

From the Director



Personal Perspectives on the GCRCs

The cover story for this issue of the *NCRR Reporter* is devoted to General Clinical Research Centers, a program that has been central to my career as an investigator and administrator. During my years as a clinical researcher at Boston University's General Clinical Research Center (GCRC), the specialized environment of the GCRC was a great support to many facets of my research as a reproductive endocrinologist. As professor of physiology

and medicine at Boston University, I relied on the center's resources—specially trained staff, services, and advanced instruments—to carry out patient-oriented investigations and provide an environment to nurture scientific inquiry. I eventually served as the head of Boston University's GCRC, and then Director of the Division of Clinical Research at NCRR, before becoming NCRR Director.

My personal history with this program allows me to provide firsthand perspectives on the centers—now totaling more than 80—and how they have progressed over the years. While the resources, instruments, and services are far more advanced than in my days of working at the bench and bedside, perhaps one of the greatest attributes of the centers today is their ability to bring together a complementary team of experts with unique skills and knowledge. These teams—physician-investigators, nurses, core laboratory specialists, nutrition research managers, dietitians, biostatisticians, bioinformaticists, computer systems managers, and others—come together to explore biomedical problems of enormous complexity.

Another benefit of these specialized environments is the opportunity they present for researchers from various disciplines to collaborate on the full spectrum of patient-oriented scientific inquiry. It is this combined, multidisciplinary approach that has become the model for how clinical research should be carried out in today's search for lifesaving drugs, devices, and therapies.

When I was on the GCRC, we made considerable effort to mentor young investigators, and since that time, NIH has introduced a number of training and career development programs to better formalize this important aspect of clinical research. An NCRR pilot program, the Mentored Clinical Research Scholar Program Award (K12), will enable us to more rapidly train clinical investigators and further support this growing need in the research community. (See page 11.)

As a young investigator, I quickly learned that conducting state-of-the-art patient research is not a lone effort. And as today's research becomes more complex, particularly as we begin to address the technological complexities of studying the thousands of proteins expressed by the human genome, we will rely on an even greater complement of skills and abilities. It is this joint effort—the whole as greater than the sum of the parts—that is the key to the future of successful clinical research.

Judith L. Vaitukaitis, M.D.
Director, NCRR

NCRR Reporter

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Cover: Dr. Branimir Sikic (right) conducts clinical trials of cancer drugs at Stanford University's General Clinical Research Center. (Photo by Arturo Beckles, Stanford University)



GCRCs

Enhancing the Nation's Clinical Research Enterprise

Enabling discoveries that enhance human health is the *raison d'être* of the National Institutes of Health (NIH). Basic research lays a critical foundation for biomedical science, but clinical research is at the pinnacle, the ultimate proving ground that brings scientific advances forward to benefit patients.

NCRR's nationwide network of more than 80 General Clinical Research Centers (GCRCs) provides enabling infrastructure for conducting clinical research. Each year the GCRCs offer state-of-the-art research environments, expert staff, and additional resources to support more than 7,000 clinical studies, most of which receive primary funding from other institutes and centers of NIH.

This year's GCRC Annual National Meeting, held March 13-16 in Baltimore, had more than 800 attendees, a record number that included 774 GCRC-supported

staff from across the country. Wide-ranging presentations and roundtable discussions focused on scientific advances, current issues in clinical research, and evolving infrastructure needs.

This special issue of the *NCRR Reporter* highlights key aspects of the meeting, including significant research results and enhanced oversight of patient safety via a new staff position, the Research Subject Advocate (see page 9), at each of the GCRCs.

Meeting participants also learned of the wide variety of NCRR grants that enhance career opportunities in clinical research. These include the Mentored Patient-Oriented Research Career Development Award (K23), which provides supervised study and training to help grantees develop independent research skills, and the Midcareer Investigator Award in Patient-Oriented Research (K24), which offers clinicians protected time for intensive research and mentoring. NCRR also has launched a pilot grant program—the Mentored Clinical Research Scholars (K12) Award (see page 11)—which provides grantee institutions with funds for mentoring promising, recently

trained physicians and dentists in clinical research.

As the following stories make clear, the GCRC program supports a wide range of clinical investigations and services.

