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NCRR Reporter

FALL 2006

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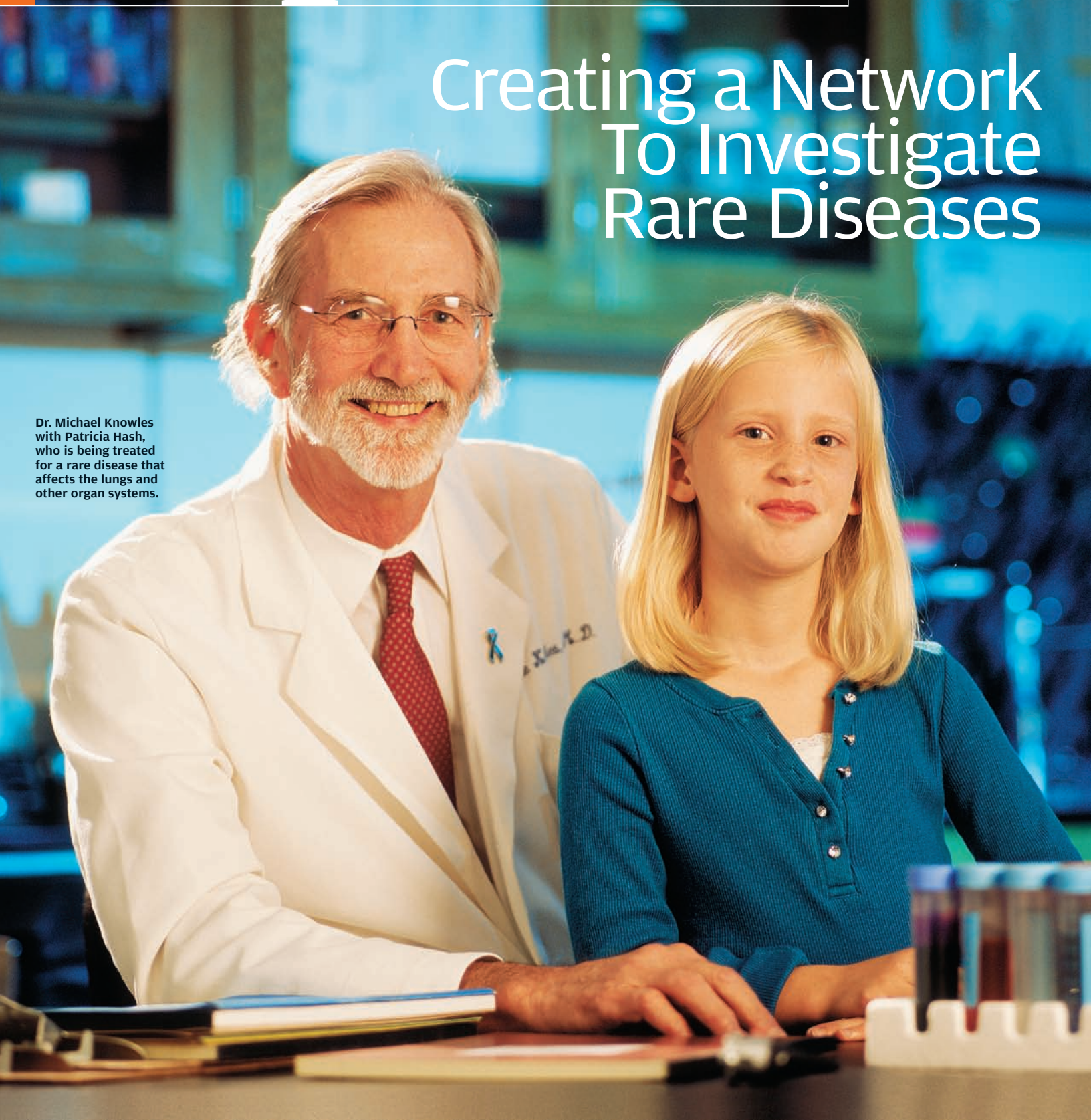
U.S. Department of Health and Human Services

Creating a Network To Investigate Rare Diseases



Dr. Michael Knowles with Patricia Hash, who is being treated for a rare disease that affects the lungs and other organ systems.

FROM THE DIRECTOR

A Shared Vision: Collaboration, Community Outreach, and Informatics

The Clinical and Translational Science Awards (CTSA) Program and the Rare Diseases Clinical Research Network, highlighted in this edition of the magazine, share three features that are key to their success: collaboration, community outreach, and clinical research informatics.

The grantees of these programs have pledged to leverage their expertise and resources with researchers, physicians, industry, advocacy groups, their communities, and beyond. Success will lie, in part, on their abilities to share an inclusive and far-reaching vision with both the research community and the public. Clinical research informatics will make the vision a reality, with networks that link the various groups together and help them attain their ultimate goal of improving human health.

The CTSAs, working as a consortium, will train and advance a cadre of multi- and interdisciplinary investigators, collaborating to translate discoveries made in the laboratory into improved therapies for patients. Through these collaborations—with basic, translational, and clinical investigators—a new discipline of clinical and translational science will be formed. At the same time, the CTSA researchers plan to expand their efforts with minority and medically underserved communities, and make broad connections across schools, institutions, and regions. Their strategic partnerships also will include the U.S. Department of Veterans Affairs, the Food and Drug Administration, and private health care organizations.

Woven into the CTSA plans are robust informatics programs that are the cornerstone of communication with the CTSA consortium and with collaborating organizations. Interoperability, security, workflow, usability, and standards are essential areas of focus. A national CTSA Informatics Steering Committee will serve as a forum for discussion and agreement on standards, best practices, and solutions.

In much the same way, the Rare Diseases Clinical Research Network is focused on a collaborative and coordinated system of investigators and patient support organizations committed to the study of rare diseases. Collaborations extend to sites in England, Japan, and Brazil. The research sites work in partnership with leaders in technology to enhance communication and sharing of resources for both investigators and patient support groups. A Data and Technology Coordinating Center provides innovative tools to collect and manage geographically distributed clinical research data on diverse diseases using standardized data elements. Researchers, physicians, and patient support groups benefit from this ability to coordinate and disseminate information.

Patients, researchers, institutions, and industry organizations will add value to the CTSA Consortium and the Rare Diseases Clinical Research Network. Bringing these many diverse participants together will depend on their willingness to collaborate, reach out to communities, and employ technologies that make communication possible.

Barbara Alving, M.D.
Acting Director, NCRR

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CRITICAL RESOURCES

SCIENCE ADVANCES

Research Briefs

NCRR Reporter

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

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On the Cover: Physician Michael Knowles, a member of NIH's Rare Diseases Clinical Research Network, is one of the world's leading experts on primary ciliary dyskinesia (PCD), the disease affecting patient Patricia Hash. Network scientists are studying PCD and more than 40 additional rare diseases in hope of better understanding and developing improved therapies for these conditions.
PHOTO BY KELLY CULPEPPER

NIH Launches Clinical and Translational Science Awards

NIH unveiled a national consortium designed to facilitate the transfer of discoveries made in the laboratory into new treatments for patients. Announced on October 3, the consortium will be funded through the Clinical and Translational Science Awards (CTSAs) Program. Initial awards will provide $100 million to support 12 research institutions throughout the country.

