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NATIONAL INSTITUTES OF HEALTH NATIONAL CENTER FOR RESEARCH RESOURCES

NCRR Reporter

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Critical Resources for Research

U.S. Department of Health and Human Services

The Operating Room of the Future

FROM THE DIRECTOR

Opportunities for Translation Through Advances in Biomedical Technologies

Countless breakthroughs in biomedical research and medicine have been made possible through the development of innovative technologies, instruments, and tools that open new doors for researchers and physicians. This issue provides excellent examples of the results.

The center featured in the cover story is just one of 50 NCRR-supported Biomedical Technology Research Resources (BTRRs) — all of which have made accomplishments in fostering translational medicine. But BTRRs don't function in a vacuum. They provide invaluable training and educational resources and are built on collaborations among basic scientists, clinicians, and engineers who strive to identify and address pressing needs in both research labs and the clinic.

Researchers at a single BTRR routinely interact with investigators supported by a wide range of NIH institutes and centers, as well as those from other NCRR programs, including the Clinical and Translational Science Awards (CTSAs). CTSA awardees, for example, use the BTRRs' expertise and resources to create new diagnostic tests, adopt advanced research computing infrastructure, and explore molecular fingerprints of specific diseases.

BTRRs actively share the technologies they develop, often forging partnerships with industry to manufacture and commercialize instruments and tools — a critical element in bringing technological discoveries to the clinic. And many BTRRs receive additional support from other NIH institutes, leveraging resources to achieve their goals.

As you'll read in this issue, investigators at the BTRR in Boston, known as the National Center for Image-Guided Therapy, have developed an FDA-approved ultrasound instrument for eradicating uterine fibroids. This tool is now being adapted for other exciting applications, including tumor removal and neuroadministration of drugs. Other technologies conceived at the center are enabling neurosurgeons to minimize damage to normal brain tissue during operations and are providing physicians with more precise and effective methods for honing in on prostate cancer and other malignancies.

The research at the National Center for Image-Guided Therapy, like that at other BTRR centers, is helping to transform patient care by providing physicians with the tools to treat patients more efficiently and safely. Thanks to such advances, the "operating room of the future" is becoming a reality.

Barbara Alving, M.D.

Barbara Alving, M.D.
Director, NCRR

INSIDE

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On the Cover: Researchers at Brigham and Women's Hospital in Boston made critical technical advances that enabled the use of ultrasound energy in performing surgery without actually cutting into a patient. The research led to the FDA-approved instrument shown on the cover, called ExAblate 2000, developed in collaboration with the Israel-based company InSightec and GE Healthcare. As new advanced technologies and instruments developed by the National Center for Image-Guided Therapy and other NCRR-funded Biomedical Technology Research Resources make their way into hospitals, they will help clinicians perform much safer and more advanced procedures.

PHOTO BY BRENDAN STEWART

Consortium for Clinical and Translational Research Grows

Fourteen academic health centers in 11 states are the newest members of NIH's Clinical and Translational Science Award (CTSA) consortium. This round of awards, totaling $533 million over five years, brings the total number of CTSAs to 38; the program will connect up to 60 CTSAs by 2012.

The 2008 CTSA grants expand state representation in the consortium to Alabama, Colorado, Indiana, Massachusetts, and Utah. They also support pediatric research at 13 dedicated children's hospitals, expand research in genetics and genomics, and increase outreach into local communities. The institutions receiving new funding are as follows: Albert Einstein College of Medicine of Yeshiva University, Boston University, Harvard University, Indiana University School of Medicine, Northwestern University, The Ohio State University, The Scripps Research Institute, Stanford University, Tufts University, The University of Alabama at Birmingham, University of Colorado Denver, The University of North Carolina at Chapel Hill, The University of Texas Health Science Center at San Antonio, and The University of Utah.

New Feature on CTSAweb.org

The continued success of the translational research process is dependent on the ability of clinical and translational researchers to work with each other, NIH, businesses, the community, and the public. Building and sustaining long-term, mutually beneficial relationships is a critical component of the CTSA consortium. To foster these critical connections, the consortium launched a new feature on CTSAweb.org called *Building Connections.* The new Web page features:

- CTSA principal investigator profiles.
- Liaisons with NIH institutes and centers.
- Public-private partnerships interested in collaboration with CTSAs.
- CTSA interactions with business schools.

The *Building Connections* page allows clinical and translational researchers to connect with one another and share their areas of research, establish lines of communication within NIH, stimulate research alliances by identifying opportunities for collaboration among the CTSAs and private-sector organizations, and learn about ways that CTSAs are forming partnerships to further enhance clinical and translational research.

"Perhaps the most unique element of the *Building Connections* feature is its clear demonstration of the ways that CTSAs are working together with their own business schools to develop innovative programs and leverage key resources," says NCRR Director Barbara Alving. "Many CTSAs and their business schools are working together to develop business plans, design and implement community surveys, and create innovative cross-educational programs." Other examples of CTSA/business school partnerships include developing case studies to pilot programs, collaborating with international colleagues, preparing cost analyses, protecting CTSA-developed patents, drafting marketing plans, and forming unique industry partnership programs.

For more information on this valuable tool, visit CTSAweb.org and click on the *Building Connections* link in the Quick Links box on the upper right-hand side.

New Tool Helps Researchers Find Core Resources

The University of California, San Francisco's Clinical and Translational Science Institute has launched a "Cores Search" feature on its Web site (http://ctsi.ucsf.edu), which allows researchers to search for information about more than 90 core research resources within the institute. Users can search and sort data by campus location, resource category, and specific service or equipment. Information about the full range of services available for each core is also accessible. Many CTSAs have included similar features on their Web sites, and it is hoped that this approach will be established across the entire consortium and accessible through CTSAweb.org. ■

The Clinical and Translational Science Award (CTSA) program is a national consortium designed to transform how biomedical research is conducted across the country. Its goals are to speed the translation of laboratory discoveries into treatments for patients as well as to train the next generation of clinical researchers. The CTSA program is led by NCRR. For more information, visit CTSAweb.org.

The Operating Room of the Future

Advanced imaging technologies are transforming therapy. **BY LAURA BONETTA**

"When you visit a hospital today, the most low-tech place is the operating room," says Ferenc Jolesz, director of the National Center for Image-Guided Therapy (NCIGT) at Brigham and Women's Hospital and Harvard Medical School in Boston. "Advanced technologies are available for diagnosis but not for therapy. That is at the heart of what we are trying to do."

The center is one of 50 NCRR-funded Biomedical Technology Research Resources nationwide (see sidebar "Biomedical Technology Research Resources for Imaging Technologies"), each focused on developing advanced technologies for biomedical research and clinical practice. With co-funding from the National Cancer Institute and the National Institute of Biomedical Imaging and Bioengineering, NCIGT serves as a test bed for new imaging technologies and their application in the operating room, where they can assist surgeons in delivering safer and more effective treatments.