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Silent Scourge of Insulin Resistance

Insulin resistance is an insidious and all too common condition, affecting as much as one-third of the U.S. population. Many individuals are not even aware that they have insulin resistance, which arises when the pancreas manufactures sufficient insulin but the body responds only weakly to the hormone. To compensate for the body's muted reaction to insulin, the pancreas steps up insulin secretion, which eventually wreaks havoc on a variety of tissues and organs. Insulin resistance is often associated with cardiovascular disease, type 2 diabetes, hypertension, polycystic ovary syndrome, fatty liver disease, and even some cancers. "In short, insulin resistance can give rise to a

Dr. Henry Blumberg (at keyboard), associate professor of medicine at Emory University, oversees the institution's Mentored Clinical Research Scholars Program, which provides career development training to physicians like Dr. Yohannes Endeshaw (left), an instructor in medicine. See page 11 for more on the program. (Photo by Jack Kearse, Emory University)

lot of devastating conditions,” says Dr. Gerald Reaven, professor of medicine emeritus, at the Stanford University School of Medicine.

To get to the root of these medical complications, Dr. Reaven often relies on the state-of-the-art resources of the university’s GCRC, where he has had a long history. “I helped to write the first GCRC proposal at Stanford in the 1960s,” says Dr. Reaven. “With the GCRC, patients are admitted to a unit with excellent nursing and nutritional support during our clinical trials.”

In experiments reported at the GCRC meeting in Baltimore, Dr. Reaven and his colleagues measured the steady-state plasma glucose and steady-state plasma insulin levels in more than 300 healthy, nondiabetic volunteers with normal blood pressure. The volunteers first received infusions of somatostatin, which inhibited natural production of insulin, and then received measured doses of insulin and glucose. Dr. Reaven observed considerable variability in glucose uptake in this population and identified two “lifestyle” factors, body mass index (a measure of obesity) and physical fitness, that each accounted for about 25 percent of the variability. “These are modulators of insulin action,” Dr. Reaven explains. “They are not trivial, but neither are they the whole cause of insulin resistance. Half the variability comes from lifestyle and maybe half from genetics, although the genes are unknown. We do see that most non-European ethnic groups are more insulin resistant.”

Since obesity often is associated with insulin resistance, some researchers have speculated that losing weight might help to restore insulin sensitivity and other indicators of health. To test this notion, Dr. Reaven and his research team put obese, insulin-

resistant volunteers on a low-calorie diet. The volunteers not only lost weight but also gained some insulin sensitivity, and their levels of C-reactive protein, a measure of inflammation, declined.

These findings may help physicians to customize effective interventions for particular patients. “We could look for obese individuals

who are insulin resistant, and therefore most at risk for severe complications, and then intervene with weight reduction or drugs,” he says. Such a targeted approach could have maximal impact on public health by focusing resources on those who will benefit the most from weight loss.

—*Aaron Levin*

• • • • • • • • • • **Dissecting the Viral Dynamics of AIDS** • • • • • • • • • •

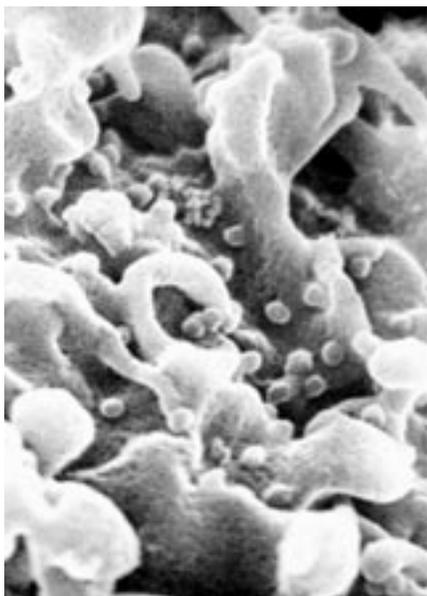
For Dr. David Ho, an important key to understanding HIV and its tenacity lies not only in its DNA and ability to hide from the immune system, but also, quite simply, in its numbers. “We’ve learned that 10 billion to 1 trillion HIV viruses are produced in one day in the human body,” says Dr. Ho, scientific director of the Aaron Diamond

AIDS Research Center and professor at the Rockefeller University in New York City. “Every position on the virus can mutate every day, and that means that there are 10 million new viral variants each day. We’re facing Darwinian evolution on fast-forward.”