The CTSA Program—developed after extensive consultation with the scientific community, academia, and private organizations—will encourage the union of expertise and resources and help transform the way scientists conduct clinical and translational research.

"We are not presenting various independent awards, but rather a series of awards that will create a consortium of institutions working together," says NIH Director Elias A. Zerhouni. "These awards represent the first systematic change in our approach to clinical research in the last 50 years. Ultimately, patients will be better served."

According to Zerhouni, medical successes in the past few decades have enhanced lifespan and shifted the burden of disease. Rather than treating primarily acute, lethal conditions, health care providers increasingly must contend with more protracted and chronic disorders.

To address this and other emerging health care challenges, NIH has developed a series of strategies that have been embodied in the CTSA Program. Through the CTSAs, scientists from diverse backgrounds will become part of an academic "home" in their institutions. Each home will integrate clinical and translational science across multiple departments, schools, clinical and research institutes, and hospitals. Such integration will help assemble interdisciplinary teams that cover the complete spectrum of research—biology, clinical medicine, dentistry, nursing, biomedical engineering, genomics, and population sciences. Academic homes also will provide support to educate and develop the next generation of researchers trained in the complexities of translating research into clinical trials and ultimately into practice.

With CTSA funding, institutions are planning to design new and improved clinical research informatics tools, forge new partnerships with private and public health care organizations, expand outreach to minority and medically underserved communities, and develop better designs for clinical trials to ensure that patients with rare as well as common diseases benefit from new medical therapies.

"This consortium will spur innovation, integration, and dissemination, not only among institutions receiving these awards, but also among other organizations involved in health care throughout the country," says Barbara M. Alving, acting director of NCRR. The CTSA consortium will be led by NCRR as part of the NIH Roadmap for Medical Research.

An additional 52 academic health centers have received planning grants to help them prepare applications to join the CTSA consortium. When fully implemented in 2012, the CTSA Program is expected to provide a total of $500 million annually to a consortium of 60 academic health centers.

A young participant in a sleep study talks with Carole Marcus, co-principal investigator of a new CTSA grant and director of the Sleep Center at the Children's Hospital of Philadelphia.

The following 12 institutions will receive awards for nearly a five-year period:

- Columbia University Health Sciences
- Duke University
- Mayo Clinic College of Medicine
- Oregon Health and Science University
- Rockefeller University
- University of California, Davis
- University of California, San Francisco
- University of Pennsylvania
- University of Pittsburgh
- University of Rochester
- University of Texas Health Science Center at Houston
- Yale University

- A list of the 52 planning grant recipients is available at www.ncrr.nih.gov/ncrrprog/roadmap/CTSA_Planning_9-2006.asp.
- For more information on the CTSA Program, please visit www.ncrr.nih.gov/clinicaldiscipline.asp.

PHOTO COURTESY OF CHILDREN'S HOSPITAL OF PHILADELPHIA

The Burden of Being Unique

The Rare Diseases Clinical Research Network seeks to improve diagnosis and treatment of patients with rare diseases. **BY AL STAROPOLI**

■ Born with a rare disease, Meghan Manion keeps active and healthy by running and riding horses. Meghan has PCD, a disease that affects less than 1 percent of the U.S. population.

Meghan Manion knows what it's like to be different. Since birth she's had primary ciliary dyskinesia (PCD), a rare disease that affects the lungs and other organ systems. "It's like having a cold that lasts all your life," says Meghan, who is 23. She has been hospitalized almost 50 times, nearly half of these for bouts of pneumonia. "I wake up most days and don't feel good. Something in my body hurts, whether it be my lungs, sinuses, or stomach." PCD is characterized by chronic infections due to inherited defects in tiny hairlike structures in the lungs, called cilia, that clean the accumulation of mucus and bacteria.

Nationwide about 25 million individuals, like Meghan, are affected by a rare disease. To date nearly 6,800 unique rare diseases have been identified, each one striking less than 1 percent of the U.S. population. Most of these diseases are difficult to diagnose and treat because they are so poorly understood. Meghan's PCD wasn't recognized until she was 7 years old, says her mom, Michele Manion. "Earlier diagnosis would have helped us start Meghan on an appropriate therapy sooner, and she might not have had such extensive damage to her lungs," she adds.

To improve the diagnosis, treatment, and understanding of rare diseases, NIH created the Rare Diseases Clinical Research Network and awarded $71 million in funding towards its support. The initiative unites more than 300 investigators at dozens of hospitals, universities, and research centers in the United States and abroad to study more than 40 rare diseases. "The network is pioneering a collaborative approach where physicians, researchers, and families work to address the medical challenges associated with rare diseases," says Elaine Collier, assistant director for clinical research at NCRR. "This initiative is helping us move discoveries more quickly to patients." In 2003, NCRR and the NIH Office of Rare Diseases—the two principal NIH

Nearly 6,800 unique rare diseases have been identified, each one striking less than 1 percent of the U.S. population.

components involved in coordinating the network—worked together to launch this effort.

The network's approach is highly strategic and collaborative. Ten mutually supporting research consortia, each studying a particular set of diseases, work closely with various patient advocacy groups. The groups, in turn, are organized into an overarching coalition supporting outreach to affected families. (See box on page 7.) Families have a voice in the consortium's activities through the coalition and participate in the design of its research studies. And by becoming involved in clinical research, physicians are trained and prepared to participate in the study of rare diseases. Sharing of data and information relevant to all groups is facilitated by the Data and Technology Coordinating Center, a centralized informatics resource.

"This is the largest and most diverse effort to study rare diseases to date," says Stephen Groft, director of the NIH Office of Rare Diseases. Groft has been involved in rare disease research for nearly 25 years. "This vast cooperative network allows for the fusion of resources to study disorders that have received little attention in the past, in hopes of producing better diagnoses and treatments for the future," he adds.

The network builds on other already successful NIH efforts

PHOTOGRAPH BY THOMAS STRAND

such as the Collaboration, Education, and Test Translation program, which supports genetic test development for rare diseases; the Genetic and Rare Diseases Information Center, which answers questions and disseminates information on rare diseases; and GeneTests, an online listing of tests for many diseases, including rare diseases. (See box on page 9.) Other NIH-funded consortia or groups also have supported research on specific rare diseases, but the network is the first concerted effort to tackle many rare diseases at once.