"In traditional surgery, the surgeon's vision is limited to the surface," Jolesz says. "With imaging, you can see every layer of tissue without having to cut through the patient." New imaging technologies allow surgeons to "see" where tumors are located, for example, even before starting an operation. Imaging-based approaches also enable new treatment methods that do not require any cutting at all. And imaging methods allow medicines to be delivered to the intended target with greater precision and effectiveness.

■ The NCRR-supported National Center for Image-Guided Therapy (NCIGT) at Brigham and Women's Hospital and Harvard Medical School in Boston will soon unveil the first prototype of its "operating room of the future." This will comprise several imaging systems, a sophisticated surgical table that moves patients between stations, and detailed visual displays to guide a clinician during medical procedures. By developing approaches that incorporate powerful imaging technologies in the operating room, NCIGT researchers will assist clinicians in delivering safer and more effective treatments.

IMAGE BY PAYETTE ASSOCIATES

> There has to be a clinical need to do something better than the current treatment. Technology is never the initiating process. We don't develop a technology and then look for an application.
>
> —FERENC A. JOLESZ, DIRECTOR OF THE NATIONAL CENTER FOR IMAGE-GUIDED THERAPY

NCIGT's accomplishments in the past decade illustrate both the promise and the challenges of bringing advanced technologies from the laboratory to the clinic. They also reveal the key ingredients for making this transition possible: a strong research tradition, teams of basic scientists and physicians focused on translating a research finding to a particular application, and collaborations among different research institutions and between academic researchers and industry.

ULTRASOUND AS A SCALPEL

A technology that progressed rapidly from discovery to clinical implementation is magnetic resonance–guided focused ultrasound. Physicians typically use ultrasound to image tissues in the body (see sidebar "An Imaging Primer"); when high-frequency sound waves bounce off internal tissues, the echoes they produce can be analyzed as images of tissues. However, it has been known for more than 60 years that focusing a beam of ultrasound to a particular point in the body could be used to destroy or remove a tissue — akin to performing surgery but without a scalpel.

In the early 1990s, Kullervo Hynynen and Jolesz, both at Brigham and Women's Hospital at the time, showed that this type of "surgery" could be performed inside a magnetic resonance imaging (MRI) scanner to guide and monitor the procedure. Use of the MRI allows surgeons to carefully plan where to point the ultrasound and to immediately visualize the results of the operation. In addition, because energy from the ultrasound beam produces heat, a special application of MRI allows surgeons to monitor the temperature in the target tissue and maintain it within a certain range.

Hynynen and Jolesz have taken their research to the clinic. Research by the Focused Ultrasound Laboratory core at NCIGT led to the development of an instrument, called ExAblate 2000, for transmitting focused ultrasound waves. This instrument was approved by the U.S. Food and Drug Administration (FDA) in 2004 for the removal of fibroids.

Fibroids are generally benign muscular tumors that grow in the wall of the uterus. Most women with fibroids do not have symptoms, but for those whose fibroids cause pain or severe bleeding, removal of the uterus is one of the few options available to them. But with focused ultrasound, a fibroid can be removed without surgery.

A woman lies facedown on the MRI scanner, and beneath her the ExAblate 2000 ultrasound transducer transmits a focused stream of waves for up to several hours. The heat generated by these waves gradually destroys the fibroid, while the MRI scanner continuously monitors the temperature of tissues in the uterus as well as the position of the fibroid. The recovery time for the patient is reduced, and she is able to return to normal activities more quickly than after traditional surgery.

Because of the success of focused ultrasound with uterine fibroids, NCIGT researchers are testing the same technology on different organs, such as the prostate or brain, by modifying the transducer and how the treatment is delivered. These procedures are at various stages of testing in animals or in clinical trials in patients.

Focused ultrasound is also proving useful for the delivery of medicines to the brain. Humans have a collection of tightly packed epithelial cells within the blood vessels leading to the brain — called the blood-brain barrier — which prevents most larger molecules, including drugs, from passing through the bloodstream into the brain. Researchers in the Focused Ultrasound Laboratory core have developed a technology that uses focused ultrasound to poke temporary holes in the blood-brain barrier to allow drugs through. So far, the strategy has been successful in delivering chemotherapy for brain tumors in animal models.

FORGING NEW PATHS

The first step in applying any technology to a clinical area, such as prostate or brain tumor treatment, is to assess whether there is a need for it. "There has to be a clinical need to do something better than the current treatment," Jolesz explains. The second step is to look for a technology that can provide the needed improvement. "Technology is never the initiating process. We don't develop a technology and then look for an application."

NCIGT researchers benefit from working at a hospital and having access to and interactions with physicians who can both communicate their needs and provide feedback on new

technologies. "When you are using imaging in either research or diagnosis, it is like reading pages in a book," Jolesz says. "But when you use it in therapy, the imaging system has to change in relation to what the surgeon is doing. It becomes an interactive system, so the requirements are different."

But the application of new technologies to the clinic doesn't require just collaboration with physicians. Usually new tools and instruments are needed, and researchers must work closely with industry to develop them. "We might have an existing technology available for a diagnostic system but need new features to make it suitable for surgery," Jolesz says. "You need a company to make the devices and components. They are complex and expensive and cannot be developed in our center."

The ExAblate 2000 ultrasound device, for example, was built by InSightec, a company based in Haifa, Israel. General Electric developed the MRI device used to image the uterus while ultrasound energy is applied to fibroids. "We are constantly meeting with people from different companies," Jolesz says, adding that for some applications, as many as 100 distinct companies may become involved at different stages of development.

Sometimes companies do not step forward to develop the needed tools. For example, NCIGT researchers developed a technology to improve the treatment of cardiac arrhythmia, a form of heart disease caused by abnormally fast or unusually slow heart rates, but the researchers are missing a crucial piece. To treat some types of cardiac arrhythmias, a physician guides a catheter with an electrode at its tip to the area of heart muscle at which there is abnormal electrical activity. The catheter is typically guided by X-ray imaging, but NCIGT researchers have developed a technology that uses more powerful and accurate MRI. "We need new types of catheters that are MR compatible, but there are no products available," Jolesz says. "Without them, the technique is not going to work. So we have to wait."

Collaborations also are ongoing between NCIGT researchers and researchers at other institutions and organizations. One such example is a collaboration to try to make surgery guided by powerful MRI instruments more widely used.

The collaboration involves Clare Tempany, who codirects NCIGT with Jolesz and heads the Image-Guided Prostate Therapy core. Over the past decade, she has pioneered many new procedures and tools to perform prostate biopsy and therapy under the guidance of MRI. Therapy for prostate cancer is often administered using "seeds," small radioactive rods implanted directly into the tumor and prostate gland. The seeds are very powerful but only deliver radiation within a few millimeters of where they are implanted, so their placement is of critical importance. Tempany and colleagues have developed MRI-based methods of imaging the tumor, mechanically controlling the needle that carries the seeds, and recognizing the placement of the needle. Now they are trying to adapt these same procedures to much more powerful, high-field MRI scanners, such as those that are 3 Tesla — the unit used to measure magnetic field — in field strength.

