCRR RESOURCES: The nation's 10 Islet Cell Resource Centers were created in 2001 to harvest, purify, store, and ship human pancreatic islets for experimental transplantation into patients with severe type 1 diabetes. Through a unique partnership with the Juvenile Diabetes Research Foundation International, the ICRs also provide islets for basic research studies at no cost to approved investigators. Detailed information on the ICRs—which are funded by NCRR and the National Institute of Diabetes and Digestive and Kidney Diseases— and how to request islets, are available at http://icr.coh.org.

PHOTO COURTESY OF MASSACHUSETTS GENERAL HOSPITAL

Awards Honor Clinical Researchers

Michael Holick received the 18th Annual Award for Excellence in Clinical Research. Holick is a professor of medicine, physiology, and biophysics at Boston University Medical Center. The award was presented at the General Clinical Research Center (GCRC) Program Directors Meeting, held March 16-17 in Washington, D.C. The GCRC Program Directors Association conferred the award on behalf of the Jane and Charles Pak Foundation, which funds the award to recognize outstanding clinical investigators who have conducted studies at GCRCs within the previous decade.

Holick received the $5,000 award for his pioneering contributions in the basic science of vitamin D. After closely evaluating vitamin D in whole and skim milk, Holick and his colleagues determined that vitamin D also could be made available in orange juice. This important study influenced Minute Maid and Tropicana in fortifying their orange juice with vitamin D. Holick was also the first to isolate and identify the biologically active form of vitamin D3. He participated in the chemical synthesis of 1,25-dihydroxy vitamin D3


MICHAEL HOLICK


SYLVIA FRAZIER-BOWERS

and demonstrated that its use was safe and effective for treatment of psoriasis in children and adults. Holick also pioneered research on the photobiology of vitamin D and established guidelines for sensible sun exposure for bone health.

At the Clinical Research 2006 meeting, held in tandem with the GCRC Program Directors Meeting, **Sylvia Frazier-Bowers** of the University of North Carolina at Chapel Hill received the $2,000 GCRC Outstanding Trainee Award. Her research focuses on the genetic basis of craniofacial and tooth disorders.

Frazier-Bowers, an orthodontist, was recognized for an abstract she presented on mandibular prognathism, a disorder characterized by an overgrown lower jaw or a deficient upper jaw. The trait is believed to develop due to both hereditary and environmental factors. Frazier-Bowers performed a genome-wide scan in four families with the condition. Her results indicated that the trait is largely under strict genetic control with distinct sub-phenotypes.

Frazier-Bowers is an assistant professor in the department of orthodontics at the University of North Carolina School of Dentistry. She received her D.D.S. from the University of Illinois at Chicago and holds a Ph.D. in genetics and molecular biology from the University of North Carolina at Chapel Hill.

NCRR Tracks State of Clinical Research Informatics

As part of its clinical research activities, NCRR has contracted the MITRE Corporation to produce clinical research informatics "snapshots," brief reports describing the state-of-the-art in information technology for clinical research. Over a two-year period, MITRE will investigate current informatics used for clinical research, propose and analyze approaches, monitor trends, and track the evolution of related technologies in both public and private sectors. The reports are expected to help guide strategic planning efforts across NIH and among its grantees. Information, best practices, analysis, and recommendations will be posted monthly at http://www.ncrr.nih.gov/informatics_reports.asp.

Nicotine Expert Receives Award

Nicotine expert **Neal Benowitz** has received the Oscar B. Hunter Memorial Award in Therapeutics, which honors scientists for their outstanding contributions in drug research, patient care, and teaching. Benowitz, a professor of medicine at the University of California, San Francisco, received the award at the annual meeting of the American Society for Clinical Pharmacology and Therapeutics, held in Baltimore on March 11.

He has studied the human pharmacology of nicotine, including nicotine addiction, through the university's GCRC. "I did my very first studies on the GCRC in about 1975, and the GCRC has been the site of virtually all of my research since," says Benowitz. Benowitz was the senior sci-

[CONTINUED ON BACK COVER ➤]

PHOTO COURTESY OF BOSTON UNIVERSITY(HOLICK), PHOTO BY RAMONA HUTTON-HOWE, UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL (FRAZIER-BOWERS)

[CONTINUED FROM PAGE 15]

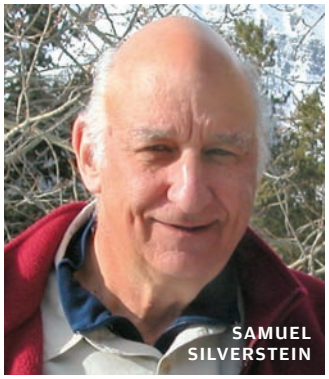
entific editor of the U.S. Surgeon General's 1988 report on nicotine addiction, which has been used as a blueprint around the world in developing tobacco control policies.

Web Portal for Animal Resources

NCRR plans to create a Web-based portal to integrate and coordinate use of all NIH-supported animal and related biological resources. This Animal Information Center will enhance access and retrieval of information from existing model databases and accommodate the addition of new ones. "Resources for translational science are needed to quickly and effectively move between basic discovery and clinical studies," says Harold Watson, health scientist administrator for NCRR's Division of Comparative Medicine. "There has never been a greater need for easily accessible and broadly informed disease modeling systems to guide the translational researcher to and through the preclinical studies," he adds.

To plan the design of the portal, invited experts met on the NIH campus, March 6-7, for the workshop "Navigating the Translational Researcher Through a Complex of Animal and Biological Resources." Participants identified the portal's user community and its needs and described the range of expertise and technology needed to staff and support the resource. Invited workshop members included animal researchers, clinical and translational science researchers, resource managers and developers, industry representatives, and NIH intramural and extramural staff.

For more information on the workshop, visit www.ncrrworkshops.com/navigating/index.aspx.



SAMUEL SILVERSTEIN

Science Educator Honored

Samuel Silverstein, physiology professor at Columbia University, has received the Bruce Alberts Award for Excellence in Science Education from the American Society for Cell Biology. The award is bestowed for innovative and sustained activities in science education.

Silverstein directs the university's Summer Research Program for Science Teachers, which is funded through a Science Education Partnership Award (SEPA). The project mentors middle and high school teachers in the New York metropolitan area through two summers of intensive eight-week sessions that provide hands-on experiences in Columbia's research laboratories.

Throughout the program, teachers acquire in-depth knowledge of a scientific discipline—such as biology, organic chemistry, or medical sciences—and master several technologies employed in the discipline. The program allows teachers to translate what they have learned to the classroom and, ultimately, to transmit the practice of scientific research to their students.

PHOTO BY RALPH MILLER

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