UNIQUE DISEASES, COMMON CHALLENGES

The Rare Diseases Clinical Research Network offers hope to patients and families by investigating rare diseases that are seldom studied. These diseases include rare pediatric liver diseases; vasculitis diseases, marked by inflammation of blood vessels; bone marrow diseases such as myelodysplastic syndromes, in which the bone marrow fails to make healthy blood cells; urea cycle disorders, which cause toxic ammonia buildup in the blood; rare diseases of the lungs and airways; and Angelman, Prader-Willi, and Rett syndromes, three developmental childhood disorders.

Although symptomatically different, these and other rare diseases have much in common. They can be physically devastating, frequently misdiagnosed, and difficult to treat. Clinical trials to develop potential therapies often are stymied because of the inability to accrue sufficient numbers of participants. Few drug companies are willing to develop therapies for such a small prospective market and, in families, the psychological and emotional toll of living with a rare disease tends to be overwhelming, eliciting feelings of isolation and powerlessness.

The network's strong collaborative component circumvents many of the challenges traditionally associated with rare disease research. Uniting large numbers of investigators generates wide-ranging expertise for producing new treatments and understanding disease development. Working collaboratively through multiple sites also improves the ability to recruit a larger pool of participants for studies and increases the exposure of physicians and investigators to rare diseases.

A good example of the network's strength in numbers comes from research on Meghan's disease, PCD. Before the network was created, PCD was investigated primarily at only one location, the University of North Carolina at Chapel Hill. Now the disorder is also studied at five additional sites.

Network support to these sites has helped to speed the devel-

The NIH Rare Diseases Clinical Research Network involves:

300+ investigators studying **40+** rare diseases through dozens of research studies at **40+** universities, hospitals, and research centers supported by **30+** advocacy groups and **$71 million** in funding from **7** NIH institutes and centers with the goal of helping **25 million** Americans with rare diseases

■ Physician Peter Merkel examines Lindsay Schoolcraft, who has been diagnosed with a form of vasculitis, a rare disease causing the inflammation of the aorta. The cause of this type of vasculitis is unknown.

PHOTO BY EUGENE Y. KISSIN, BOSTON UNIVERSITY SCHOOL OF MEDICINE

The Rare Diseases Clinical Research Network is the largest and most diverse effort to study rare diseases to date.

opment of the first clinical genetic test for PCD, according to Michael Knowles, professor of medicine at the University of North Carolina at Chapel Hill. Knowles is the physician who leads the team studying PCD in the network. The test can conclusively diagnose about one-third of the patients with the disease. "We've moved from a situation where it was difficult to diagnose PCD five years ago to a place where we can now make accurate diagnosis by offering clinical genetic tests. This is an astonishing advance," says Knowles.

Previously, the only way to diagnose PCD was to biopsy cells from the nose or lungs and then perform a sophisticated and tedious analysis by electron microscopy. Most clinics, however, lack the equipment or expertise necessary to make this diagnosis. The new clinical genetic testing is expected to reduce the need for this cumbersome microscopy analysis and provide an avenue for faster diagnosis without expensive equipment.

Scientific collaboration also is seen in the training offered by the network. Every consortium has a component dedicated to training health professionals and researchers—particularly early-career physicians—on rare diseases. Through involvement in research studies and mentoring by senior physicians, these clinicians become part of an increasing number of investigators studying a specific rare disease.

The network's researchers perform two broad types of clinical investigations: interventional clinical trials and natural history studies. Interventional trials focus on evaluating potential therapies or drugs while natural history studies collect and analyze information about the fundamental characteristics of rare diseases and their progression over time.

At Boston University School of Medicine, a natural history study of Churg-Strauss syndrome is led by Peter Merkel, an associate professor of medicine who also heads the network's research consortium on vasculitic diseases. Churg-Strauss syndrome, a form of vasculitis, is a rare disorder in which small and medium-sized blood vessels become inflamed, resulting in impaired blood flow and potential damage to various organs. The cause of the disorder is not known. Symptoms include asthma, abdominal pain, rashes, and fatigue. Through this natural history study, researchers at Boston University, The Cleveland Clinic, Johns Hopkins University, and the Mayo Clinic will col-

The Rare Diseases Clinical Research Network

RESEARCH CONSORTIUM	CONSORTIUM CHAIR
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ADVOCACY	CONTACT
Coalition of Patient Advocacy Groups	Patrick E. Cochran c/o Periodic Paralysis Association pcochran@periodicparalysis.org Tracy, CA

The network offers hope to patients and families by investigating rare diseases that are seldom studied.

lect patient clinical and laboratory information to study the disease over an extended period of time. The resulting data will be then used to study the genetics and causes of the disorder, find improved ways to track it, and perhaps develop new approaches for treating patients.

At Baylor College of Medicine, an interventional clinical trial is examining the effect of sodium phenylbutyrate in treating patients with argininosuccinic aciduria. This rare disease is characterized by elevated levels of ammonia in the blood, which arise when specific enzymes are deficient or not working properly. Elevated ammonia can cause vomiting, breathing problems, seizures, brain damage, and death. Through this trial, researchers are investigating the drug's effect on the frequency of episodes of elevated ammonia in the blood.

CRUNCHING NUMBERS, SHARING INFORMATION

Coordinating dozens of research studies involving hundreds of participants is a significant challenge. The smooth flow of clinical data and participant information is accomplished in part by the network's Data and Technology Coordinating Center (DTCC), a strategic informatics resource. Although the center is physically located at the University of South Florida, it supports research studies across the world. "We help investigators by providing statistical support for data collection and adverse event monitoring," says Jeff Krischer, division chief of informatics and biostatistics at the University of South Florida and head of the DTCC's informatics team. "We also analyze data to help investigators develop their findings and hopefully improve the lives of individuals with a rare disease."

■ Stephen Groft, director of NIH's Office of Rare Diseases, works closely with scientists and patient advocacy groups to stimulate research on rare diseases.

PHOTO BY BRUCE H. CAMPBELL

The DTCC has created a myriad of standard research tools for the network. These tools are available to network researchers through secure online sites that keep participant information private. Tools used by health professionals in the network include electronic case report forms that allow physicians to enter clinical data, images such as MRIs, and even genetic data pertaining to each participant in a research study. Using tools like these, the DTCC can store data for hundreds of individuals participating in dozens of studies—secure data that is statistically analyzed by the center and commonly shared by investigators in the network.

Knowles in North Carolina, for example, can review these data, check the number of participants enrolled, and evaluate preliminary results from other PCD study sites as they unfold, thereby evaluating progress and coordinating actions. "The DTCC can tell us if there is a correlation between variables in an ongoing study. This helps us validate or reject a preliminary hypothesis," he says.

By providing extensive statistical data analysis for researchers, the DTCC assists investigators with a difficult task, and so frees up their time to uncover connections to other diseases. "Insights we are gaining in PCD are already beginning to translate into understanding more common diseases, like asthma. Molecular abnormalities operate in the two diseases, so dissecting PCD can give us insight into the pathogenesis of asthma," says Knowles.