AN IMAGING PRIMER

Magnetic resonance imaging (MRI) uses a powerful magnetic field and pulses of radio wave energy to construct images of the structures and organs inside the body. MRI can provide a greater level of detail for some areas of the body than can other imaging systems. It is especially useful in neurological, musculoskeletal, cardiovascular, and oncological imaging. The strength of the magnetic field in an MRI scanner is measured in Tesla units. The standard MRI systems used for patient care imaging are 1.5 Tesla. But more powerful and faster 3-Tesla MRI systems are becoming more common in hospitals and research institutions.

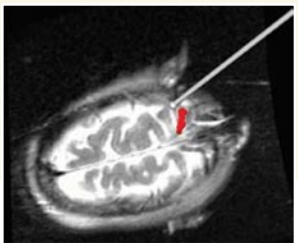
Functional MRI (fMRI) measures signal changes in the brain due to changing activity. Increased neural activity causes an increased demand for oxygen and thus an increase in the amount of oxygenated hemoglobin relative to deoxygenated hemoglobin, which can be detected as a stronger MR signal.

X-rays are a form of ionizing radiation that can travel through the body. When X-rays strike a film, they produce a picture. Dense tissues in the body, such as bones, absorb many of the X-rays and appear white on the film, whereas less dense structures appear as different shades of gray.

Computed tomography (CT) uses X-rays and computer processing to generate a three-dimensional image of the inside of the body from a series of images taken from different angles. CT scanning is a good tool for examining bone and calcifications within the body or such structures as blood vessels.

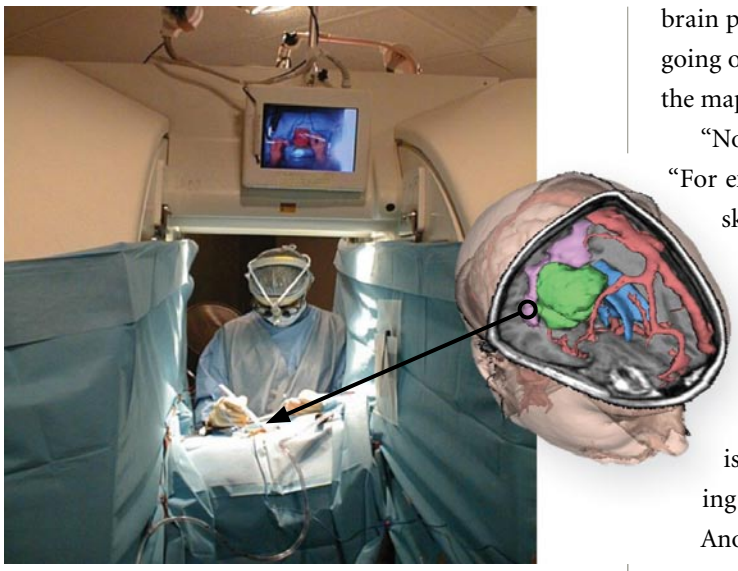
Ultrasound consists of high-frequency sound waves that can produce images when they reflect off organs and other structures in the body. The most well-known imaging application for ultrasound is producing pictures of fetuses in the womb.

Positron emission tomography (PET) detects gamma rays emitted by a positron-emitting radionuclide (tracer) ingested by a patient. Images of tracer concentration in three-dimensional space within the body are reconstructed by computer analysis. The reconstruction is typically accomplished with the aid of a CT scan performed on the patient during the same session in the same machine.



■ Functional magnetic resonance imaging reveals areas of the brain that become active when an individual performs a particular task. This type of imaging is used to create maps of human brain function.

PHOTO BY NATIONAL CENTER FOR IMAGE-GUIDED THERAPY



■ During a surgical procedure, a clinician not only views the organ being operated on but also has access to digital displays of a variety of images obtained before or during the procedure. For example, several imaging technologies can be combined to provide neurosurgeons with unparalleled views of physical structures and functional areas of the brain. The images, such as the one shown to the right of the photograph, serve as roadmaps to guide a surgeon throughout a procedure.

High-field MRI scanners have a strong magnetic field and a small physical space within the scanner where the patient lies, making their use in therapy difficult. For example, researchers cannot use typical needles or other instruments made of metal because they would be immediately drawn to the powerful magnet. In a collaborative effort among three sites — Brigham and Women's Hospital, Johns Hopkins University, and the Image Guidance Division of the company CMS, Inc. — Tempany and colleagues are trying to overcome these difficulties. "It is still very much in the stage of development, but we are starting to migrate technologies for image-guided therapy of the prostate into high-field MRI," she says.

IT ALL STARTED WITH THE BRAIN

The development of many imaging approaches now applied to different diseases and conditions was initially driven by a need in neurosurgery. The brain is enclosed in a bony box, making it difficult for the surgeon to visualize various structures, and yet more than in any other organ of the body, surgeons need to know precisely where and what they are cutting. "It is critical to preserve any healthy tissue," says Alexandra Golby, head of NCIGT's Image-Guided Neurosurgery core. "You cannot take a little bit extra because that could lead to lifelong deficits."

Thanks to advances in several types of imaging technologies over the past 100 years, neurosurgeons today have access to images of the main structures, or landmarks, in a patient's brain prior to an operation — like having a roadmap before going on a trip. Golby has been working to add "function" to the map.

"Not all areas of the brain are equally important," she says. "For example, some areas are critical for motor and visual skills. But no labels in the brain read 'Don't cut here.'"

To determine where these critical areas are, Golby uses functional MRI, a technique that detects blood flow changes in the brain, indicating brain activity. "Functional MRI is becoming slowly accepted as a clinical tool for presurgical mapping," Golby says. "It is a technically demanding procedure. What we are trying to do now is to make it more turnkey."

Another imaging technique that adds new landmarks to the preoperative map is diffusion tensor imaging, a variation of MRI that detects connections between different brain areas. "We are trying to combine as much information as possible," Golby says. "The goal is to get as complete a picture as possible." In addition to taking images before an operation, NCIGT researchers have pioneered the use of MRI to obtain pictures of the brain during an operation, or intraoperatively. "During surgery, the brain shifts due to many factors, including resection of tissue, making preoperatively acquired information progressively less useful," Golby explains. "So intraoperative imaging helps the surgeon know where the limits of resection should be."

But how can all these pre- and intraoperative imaging data fit onto the surgeon's roadmap? This is where bioinformatics and computer programming play a part. In collaboration with researchers at the Center for Integration of Medicine and Innovative Technology, another NCRR-funded Biomedical Technology Research Resource, and the NCRR-funded Biomedical Informatics Research Network (BIRN), NCIGT scientists have developed computer programs and algorithms to analyze and integrate different imaging data. (More information about BIRN can be found at www.nbirn.net.)