The DTCC also has created contact registries for many rare diseases. Through these registries, more than 2,000 self-selected individuals have signed up to receive notices on open studies and information on the network's progress toward treating a rare disease. "Through the registry we can support participant accrual, an essential step in conducting rare disease studies for which there are usually so few individuals," says Krischer. Announcements of upcoming studies also are made through

the network's advocacy groups, which play a crucial role in encouraging patients to participate.

REACHING OUT, RAISING AWARENESS

Altogether the network includes 34 patient advocacy groups, many of which were established by people who have experienced the rare disease first hand. One of them is Michele Manion, Meghan's mom. Michele started the PCD Foundation after trying to locate a national advocacy group for PCD and discovering that none existed. Now she regularly fields e-mails and calls from others affected by the disease. "I get up every day at six in the morning and spend about two hours answering e-mails. They come from all over the world, from families and physicians who want to know more about PCD," says Michele. "It's really a relief for them to talk to others who know about disease."

Patient advocacy groups are often the first point of contact for those with rare diseases and act as a nexus between families, resources, and researchers. They range from the very small and simple to large and established institutions; but in essence, all advocacy groups have the same goals of educating the public at large and helping those affected by a rare disease.

Advocacy groups in the network also help to shape research. The PCD Foundation, for example, holds a seat on one of the network's steering committees, which sets goals and priorities for future PCD studies. By being part of the steering committee, the foundation ensures that the needs of patients and families with PCD will be taken into consideration as the research agenda is set.

Working on so many fronts can be daunting for a small organization like the PCD Foundation. "Most people involved in rare diseases realize that they won't be able to do it all, so we have to join forces," says Michele Manion. To help disparate patient groups achieve their shared goals, a unique umbrella organization called the Coalition of Patient Advocacy Groups was created. The Coalition unites all of the advocacy groups involved in the network. Its role is to keep the big picture in the forefront, while advocacy organizations perform the day-to-day work for their constituents.

"In forming this coalition of rare disease groups, NIH has created a powerful vehicle for us to collaborate and communicate with one another," said Patrick Cochran, the coalition's chair. "This has brought many dividends. We have been able to learn from each other and also secure private funding for some advocacy groups to continue doing their work." The coalition has been instrumental in outreach to affected populations, gaining their input into the development of clinical studies and offering valuable feedback on the creation of the rare disease registry.

One person who plans to add her name to the registry is Meghan Manion, who is hoping to enroll in upcoming PCD studies at Washington University in St. Louis. The studies seek to better understand the disease in order to assist in identifying novel therapeutic approaches. "I'm really excited that someone is paying attention to this disease that I've been living with my whole life," says Meghan. "Ultimately, as do many other people, I hope they find a cure. Right now I've set slightly more realistic expectations and would be thrilled if they could find a more effective treatment."

For More Information on Rare Diseases

Collaboration Education and Test Translation Program. Facilitates the translation of genetic tests from research laboratories to clinical practice.
www.cettprogram.org

GeneTests. Lists 1,200+ existing genetic tests, including tests for rare diseases.
www.geneclinics.org

Genetic Alliance. Enhances the capacity of genetic advocacy organizations to achieve their missions.
www.geneticalliance.org

Genetic and Rare Disease Information Center. Responds to queries from those affected by a genetic or rare disease and points them to helpful resources. Disseminates print and online information.
http://rarediseases.info.nih.gov/html/resources/info_cntr.html

National Organization for Rare Disorders. Nonprofit organization dedicated to helping people with rare diseases. Information on 1,000+ rare diseases.
www.rarediseases.org

NIH Office of Rare Diseases. Stimulates and coordinates research on rare diseases.
http://rarediseases.info.nih.gov/

Rare Diseases Clinical Research Network. Unites more than 40 universities, hospitals, and research centers for the study of more than 40 rare diseases.
http://rarediseasesnetwork.epi.usf.edu/

TO LEARN MORE: Details on the diseases studied by the Rare Diseases Clinical Research Network, as well as advocacy organizations and other resources, can be found at http://rarediseasesnetwork.epi.usf.edu. The network is a collaborative initiative funded by the following NIH components: Office of Rare Diseases; NCRR; National Heart, Lung, and Blood Institute; National Institute of Child Health and Human Development; National Institute of Neurological Disorders and Stroke; National Institute of Arthritis and Musculoskeletal and Skin Diseases; and the National Institute of Diabetes and Digestive and Kidney Diseases. For more information, visit http://rarediseases.info.nih.gov/html/resources/extr_res.html.

Incubating and Sharing Novel Technologies

Annual meeting of NIH centers highlights collaboration, accessible research tools, and clinical potential of new technologies. **BY VICTORIA L. CONTIE**

As a place to explore innovative ideas, nurture fledgling technologies, and foster interdisciplinary research, the NCRR-funded Biomedical Technology (BT) Resource Centers have been uniquely successful in creating new research tools for the scientific community. Technologies now widely used in scientific laboratories—including functional magnetic resonance imaging of the brain, multiphoton microscopy, and peptide sequencing by mass spectrometry—were originally invented and developed by scientists at BT Resource Centers. In addition, recent Nobel laureates have depended on the NCRR centers for their award-winning research, including Roderick MacKinnon, who won the Nobel Prize in chemistry in 2003, and Roger D. Kornberg, who won this year's chemistry prize. (See the "News" piece on page 15).

Each BT Resource Center focuses either on a particular core technology, such as mass spectrometry or computational science, or an integrated suite of technologies designed to tackle complex issues. Biomedical researchers nationwide have access to these unique resource centers. Today NCRR supports 52 BT Resource Centers across the country, and an additional 20 are funded by the National Institute of Biomedical Imaging and Bioengineering.

Each year the principal investigators of all BT Resource Centers gather in Bethesda, Maryland, to report their latest discoveries and seek new ideas for collaborations and future research. At the latest meeting, held June 19-20, 2006, the central theme was "Creating Biotechnology for Tomorrow's Clinic." Among the scientific presentations were reports from three established NCRR-funded BT Resource Centers, described below, as well as presentations from two recently funded NCRR centers, described in the Winter 2006 issue of the *NCRR Reporter*, page 11. For more information about NCRR's BT Resource Centers, visit www.ncrr.nih.gov/biotech/btresctr.asp.

SOPHISTICATED MICROSCOPY PROBES MOLECULAR MACHINES

With advanced electron cryo-microscopy (cryo-EM) techniques, scientists have gained their closest look yet at a cellular calcium channel important to normal functioning of the heart and skeletal muscles. Faulty operation of this channel—known as the ryanodine receptor, or RyR—has been implicated in some cardiomyopathies, arrhythmias, and malignant hyperthermia.

"We were the first to look at RyR structures at a resolution that reveals the portion of the channel where the ions go in and out of the membrane," says Wah Chiu, director of the NCRR-supported National Center for Macromolecular Imaging, located at Baylor College of Medicine in Houston. Visualizing this level of detail may offer clues to developing highly targeted therapies for RyR-related disorders.

Chiu heads one of six national BT Resource Centers that house

and develop state-of-the-art tools for electron microscopy, a technology increasingly in demand for biomedical studies. New computational and cryo-EM techniques developed at NCRR-funded centers in recent years have significantly enhanced the capabilities of electron microscopy.

"Over the past 15 years, the number of scientific papers that depend on cryo-EM has increased approximately 25-fold, from about 10 papers in 1990 to nearly 250 papers in 2005," says Chiu, the Alvin Romansky professor of biochemistry at Baylor. A decade ago, cryo-EM could visualize cellular structures at a resolution of 30-40 angstroms, allowing a view of the overall shape of a macromolecular complex, such as a ribosome or an ion channel. Recent technological developments have in some cases enabled nearly 4-5 angstroms resolution, providing a much more detailed view of molecular machines.

Using a sophisticated cryo-EM method known as single-particle analysis, Chiu and his colleagues created a 3-D reconstruction of a type-1 RyR channel at 9.6 angstroms, the highest resolution achieved for this particular ion channel. At this level of resolution, the researchers could detect previously unseen details of the calcium channel. The scientists were able to discern the membrane-spanning helices of the channel (represented by red and blue cylinders in the figure) that play a key mechanistic role in calcium gating. Located in the internal membranes of skeletal muscle cells, type-1 RyR channels open up to release calcium ions into the cytoplasm when triggered by cellular signals, stimulating muscle contraction. (*Structure* 13:1203-1211, 2005)

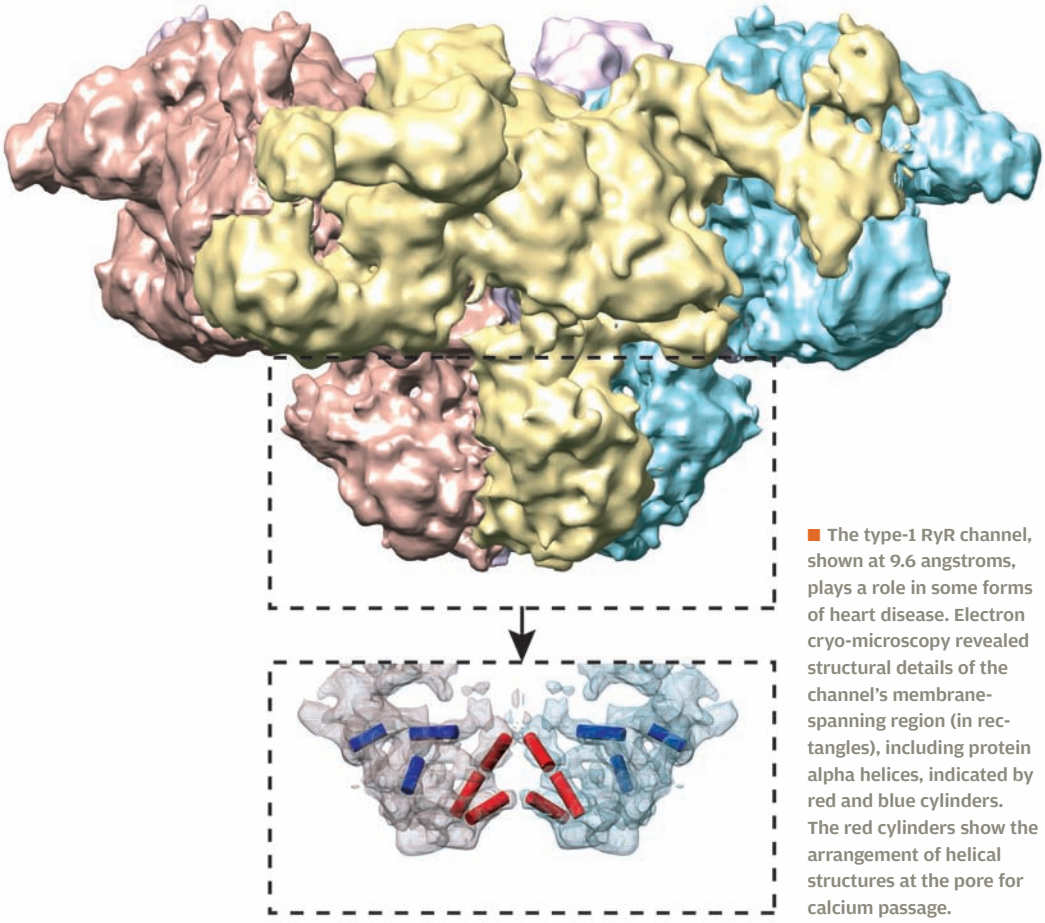
"Knowing the structures of protein complexes is important for understanding biological processes and diseases," says Chiu. "With new and recently enhanced cryo-EM technologies, we can now look at proteins in the context of a functional, biological unit—a macromolecular complex—the way they operate in the cell."

To learn more about the National Center for Macromolecular Imaging, visit their Web site at http://ncmi.bcm.edu. For many of their studies, including visualization of the RyR channel, Chiu and his colleagues depend on use of the Chimera software, developed at another BT Resource Center and described below.

SOFTWARE SIMPLIFIES MOLECULAR COMPLEXITIES

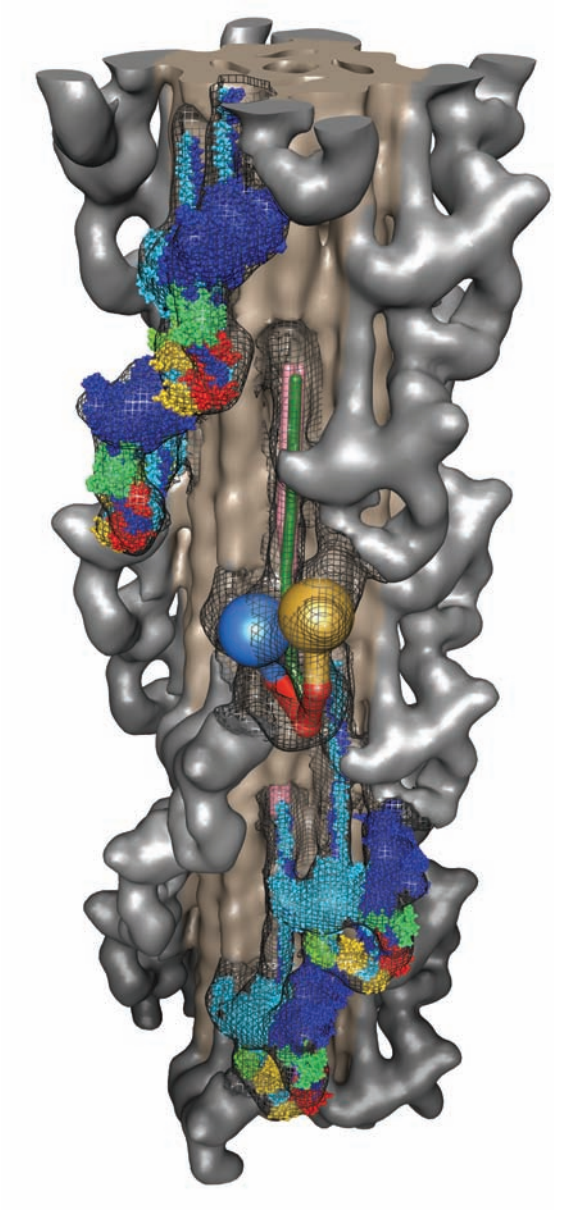
When researchers at the University of Massachusetts Medical School needed an easy-to-use software package to view the molecular details of a muscle filament, they turned to a reliable and cost-effective source—the Resource for Biocomputing, Visualization, and Informatics at the University of California, San Francisco (UCSF). Headed by Thomas E. Ferrin, this BT Resource Center created and now distributes the versatile, user-friendly Chimera software system, which can visualize and analyze a wide range of biomolecular structures, from small molecules to large proteins and complete multimolecular machines, including viruses, ribosomes, and muscle filaments.