The software package 3D-Slicer (freely available to all researchers at www.slicer.org) is widely used to construct and visualize collections of MRI data. With Slicer, the surgeon can manipulate the data to obtain images of the brain from different angles and zoom in at different sites. In addition to producing 3-D models from conventional MRI images, Slicer presents information derived from functional MRI, diffusion tensor imaging, and electrocardiography. Researchers are now adapting Slicer to other applications. "Neuroimaging is very sophisticated, but many of the same techniques are now being adopted in other areas, such as prostate surgery," Tempany says.

PHOTO BY NATIONAL CENTER FOR IMAGE-GUIDED THERAPY

LOOKING FORWARD

Many of the technologies used to image the body before and during surgery are becoming components of routine surgical care. Eventually, Jolesz and Tempany would like to see all these modalities present in the operating room and seamlessly interacting with each other. Next year, they will unveil the first prototype of their "operating room of the future," which will integrate several imaging devices, instruments, and tools into a single, multimodal image-guided surgical suite (see image on page 4).

Although plans for most operating rooms of the future combine one or two modalities, NCIGT's advanced multimodality image-guided operating suite will comprise a 3-Tesla MRI scanner, a positron emission tomography and computed tomography scanner, an X-ray machine, a surgical microscope, and a sophisticated surgical table that moves the patient between stations. It also will include detailed visual displays to guide a surgeon during medical procedures. "We are completely changing the operating room," Jolesz says. "Today, it is a non-tech environment, but in 10 years, there will not be any operating rooms without imaging systems."

The NCIGT is somewhat unique in receiving core funding from several NIH institutes, and its investigators also have individual research grants. This integrated support allows them to conduct cutting-edge research and development that would be difficult to do elsewhere. But another important component of the NCRR grant is dissemination. "Our methods are given to other people," explains Jolesz. "That is the difference the NCRR grant makes. It allows for the spread of technology. We also provide training. An important aspect of technology is education, which is critical if we want new approaches to be adopted."

And as the approaches developed by researchers at NCIGT and other biomedical technology research resources continue to make their way into the clinic, patient care will be dramatically transformed. The biggest change that will occur, according to Jolesz, will be minimizing the invasiveness of the surgery. With new imaging methods, tumors will be destroyed while other tissues are left intact, and surgeons will have tools to better navigate the brain and help patients with Parkinson's disease or epilepsy. The operating room of the future will result in safer procedures, fewer complications and side effects, and shorter hospitalizations. Some patients have already reaped the benefits. ■

BIOMEDICAL TECHNOLOGY RESEARCH RESOURCES FOR IMAGING TECHNOLOGIES

Twelve of the 50 NCRR-funded Biomedical Technology Research Resources (BTRRs) focus on pursuing cutting-edge development and improvement of methodologies and technologies for imaging and spectroscopy. These technologies are used to study organ structure and function, perfusion, and oxygen extraction and metabolism for the diagnosis, staging, treatment, evaluation, and investigation of diseases and abnormalities. The imaging centers are located in major research-intensive medical centers, providing a nurturing environment for interdisciplinary research and exceptional opportunities to identify proper collaborations to drive the development of technology. This proximity contributes as well to the reduction in translation barriers to clinical applications.

BioCurrents Research Center – development of tools to follow the dynamic properties of living cells. Principal Investigator: Peter J.S. Smith, Ph.D.

Center for Advanced Magnetic Resonance Technology at Stanford – development of magnetic MRI techniques in humans and animals. Principal Investigator: Gary H. Glover, Ph.D.

Center for Functional Imaging Technologies – development of neuroimaging techniques in humans. Principal Investigator: Bruce R. Rosen, M.D., Ph.D.

Integrated Center for *In Vivo* Microscopy – development of techniques for very high-resolution imaging of small animal models. Principal Investigator: G. Allan Johnson, Ph.D.

National Center for Image-Guided Therapy – image-guided therapy. Principal Investigator: Ferenc A. Jolesz, M.D.

National Center for Microscopy and Imaging Research – development of tools and techniques for electron microscopy at the cellular level. Principal Investigator: Mark H. Ellisman, Ph.D.

National Center for X-Ray Tomography – X-ray microscopy at the cellular level. Principal Investigator: Carolyn Larabell, Ph.D.

Neuroimage Analysis Center – understanding the human brain through imaging. Principal Investigator: Ron Kikinis, M.D.

NMR Imaging and Localized Spectroscopy – MRI using ultra-high magnetic fields. Principal Investigator: Kamil Ugurbil, Ph.D.

Resource for Magnetic Resonance and Optical Imaging – high-performance computing. Principal Investigator: John S. Leigh, Ph.D.

Resource for Quantitative Functional MRI – development of MRI techniques in humans. Principal Investigator: Peter C.M. van Zijl, Ph.D.

Southwestern NMR Center for *In Vivo* Metabolism – imaging techniques to understand metabolic changes in humans. Principal Investigator: Craig R. Malloy, M.D.

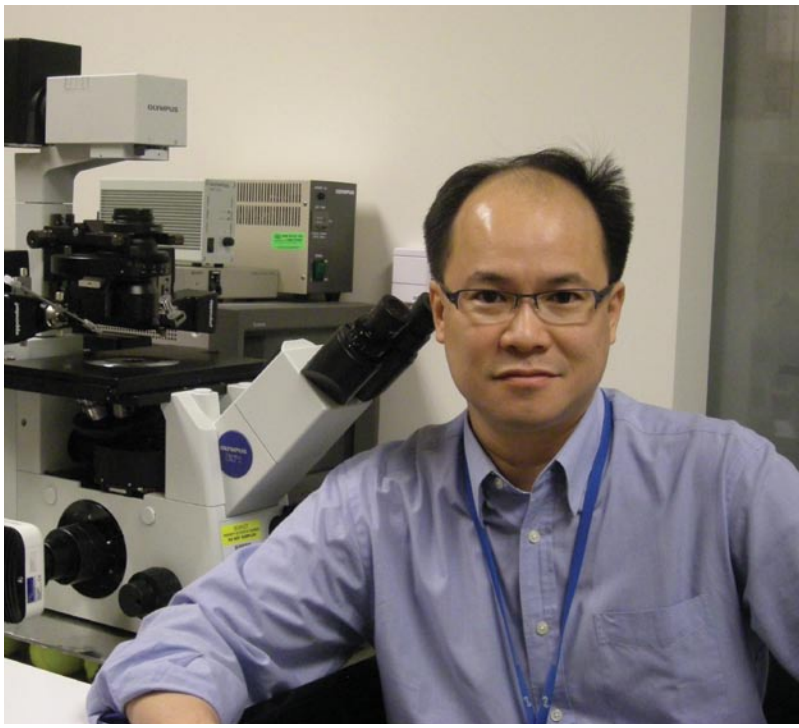
For more information about these and other technologies that are supported at BTRRs, visit www.ncrr.nih.gov/btrr.