"Chimera's ability to display and interactively manipulate macromolecular assemblies is a tremendous aid in understanding how these cellular machines operate, how they might malfunction in disease, and how they might be targeted when developing new therapies," says Ferrin, a professor of pharma-



■ The type-1 RyR channel, shown at 9.6 angstroms, plays a role in some forms of heart disease. Electron cryo-microscopy revealed structural details of the channel's membrane-spanning region (in rectangles), including protein alpha helices, indicated by red and blue cylinders. The red cylinders show the arrangement of helical structures at the pore for calcium passage.

IMAGE COURTESY OF IRINA I. SERYSHEVA, STEVEN L. LUDTKE, AND SUSAN L. HAMILTON, BAYLOR COLLEGE OF MEDICINE



■ With the Chimera software suite, scientists can visualize and manipulate biomolecular structures like these colorful and detailed myosin subunits, which have been maneuvered to fit into a larger scale map of the myosin thick filament.

ceutical chemistry and biopharmaceutical sciences at UCSF.

For the study of muscle filaments, headed by Roger Craig of the University of Massachusetts, the researchers used advanced cryo-EM techniques to examine chain-like myosin molecules derived from striated muscle, which controls contractions of the heart and movement of limbs. The resulting 3-D reconstructions had a resolution about two times higher than previous structural images of myosin. Using Chimera, the scientists visualized atomic-level details of how myosin must interact with other molecules, providing new clues to how muscles relax and contract and offering insights into muscle diseases in which that process goes awry. (*Nature* 436:1195-1199, 2005)

Development of Chimera first began in 1995, with the goal of creating an advanced molecular visualization system that could be easily modified, or extended, to meet the specialized needs of multiple research groups. "A key strength of Chimera—and one that is fairly unique—is that researchers can add new functionality, without much effort, to specifically address their own research needs. This is just not possible with commercial software, yet it is critically important to cutting-edge research," Ferrin says.

Since its official release in April 2002, the Chimera software package has been downloaded more than 54,000 times and has been acknowledged in more than 290 peer-reviewed research papers. Because Chimera is intended for a wide range of scientists—not just those in computational disciplines—Ferrin and his colleagues have developed extensive user manuals and other documentation to enhance usability.

Chimera is available at no cost to noncommercial users. "Licensing costs for commercial molecular graphics packages can be more than $100,000 per year, which is simply not affordable to individual NIH-funded research labs," Ferrin says. "By funding our resource center, NCRR enables other research groups to acquire needed software and make health-related discoveries that might not otherwise occur."

To learn more about the Resource for Biocomputing, Visualization, and Informatics, visit their Web site at www.cgl.ucsf.edu/Overview.

Metal-enhanced fluorescence may help speed the diagnosis of heart attack, stroke, and other conditions in which rapid diagnosis may be lifesaving.

ENHANCING THE GLOW

By adding metallic nanostructures to a familiar research tool—fluorescent molecules—scientists at the NCRR-supported Center for Fluorescence Spectroscopy say they can significantly boost the sensitivity and versatility of fluorescence imaging and assays for biomedical investigations. Patients too may eventually benefit from this unique combination of metallic and fluorescent materials. Preclinical studies suggest that metal-enhanced fluorescence holds potential for speeding the diagnosis of heart attack, stroke, infections, and other medical conditions in which a rapid diagnosis may be lifesaving.

IMAGE COURTESY OF THE RESOURCE FOR BIOCOMPUTING, VISUALIZATION, AND INFORMATICS

Fluorescent molecules, or fluorophores—like the green fluorescent protein derived from jellyfish—have been a boon to biomedical studies for more than a half century. Fluorophors absorb light energy from an external source; become excited, reaching a higher energy state; and then emit their own distinctive wavelengths of light. In recent years, fluorescence technologies have allowed scientists to visualize gene expression and protein activities in living cells and to identify and trace molecules and cells in living organisms.

Under the leadership of Joseph R. Lakowicz, professor of biochemistry at the University of Maryland School of Medicine, scientists at the BT Resource Center have been creating and enhancing fluorescent molecules and technologies for more than a decade. In 2001, Lakowicz and his collaborators hit on the idea of combining metallics with fluorescence to create a new approach called metal-enhanced fluorescence, which can heighten the glow of weakly fluorescing molecules. "We're transitioning away from how fluorescence is traditionally done—which is shining a light on a fluorescent molecule and detecting the light that comes back—to controlling that process by having the fluorophor right next to metallic structures," says Lakowicz. (*Plasmonics* 1:5-33, 2006)

In one series of studies led by Chris Geddes, associate director of the Center for Fluorescence Spectroscopy, researchers found that they could detect minute amounts of myoglobin, a protein that might be indicative of a heart attack, in less than 30 seconds, compared to the 30 minutes or more typically needed for traditional chemical analyses used in hospital emergency rooms. The low-cost fluorescence technique employs a glass microscope slide coated with a thin layer of silver, along with myoglobin-binding antibodies tagged with fluorescent molecules. When a liquid that contains myoglobin is added to the slide, and then briefly heated with microwaves, the fluorescent molecules emit a characteristic glow. The researchers are now working to expand the types of diagnostic molecules that can be detected with this technique. (*Plasmonics* 1:53-59, 2006)

Lakowicz predicts that the metal-enhanced fluorescence technologies developed at the BT Resource Center will lead to a new generation of probes and devices for biomedical research. "Already, LI-COR Biosciences, a small business in Nebraska, has funding from NCRR to develop our technology for use in their DNA readers and their fluorescence imagers for proteomics," says Lakowicz. "As a BT Resource Center, we always try to find new applications to disseminate our technologies."

For more information on the Center for Fluorescence Spectroscopy, visit their Web site at http://cfs.umbi.umd.edu/cfs/.