New Opportunity to Better Understand Huntington's Disease

New primate model may help scientists to develop more effective therapies for Huntington's disease and create similar primate models for other genetic disorders. **BY KAREN EDDLEMAN**

Although strides have been made in understanding neurodegenerative disorders such as Alzheimer's, Parkinson's, and Huntington's diseases, a lack of useful animal models has stood in the way of advancing research that might lead to effective treatments or cures. Now — for the first time ever — a team of researchers has successfully introduced a gene for a human disease into a primate, creating an animal model that shows disease progression and symptoms characteristic of human Huntington's disease, an incurable and inherited genetic disorder affecting the brain. This advance was achieved by a team of scientists led by Anthony W.S. Chan, principal investigator, at the NCRR-supported Yerkes National Primate Research Center (NPRC), Emory University, one of eight primate research centers supported by NCRR. Chan and his colleagues hope the new animal model will herald a new age in Huntington's disease research and ultimately help lead to a cure.

As reported in the journal *Nature* (453:921–924, 2008), Chan's team introduced a gene that can cause Huntington's disease in humans (an altered form of the gene *HTT*) into the germline DNA of a rhesus macaque monkey (*Macaca mulatta*), resulting in what is termed a transgenic animal model. Although scientists identified the precise location of the *HTT* gene 15 years ago and have engineered rodents and other animals to carry the altered *HTT* gene, research has been hampered because these models do not experience the same brain and behavioral changes as observed in humans.



■ Anthony Chan heads the team at the NCRR-supported Yerkes National Primate Research Center that developed the first monkey model genetically modified to have a human disease.

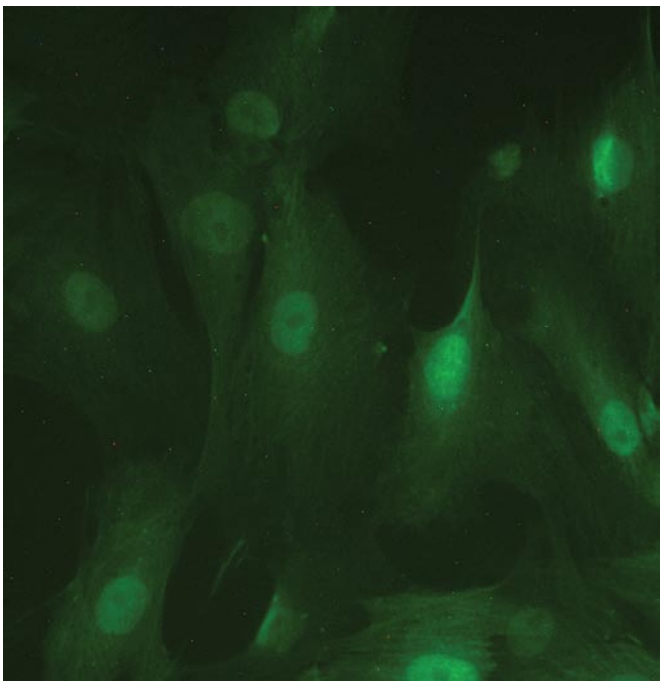
Huntington's disease occurs in one of every 10,000 persons — nearly 30,000 in the United States — and about 150,000 more are at risk of inheriting the disease from a parent. It causes uncontrolled movements and stumbling, short-term memory loss, depression, mood changes, and sometimes aggressive or

PHOTO BY KAREN W.Y. CHONG

> ... Chan's team introduced a gene that can cause Huntington's disease in humans ... into the germline DNA of a rhesus macaque monkey ... resulting in what is termed a transgenic animal model.

antisocial behavior. The disease inevitably leads to death 15 to 20 years after symptoms appear, usually in middle age. It is one of several diseases caused by abnormal repetition within the DNA of the *HTT* gene, which codes for a protein called huntingtin. The modified form of the huntingtin protein contains a section with extra glutamine amino acids; it causes cells to die in certain areas of the brain, affecting neurological functions. Currently, there is no treatment to delay or prevent Huntington's disease.

Now, research into Huntington's disease has been jumpstarted by Chan's work, which was supported by NCRR and the National Institute of Neurological Disorders and Stroke. Because the transgenic macaque model developed at the Yerkes NPRC shows many of the symptoms and the disease progression seen in humans with Huntington's disease, it offers the possibility of testing innovative therapies intended to ameliorate disabling symptoms and perhaps extend the lives of Huntington's patients.



■ A tissue culture established with the bone marrow stem/stromal cells from a transgenic Huntington's monkey emits a greenish light when viewed under a fluorescent microscope. The cells glow because they express a jellyfish gene encoding for green fluorescent protein, which is a marker for incorporation of the *HTT* gene into the macaque DNA.

In 2001, Chan, while working at the NCRR-funded Oregon NPRC, successfully introduced a jellyfish gene for green fluorescent protein (GFP), creating the world's first transgenic nonhuman primate. According to Chan, "The next step was to try to insert a human gene that causes disease."

In 2002, Chan joined the team at the Yerkes NPRC, where studies of neurodegenerative disorders, including Alzheimer's and Parkinson's diseases, are a main focus. "Dr. Chan is one of the very few investigators who could do this work. He has experience in manipulating monkey embryos," says John Harding, director of primate research at NCRR. Chan's research is critical, in his view, "because rodent models cannot give the answers we need; we have to rely on nonhuman primates, which are physiologically very similar to humans."

The study team developed this transgenic monkey model by introducing a genetically altered human *HTT* gene as well as the jellyfish *GFP* gene (used as a marker to show that gene transfer has been achieved) into monkey eggs using a viral vector. The eggs were fertilized, and the resulting embryos were introduced into surrogate mothers, resulting in five live births. All of the monkeys were shown to have the modified human *HTT* gene incorporated into the DNA of all of their cells, and three expressed very high levels of the mutant huntingtin protein.

The Yerkes NPRC was the ideal setting for this work. NCRR's eight NPRCs together have more than 26,000 animals representing more than 20 species of nonhuman primates, mostly macaques. Research studies at these facilities are tackling questions about human health and disease that cannot be assessed ethically in humans or answered in other species. "The Yerkes NPRC is one of the few places in the world where scientists can find expertise in neurobiology and nonhuman primate transgenesis, noninvasive imaging technology, husbandry, and behavioral and cognitive assessment tools in one place," says

Continued on page 15

PHOTO BY ANTHONY CHAN

Mass Producing Antibodies

Supported by an IDeA grant, researchers find a way to rapidly generate human monoclonal antibodies to potentially treat the flu and other infectious diseases. **BY LAMONT WILLIAMS**

The human immune system is a formidable wall of defense against bacteria and viruses, but it is not impenetrable and is always a work in progress. Recently, at the Oklahoma Medical Research Foundation (OMRF), a team of researchers supported by NCRR's Institutional Development Award (IDeA) program found a way to help fortify the immune system like never before. "Scientists have been searching for technology like this for 25 years," says immunologist J. Donald Capra, president emeritus of OMRF and former principal investigator of the IDeA grant that funded this work.