Unusual Cell May Contribute to Asthma

A recent study points to an unexpected culprit behind the overprotective immune responses that cause asthma. A team of immunologists and physicians has shown that a newly recognized type of immune cell, which is virtually absent from normal lungs, is surprisingly abundant in the lungs of some people with this increasingly common disease. The cells, known as natural killer T (NKT) cells, appear to be more prevalent in the lungs of patients with severe persistent asthma than are the helper T cells that have long been suspected of triggering asthma attacks. The finding may explain why some patients with asthma do not respond to treatment with corticosteroids, which cripple helper T cells but appear to have little effect on NKT cells.

Dale Umetsu and his colleagues found that natural killer T cells were abundant in the lungs of asthma patients but mostly absent from healthy lungs.

"This is a big change for the whole field," says the study's lead author, Dale Umetsu, an immunologist at the Harvard-affiliated Children's Hospital in Boston. In earlier studies conducted at Stanford University in California, Umetsu and his coworkers began looking for NKT cells in human patients with asthma after their studies of mice hinted at the cells' importance. In 2003, for instance, the researchers found that mice lacking NKT cells are not susceptible to the mouse form of asthma. Then in 2006, a study led by Umetsu reported that mice with NKT cells can develop asthma even if they lack helper T cells.

In their more recent clinical study, the researchers found that humans with moderate-to-severe asthma have an even higher percentage of NKT cells in the lungs than do asthmatic mice. The 25 human volunteers who participated in the latest study were examined at the NCRR-funded General Clinical Research Center (GCRC) at Stanford University. "The GCRC has been very helpful. We've depended on the staff's clinical research skills," says Umetsu, who has used GCRC resources for earlier research projects. For instance, skilled nurses at the GCRC cared for patients before and after undergoing bronchoscopy, a procedure during which a flexible, lighted tube was inserted through

PHOTO COURTESY OF CHILDREN'S HOSPITAL BOSTON

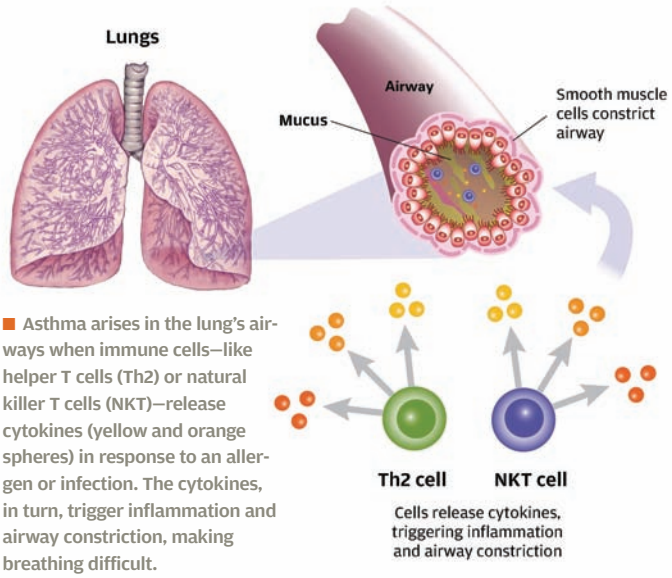
the airways into the subjects' lungs to allow the removal of fluid washings and biopsy specimens. Of the T cells recovered from the specimens, about 58 percent to 86 percent were NKT cells in the 14 patients who had moderate-to-severe asthma. In contrast, NKT cells made up less than 2 percent of the T cells in patients with another inflammatory lung disease, sarcoidosis.

Natural killer T cells have been studied for less than a decade, in part because the technology to separate them from other immune cells has been developed only recently. Scientists do not yet entirely understand the normal role of NKT cells. In healthy people, the cells are present in the blood, liver, spleen, and bone marrow and so are poised to respond rapidly to a stimulus such as infection or allergens. In contrast, "conventional" T cells increase in number by dividing in response to an immune stimulus, and therefore may require a longer lead time to become effective.

The airway inflammation and narrowing that lead to wheezing and breathlessness in people with asthma are caused by the hypervigilant response of the immune system to common triggers in the environment, such as dust and pollen. Both NKT cells and helper T cells respond to allergens. "We need to understand how they might work together or in parallel to cause asthma," says Umetsu. While helper T cells typically begin to multiply after recognizing specific proteins, pre-existing NKT cells are activated in the presence of fatty molecules known as lipids and glycolipids. In a study published in 2005, other investigators showed that NKT cells can respond, in particular, to the lipids found in a specific kind of pollen.

Still, it's not yet clear which lipids or glycolipids might activate NKT cells in the lungs of people with asthma. The molecular culprits might be found in pollen, or they might be made by the body in response to allergens. "Clearly, more research is needed to understand how NKT cells function," says Umetsu. "They're really quite newly described, and the little we know about them is truly intriguing." (*New England Journal of Medicine* 354:1117-1129, 2006)

—KARIN JEGALIAN



■ Asthma arises in the lung's airways when immune cells—like helper T cells (Th2) or natural killer T cells (NKT)—release cytokines (yellow and orange spheres) in response to an allergen or infection. The cytokines, in turn, trigger inflammation and airway constriction, making breathing difficult.

NCRR RESOURCES: The General Clinical Research Center (GCRC) at the Stanford University Medical Center is one of 59 GCRCs nationwide. GCRCs provide settings for inpatient and outpatient clinical studies. For more information, visit www.ncrr.nih.gov/clinical/cr_gcrc.asp.

The research described in this article was also supported by the National Institute of Allergy and Infectious Diseases; the National Heart, Lung, and Blood Institute; the National Cancer Institute; the American Lung Association of California; and the Swedish Heart-Lung Foundation.

A Closer Look at Hepatitis C

■ A cultured strain of hepatitis C developed by Charles Rice and his colleagues will aid studies of the viral life cycle and may provide clues for improving therapies or vaccines.

Virologists seeking to understand hepatitis C have an important new research tool for studying the infectivity and pathogenesis of this virus, a major cause of chronic liver disease. An international team of scientists has shown that a cell-culture version of hepatitis C virus (HCV), developed at Rockefeller University, is fully infectious in certain animals. In addition, when recovered from the bloodstream, the virus can be easily recultured and remains infectious in vitro, unlike most other HCV strains isolated from infected animals or people.

HCV infection is a significant public health problem, with an estimated 3.9 million Americans currently carrying the virus. HCV is usually transmitted by sexual contact or the sharing of contaminated needles. In some cases, the virus produces no symptoms, but in others the consequences can be serious, ranging from cirrhosis to cancer.