First, the research team, led by Patrick Wilson at OMRF in collaboration with Rafi Ahmed of Emory University, made the important discovery that there is a rapid production of antibody-secreting plasma cells in patients following vaccination for influenza in which the antibodies produced have a strong affinity for the vaccine. Armed with this knowledge, they devised a way to isolate a substantial population of these immune cells, which can be used to quickly produce what are called human monoclonal antibodies. Monoclonal antibody therapy has been shown to be useful in the treatment of a variety of diseases. "Vaccines may not give full protection and may cause adverse side effects in some patients," Wilson says. "Human monoclonal antibody therapy will likely be more effective and has a low risk of being rejected by a patient's immune system."

The method devised by Wilson and his colleagues allows them to identify and isolate specific antibody-secreting cells from people who have previously been administered an influenza vaccine. They can then clone the antibody genes from those cells and use those genes to quickly produce an abundance of antibodies to the particular strain of influenza virus the vaccine was designed to fight. The antibodies can potentially be used in patients to augment the treatment of the deadly illness; one that claims more than 25,000 Americans every year.

Patrick Wilson (pictured) and colleagues have discovered a method to create human monoclonal antibodies directly and within only a few weeks of vaccination.

Although researchers have known that human monoclonal antibody therapy can treat a multitude of diseases effectively, it has not been widely used because of the enormous time and expense needed to generate the antibodies. Monoclonal antibodies can be made by using mice, but these antibodies are often

PHOTO BY OKLAHOMA MEDICAL RESEARCH FOUNDATION

> "Scientists have been searching for technology like this for 25 years."
>
> —IMMUNOLOGIST J. DONALD CAPRA

not compatible with human physiology, causing illness in some patients. The antibodies produced by Wilson and colleagues are fully human, circumventing such problems, and they have demonstrated that they can produce them quickly. "We have shown that we can create human monoclonal antibodies from antibody-secreting cells directly and within only a few weeks of vaccination," Wilson says.

NIH laid the foundation for this success story more than 15 years ago through the establishment of the IDeA program. Administered by NCRR's Division of Research Infrastructure, the IDeA program is designed to foster health-related research at institutions in states where per capita NIH funding historically has been low. IDeA grants offer junior investigators research opportunities, support faculty development, enhance research infrastructure, and increase the number of competitive investigators in 23 states and Puerto Rico. "Efforts and success stories similar to that of Wilson and his team also are occurring in other IDeA states, with regard to other research challenges," says Fred Taylor, NCRR's IDeA program director.

One component of the IDeA program is the Centers of Biomedical Research Excellence (COBRE) initiative, which facilitates the development of new disease-specific research centers or augments the capability of existing centers. Wilson was supported by a COBRE grant entitled "Mentoring Immunology in Oklahoma: A Biomedical Program." Institutions in the IDeA network have very limited funds to establish research centers and, in particular, recruit new investigators. The COBRE program provides funds for these efforts. "Without the program, Wilson may not have gotten in the door," Capra says. "The COBRE provided funds for his recruitment and for pilot projects and, in general, gave him the freedom to operate in a way that he would likely not have if the COBRE did not exist."

Another contributing factor to Wilson's success, Capra says, was the core facilities at OMRF, many of which were largely established by COBRE funds. The program supports infrastructure, such as these core facilities, that most institutions in IDeA states cannot afford. As a COBRE investigator at OMRF, Wilson had access to these cores, where he could have such work as DNA sequencing, cell sorting, and microscopy done inexpensively and quickly. "The COBRE program helped me to hit the ground running," Wilson says. "The cores were a central element of my success." Capra notes that his successor, Steve Prescott, used institutional funds to establish a new core at OMRF to perpetuate Wilson's monoclonal technology. "Dozens of scientists at OMRF and surrounding institutions like the University of Oklahoma Health Sciences Center are using the technology in their own research areas," Capra says.

Although the COBRE is designed to establish biomedical research centers at institutions that historically have been at a funding disadvantage, the ultimate goal is to train young investigators at these institutions to become leaders in critical areas of research with independent funding support. "To a large extent," Capra says, "the investigators recruited through our COBRE have remained at the institution to stay close to the mentors they obtained by way of the program. This is another success of the program."

Wilson's findings have important implications for therapy, not only for influenza, but for a broad range of infections and even cancer. Currently, he and his colleagues are using the same approach to isolate human monoclonal antibodies to hepatitis C, pneumococcal pneumonia, anthrax toxin, and yellow fever. "There is a plethora of emerging infectious diseases to which this technology may be applied," Wilson notes. "In the case of a highly virulent virus, we now possess the technology to quickly and efficiently produce antibodies that might be useful in treatment." In addition to immunology, the COBRE is enabling critical research in heart disease, diabetes, and dozens of other health challenges. ■

The research described in this article is supported by the National Center for Research Resources (NCRR) and the National Institute of Allergy and Infectious Diseases. One investigator on the research team was supported by the Swedish Research Council. The NIH Institutional Development Award (IDeA) program and its Centers of Biomedical Research Excellence are supported by the Division of Research Infrastructure of NCRR. For more information about the IDeA program, see www.ncrr.nih.gov/idea.

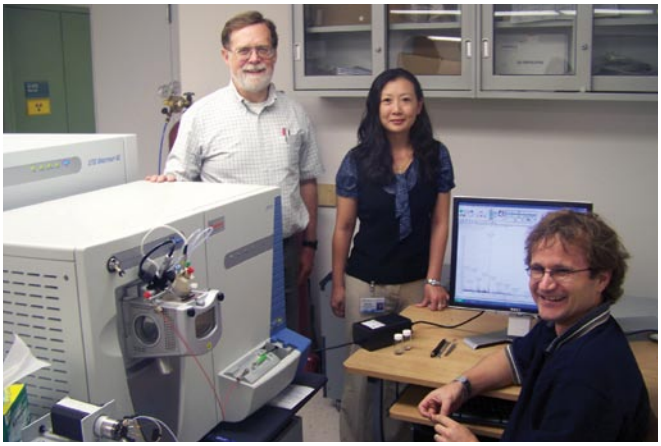
ADDITIONAL READING: Wrammert, J., Smith, K., Miller, J., et al., Rapid cloning of high-affinity human monoclonal antibodies against influenza virus. *Nature* 453:667–671, 2008.

HEI Grants Enable Cutting-Edge Research

Scientists working toward personalized medicine envision a day when patients' entire genomes are part of their medical records, and physicians can receive alerts for gene variants associated with diseases and common or rare drug-linked side effects. Computer databases could help doctors find patients at highest risk for these diseases and side effects as well as those most likely to benefit from a particular treatment. Before that future can arrive, researchers have to find and understand the genotype-phenotype associations, and they need the resources to do it.

Through a recently funded NCRR High-End Instrumentation (HEI) award to Vanderbilt University, scientists can look forward to accessing such a resource. HEI awards enable the purchase of state-of-the-art research equipment by providing $750,000 to $2 million in direct costs for these advanced instruments, which can have an extraordinary impact on a wide variety of biomedical research in many disease areas.

At the Vanderbilt Institute for Clinical and Translational Research, the HEI award will enable the university to automate its DNA specimen and databank repository with a robotics system that handles the storage, maintenance, and distribution of DNA samples. The DNA Databank, which is a core resource for the institute, will store hundreds of thousands of DNA samples linked with clinical information from electronic medical records that do not include identifying information. By using this databank, researchers will be able to make and test discoveries not just in a carefully controlled laboratory environment but also in the real world, with samples and data from patients in clinical settings. The new robotics system will dramatically accelerate the rate at which translational researchers can access this resource. Thus it provides a vital first step in moving the emerging sciences of genomics and pharmacogenomics from the research lab to clinical practice, a key function of the Vanderbilt Institute for Clinical and Translational Research.

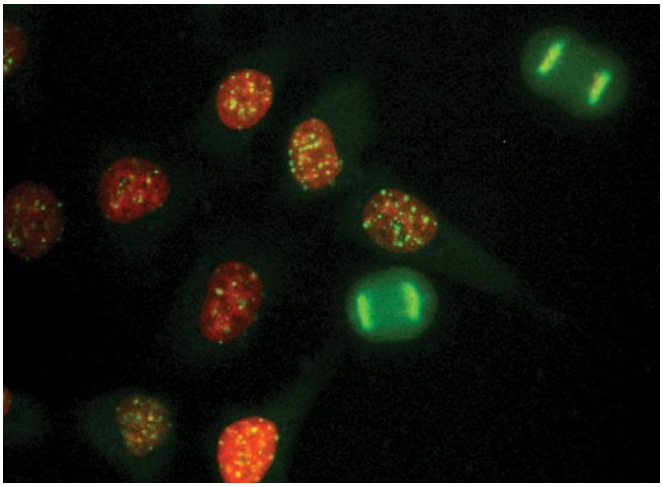


The Orbitrap XL Hybrid FT Mass Spectrometer System, purchased by Stony Brook University Medical Center with a High-End Instrumentation award, accurately measures the mass of individual molecules, helping researchers discover and characterize proteins and novel diagnostic biomarkers for major diseases. Pictured are Charles R. Iden, standing, scientific director of the Mass Spectrometer Facility and Proteomics Center; Researcher Emily Chen, assistant professor, Department of Pharmacological Sciences; and Toni Koller, technical director, Proteomics Center.

With its High-End Instrumentation award, Vanderbilt University will purchase a high-capacity robotic system, similar to the one pictured above, to support the storage, maintenance, and distribution of DNA samples in the Vanderbilt DNA Resource Core.

"The DNA Databank is a platform to get genome science to the bedside," says Dan Roden, principal investigator for the HEI grant. "It is a platform for testing future-tense medicine. But if the resource was available today, and someone asked for 5,000 samples and 5,000 controls, it would take several weeks to prepare." In addition, each individual researcher would want a custom-tailored collection for his or her study, which means databank staff would have to create individual plates from the master collection. The more individual collections are created, the more room there is for error or contamination. With the new robotics system, sample

PHOTO BY STONY BROOK UNIVERSITY (LEFT); PHOTO BY TTP LABTECH (RIGHT)



■ Indiana University received a High-End Instrumentation award to purchase a high-throughput confocal imaging system for rapidly screening large numbers of fluorescently labeled live cell samples. This equipment will aid in the potential development of new cancer and antibiotic therapies. The image above, created with this equipment, shows HeLa cells, a certain type of cell used in medical research. The cells are expressing two molecules called green fluorescent protein and mCherry fluorescent protein, which are used to mark such cell structures as kinetochores (green), spindle poles (green), and chromosomes (red).

preparation will take mere days, with little to no error. The new system will speed access to the DNA Databank and enable research on genetic variation, disease susceptibility, and drug response.

The new system typifies the work of the Clinical and Translational Science Award (CTSA) consortium, which includes Vanderbilt's Institute in its membership. Led by NCRR, the CTSA consortium is working to reduce the time it takes for laboratory discoveries to become treatments for patients and to train the next generation of clinical and translational researchers. Vanderbilt's HEI grant will serve both of these endeavors, accelerating a critical function of the institute in line with the CTSA goal of speeding the translation of discoveries from the laboratory to the clinic.

Three other institutions in the CTSA consortium also received HEI grants this year. Washington University in St. Louis is buying a high-field Fourier Transform mass spectrometer to examine protein structure and function, particularly the changes that occur after proteins are made. The new instrument will help researchers learn more about and find new treatments for arthritis, autoimmune disorders, cancer, diabetes, HIV infection, interstitial cystitis, and blood disorders.

The University of Pennsylvania is purchasing a cyclotron to make new radiotracers, which will enhance the molecular imaging research done at the CTSA-funded Institute for Translational Medicine and Therapeutics. The cyclotron will give researchers new ways of understanding biologic processes and diagnosing such diseases as cancer.

The Clinical and Translational Science Institute at the University of North Carolina at Chapel Hill will use its HEI award to replace its head-only magnetic resonance scanner with a new whole-body scanner with parallel processing. The new scanner will shorten the time needed to get high-quality images, and with enhancements supported by other university funds, the scanner will allow researchers to obtain magnetic resonance and positron emission tomography images at the same time. Thus the new scanner will facilitate a key component of the institute and greatly improve the ability to directly translate research imaging projects into the clinical arena.

This year, NCRR awarded 20 HEI grants to 18 institutions. This round of grants, which total more than $33 million, will help awardees buy specialized equipment, such as nuclear magnetic resonance spectrometers, high-powered electron microscopes, biomedical imagers, high-resolution mass spectrometers, supercomputers that rapidly process vast amounts of data, and cyclotrons that produce new probes for noninvasive molecular imaging. In synergy with the aims of the CTSA program and other NIH initiatives, HEI grants for this type of equipment open up new avenues in biomedical research, leading to further understanding of normal biology and new advances and treatments for various diseases.

—FRANCES MCFARLAND HORNE

THE HIGH-END INSTRUMENTATION (HEI) GRANT PROGRAM

Since it began in 2002, the HEI program has provided more than $187 million in 120 awards across 26 states. The awards are one-year, non-renewable grants that support $750,000 to $2 million in direct costs for a single major item of advanced equipment. They allow the purchase of equipment that is too costly for NCRR's Shared Instrumentation Grant program.

"HEI grants support the purchase of a new generation of instruments, making possible research that could not be accomplished before and speeding translation of new discoveries to the clinic," says Marjorie Tingle, director of the HEI grant program. "These grants enable breakthroughs and keep researchers at the forefront of modern biology and medicine."