The availability of a viable, cultured strain of HCV is a critical advance because, until recently, infectious HCV could not be readily grown in the laboratory. The lack of an efficient culture system has made it difficult to uncover details of the viral life cycle and to develop and test targeted HCV vaccines and therapies, says

ILLUSTRATION COURTESY OF CHILDREN'S HOSPITAL BOSTON; PHOTO COURTESY OF THE ROCKEFELLER UNIVERSITY

Charles M. Rice, scientific director of the Center for the Study of Hepatitis C at Rockefeller University. Another challenge is that the only animal model for investigating both the infectivity and pathogenesis of HCV is the chimpanzee, an animal used rarely and judiciously in NIH-funded biomedical research.

The innovation of Rice and his collaborators was to combine the structural genes of one cloned strain of HCV with a particular section of RNA from another cloned strain. The resulting virus, dubbed HCVcc, replicates and produces the infectious virus in cell culture. Collaborators in Belgium showed that the virus could establish long-term infections in an immunodeficient strain of mouse that contains human liver cells. And at the NCRR-supported Southwest National Primate Research Center in San Antonio, two chimpanzees were inoculated with the virus and had detectable levels of HCV for up to 15 weeks.

"The ability to study genetically defined virus in cell culture and in living animals allows us to completely dissect the HCV life cycle," says Rice. Access to the cultured virus also may aid development of non-primate animal models for HCV infection, as scientists learn more details of how the virus operates.

"Development of this new cell culture system is an excellent example of one of the 'three Rs' of using animals in biomedical research," says Franziska Grieder, director of NCRR's Division of Comparative Medicine. The "three Rs" philosophy seeks to reduce the number of animals used in research, for instance, by sharing animals or redesigning experiments; refine how they are being used, such as modifying laboratory procedures to enhance the animals' well-being; and replace higher order animals with lower order ones, or substituting such alternatives as computer models or tissue culture, when possible.

Still, successful culturing of hepatitis C virus will not completely eliminate the need for animal research. "In terms of vaccine efficacy and immune response studies, chimpanzees are still very valuable," Rice explains, because they alone can offer a close approximation of human-like infectivity in a whole animal. (*Proc Natl Acad Sci USA* 103:3805-3809, 2006)

—SANDRA J. ACKERMAN

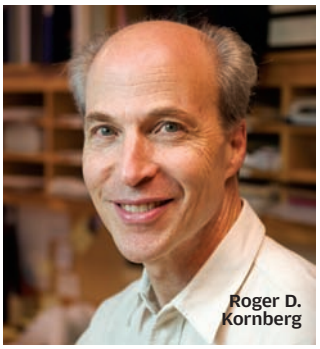
NCRR RESOURCES: The Southwest National Primate Research Center at the Southwest Foundation for Biomedical Research in San Antonio, Texas, is one of eight National Primate Research Centers funded by NCRR. The centers are affiliated with academic institutions and accessible to biomedical and behavioral investigators who have research grants from the National Institutes of Health and other sources. For more information about the National Primate Research Centers, visit www.ncrr.nih.gov/compmed/cm_nprc.asp.

The research described in this article is supported in part by the National Cancer Institute, the National Institute of Diabetes and Digestive and Kidney Diseases, and the National Institute of Allergy and Infectious Diseases.

NEWS FROM NCRR

People, Awards, Grants, and New Developments

Nobel Laureate's Research Aided by Synchrotron X-rays


Roger D. Kornberg

Roger D. Kornberg, long-time NIH grantee and this year's winner of the Nobel Prize in chemistry, performed a significant part of his award-winning research at Stanford's Synchrotron Radiation Structural Biology Resource, an NCRR-funded center. Kornberg won the prize for determining how DNA's genetic blueprint is read and used to direct the process of protein manufacture.

Since the early 1990s, Kornberg has used the resource's extremely bright synchrotron X-rays to reveal the three-dimensional atomic structures of proteins and other molecules, including the RNA polymerase that transcribes genetic instructions into a form that can be translated into working proteins.

NCRR began funding the Synchrotron Radiation Structural Biology Resource in 1980, creating one of the nation's first synchrotron laboratories dedicated solely to biomedical research. The resource, located at the Stanford Linear Accelerator Center (SLAC), is available for use by the biomedical community. "We could not have solved the problem that was noted in the Nobel Prize announcement without the exceptional facilities given to us by SLAC," says Kornberg. "They were indispensable." For more information on this resource, visit http://ssrl.slac.stanford.edu/.

Instrumentation Grants Awarded

NCRR has awarded more than $21 million in one-time grants to 14 research institutions around the country to support the acquisition of scientific instruments that cost more than $750,000. The maximum award is $2 million. High-End Instrumentation (HEI) Grants provide researchers with access to cutting-edge equipment that might otherwise be too costly to obtain. High-end instruments supported in

PHOTO BY LINDA A. CICERO, STANFORD NEWS SERVICE

[CONTINUED FROM PAGE 15]

this round of funding include supercomputers, nuclear magnetic resonance spectrometers, and cryo-electron microscopes. The HEI Program is cost-effective because purchased equipment must be shared by at least three NIH-supported scientists. Further information on the program, including a list of this year's awardees, is available at www.ncrr.nih.gov/biotech/btheinstr.asp.

AIDS Researchers Honored

Two NCRR-funded scientists at Kansas University have been recognized for their investigations related to the AIDS virus.

Heather Desaire received the 2006 Research Award from the American Society of Mass Spectrometry at its annual meeting held in June. The $25,000 award encourages young scientists to pursue research in mass spectrometry. Desaire, an assistant professor of chemistry at the Lawrence campus of Kansas University, received the award for analyzing the structure of HIV glycoproteins. Such studies may enhance development of more effective HIV vaccines.

Desaire began her research in 2002, examining small glycoprotein hormones that regulate the pituitary gland. Her work was funded by NCRR's Centers of Biomedical Research Excellence (COBRE) Program, which supports development of junior researchers and enhances research infrastructure in states that typically receive a lower share of competitive funding from NIH.

"The program kick-started my research career. Without COBRE, we wouldn't have been able to develop the tools and techniques needed to study the more complex HIV glycoproteins," says Desaire. Results obtained with COBRE support were used by Desaire to apply for and secure a five-year grant from the National Institute of General Medical Sciences to study HIV glycoproteins.


Heather Desaire


Opendra Narayan

Opendra "Bill" Narayan received the 2006 Pioneer in NeuroVirology Award for his work during a career that has spanned nearly four decades. The award was presented at the International Society of NeuroVirology's International Symposium held in May.

Narayan is chairman of the microbiology, molecular genetics, and immunology department and director of a COBRE Program at the University of Kansas Medical Center in Kansas City. "The COBRE awards allowed us to bring junior researchers up the ranks, building up institutional research," says Narayan. "This award has helped to create a larger number of NIH-funded researchers in Kansas."

Narayan has received research support from NCRR since the 1970s, when his investigations included lentivirus infections of livestock. In the 1990s, Narayan collaborated with the Yerkes National Primate Research Center for his studies on the molecular pathogenesis of lentiviruses such as SIV and SHIV in nonhuman primates. Currently, he is working to develop a vaccine against HIV-1.

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