Priority for using instruments supported by HEI grants should be given to NIH-supported scientists engaged in biomedical and behavioral research. HEI awardees also must provide the infrastructure needed to support the new equipment. For more information about the HEI program, including eligibility requirements and application guidelines, see www.ncrr.nih.gov/hei.

PHOTO BY JIM POWERS, INDIANA UNIVERSITY

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Harding. Equally important as the infrastructure made available through NCRR's support, according to Stuart M. Zola, director of the Yerkes NPRC, was NCRR's recognition that "the research was high risk, but it offered a potentially high payoff. NCRR was willing to take that risk."

According to Chan, the Hereditary Disease Foundation and several other Huntington's disease advocacy groups have expressed optimism about the prospect that these animal models can help science take the next steps toward a cure for Huntington's disease.

Future efforts by Chan and colleagues at Yerkes NPRC will be directed along several different paths. First, more tests need to be conducted to validate the nonhuman primate model of Huntington's disease. The transgenic monkeys will undergo cognitive testing and continued blood sampling to monitor their genomic and metabolic profiles and gene expression patterns. The study team will use the Yerkes NPRC's facilities to conduct noninvasive magnetic resonance imaging studies to follow any anatomical changes. "We will integrate all these studies into a picture of the disease and validate the animal models by comparing the results with information on human pathology and clinical features of Huntington's disease," explains Chan. Having a validated model will be a key step before scientists can confidently proceed to using the animals for developing and testing possible therapies.

Because the disease seems to be progressing rapidly in the two animals currently under study, Chan plans to develop additional transgenic models with later onset of disease. Having more transgenic monkeys available will allow translational research aimed toward potential cures to progress more quickly, says Chan.

Zola foresees using transgenic primate models for studying other important diseases: "One barrier in terms of neurodegenerative diseases is the lack of adequate animal models. For example, no other species develops Alzheimer's disease; therefore, it is hard to explore the dynamics and underpinnings of the disease, its stages, and how we might be able to intervene effectively," he says. "This transgenic approach in nonhuman primates is exciting, because the models show the full spectrum of the disease so we can better develop and assess interventions." ■

The research described in this article is supported in part by grants to the Yerkes NPRC, one of eight NCRR-funded primate research centers nationwide, and by grants awarded to several of the investigators by the National Institute of Neurological Disorders and Stroke.

ADDITIONAL READING: Yang, S.H., Cheng, P.H., Banta, H., Piotrowska-Nitsche, K., Yang, J.J., Cheng, E.C., Snyder, B., Larkin, K., Liu, J., Orkin, J., Fang, Z.H., Smith, Y., Bachevalier, J., Zola, S.M., Li, S.H., Li, X.J., Chan, A.W. Towards a transgenic model of Huntington's disease in a non-human primate. *Nature* 453:921–924, 2008.

NEWS FROM NCRR

People, Awards, Grants, and New Developments

Four New Members to Serve on NCRR Advisory Council

The 18 members of the National Advisory Research Resources Council advise NCRR on polices and programs and perform second-level peer review of grant applications. Four new members, who are leaders in their respective professions, have recently been appointed to serve four-year terms.

William F. Bria, II, chief medical information officer at Shriners Hospitals for Children and clinical associate professor of internal medicine at the University of South Florida in Tampa. Bria has been a leader in applied medical informatics for more than 20 years and has authored numerous articles and books on informatics. He is currently engaged in research and applied medical informatics and is developing a new five-year combined M.D./master's program for informatics at the University of Michigan.

Wendy Chaite, president of the Lymphatic Research Foundation. Chaite, whose daughter was born with systemic visceral and peripheral lymphatic disease and lymphedema, is an advocate for lymphatic research. In 1998 she founded the Lymphatic Research Foundation, a not-for-profit organization dedicated to promoting and supporting lymphatic research and to fostering an interdisciplinary field of research. Chaite also serves as emeritus director of Research!America and is a former member of the NIH Council of Public Representatives (COPR) and a former COPR liaison to the NIH Advisory Committee to the Director.

Henry N. Ginsberg, Irving Professor of Medicine and director of the Irving Institute for Clinical and Translational Research at the College of Physicians and Surgeons

DEERINCK PHOTO BY TOM DEERINCK AND MARK ELLISMAN/NCMIR

of Columbia University. Ginsberg is part of a group that will be studying the role of glycemic, lipid, and blood pressure control in the prevention of cardiovascular disease in patients with diabetes. This 10-year trial will involve 10,000 patients at six sites across the United States. Ginsberg also has a long record of research into the effects of diet on lipid and lipoprotein metabolism in humans and has conducted numerous controlled feeding studies in humans.

Dallas M. Hyde, director of the California National Primate Research Center and professor at the School of Veterinary Medicine at the University of California, Davis. Hyde conducts research on the interactions of white blood cells, epithelial cells, and other types of cells in the lungs, with an emphasis on asthma, pulmonary fibrosis, and emphysema in animal models.

NCRR Launches National Gene Vector Biorepository

NCRR has replaced its gene vector laboratories program with a national gene vector biorepository and coordinating center, with a three-year grant to Indiana University School of Medicine. The new center, directed by Kenneth Cornetta, will be a central storehouse for gene therapy materials and will promote gene therapy research by permitting the sharing of information to promote discoveries, patient safety, and compliance with the FDA and to broker material transfer agreements between researchers and owners of patent-protected or proprietary reagents.

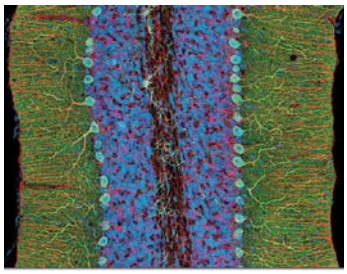
"This resource will maximize our investment in gene vector research and help translate new knowledge into tangible benefits for patients," says NCRR Director Barbara Alving. For more information, visit www.ngvbcc.org.

NCMIR Scientist Wins Photographer of the Year

Thomas J. Deerinck, a researcher at the University of California, San Diego's NCRR-supported National Center for Microscopy and Imaging Research (NCMIR), received first place in the science category at the prestigious Sony World Photography Awards. Submitted micrographs — images taken through a microscope — depicted NCMIR's cutting-edge research and included a variety of tissues and cancer cells.

An NCRR Biomedical Technology Research Resource, NCMIR was established in 1988 and is led by principal investigator Mark H. Ellisman. It leads the way in technologies for high-throughput multiscale imaging and analysis of biological systems, with an emphasis on mechanisms underlying diseases of the nervous system.

Deerinck's images have been featured on the covers of scientific journals and in museum shows. In recent years, Deerinck has won numerous prizes in various photography competitions. A gallery of his micrographs may be found at www.microscopyu.com/featuredmicroscopist/deerinck/deerinckgallery.html.



■ One of Deerinck's 10 award-winning images depicts the midsagittal section of a rat cerebellum. The image above was acquired with one of NCMIR's confocal microscopes.

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