Following initial HIV infection, the viral count rises steeply but



Dr. David Ho’s laboratory studies HIV replication dynamics during infection and treatment. Pictured from left to right are Dr. Ho, Tshaka Cunningham (graduate student), Dr. Mark Muesing (staff investigator), and Louise Noeddegaard-Schultz (summer intern). (Photo courtesy of Rockefeller University)



This scanning electron micrograph shows multiple HIV virions (small spheres) budding from the surface of an infected T cell. (Image by C. Goldsmith, Centers for Disease Control and Prevention)

then drops off to a virologic set point. To better understand the viral dynamics and pathogenesis of AIDS, Dr. Ho has spent years disturbing the virus's equilibrium within its host and then tracking both host and viral responses. For instance, in 1994, using an early anti-HIV drug, the protease inhibitor zidovudine, Dr. Ho and his colleagues elicited a rapid, exponential decline in plasma virus levels in 1.5 to 3 days. "Antiviral drugs block the next round of viral replication," says Dr. Ho. "The drop in viral load represents the combined decay in the numbers of HIV particles and the numbers of infected CD-4 T cells." Further studies showed that the viral load actually did not change during the first 24 to 30 hours of treatment, a delay that represented one viral replication cycle.

Another study, which used plasmapheresis to clear viral particles from the bloodstream, found that

viral levels snapped back to baseline in just half an hour. In summary, Dr. Ho and his team concluded that infected HIV-producing CD-4 cells have a half-life of nearly 17 hours, meaning it takes that long to clear 50 percent of infected CD-4 cells from the body.

If all cells containing the virus had a similar history, it would be easier to eradicate the virus and effect a true cure, says Dr. Ho. But after 10 to 14 days of antiviral therapy, the decay rate slows, suggesting the presence of a second compartment of latently infected cells, perhaps macrophages or resting memory T cells. Dr. Ho and his colleagues estimate that up to 7 percent of the viral load in plasma may arise from this reservoir. "It may take months or years to flush out these reservoirs, even with current regimens," he says.

In addition, the virus could reside latently within resting memory T cells, which may have half-lives of nearly four years, making eradication unlikely. "We know that single-drug therapy is not sufficient to shut off the virus," says Dr. Ho. "But we can get a sharper reduction in viral levels with a three- or four-drug treatment. Even with current regimens, this low-level pool of virus will remain in the body for years. Our challenge now is to purge this reservoir."

—Aaron Levin

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Evaluating New Cancer-Fighting Strategies

Approval of Gleevec (imatinib) for chronic myelogenous leukemia (CML) in 2001 marked the success of a new strategy for treating cancer: a specific inhibitor that blocks

a specific chemical signal that stimulates cancer growth. A recent clinical study, reported in the March 13, 2003, issue of the *New England Journal of Medicine*, involved more than 1,000 CML patients from 16 countries and showed that Gleevec delayed disease progression, produced milder side effects, and generated significantly better responses than conventional therapy with interferon. At an 18-month follow-up, 85 percent of patients on Gleevec had a significant reduction in the number of cancerous cells, compared with 22 percent of patients on conventional therapy.

However, these successes have as much to do with the relatively straightforward nature of the disease as with the approach represented by Gleevec, says Dr. Moshe Talpaz, professor of medicine and chairman of the department of bioimmunotherapy



Dr. Moshe Talpaz notes that Gleevec is not a cure for chronic myelogenous leukemia, but the drug may control the disease in its chronic stage. (Photo by Beryl Striewski, University of Texas M. D. Anderson Cancer Center)

at the M. D. Anderson Cancer Center in Houston. CML was found to be associated with the Philadelphia chromosome in 1960, its abnormal gene (bcr/abl) was described in 1984, and the inhibitor of the abnormal protein produced by that gene was developed in 1996. That inhibitor, now known as Gleevec, works because the cancer cells cannot survive without the mutant protein.

“Gleevec is a specific drug with a specific target,” adds Dr. Talpaz. The drug produces a 96 percent survival rate at 18 months. However, resistance to the drug has proved to be a problem in the

advanced stages of the disease, either because ongoing mutations in the bcr/abl gene may reduce Gleevec’s affinity for the protein’s binding pocket, or because the drug may stimulate cellular activation of alternative signal pathways, he says.

Gleevec is not a cure, explains Dr. Talpaz. Polymerase chain reaction shows that 94 percent of treated patients still have residual disease. Early CML progenitor cells seem most resistant to therapy. Thus Gleevec may serve as a nontoxic therapy, perhaps for decades, controlling the disease in its chronic stage while other avenues to a complete cure are developed.

Dr. Branimir Sikic, program director of the GCRC at Stanford University, speculates that Gleevec’s success might not be duplicated easily with other cancer drugs. “However, Gleevec is a wonderful example of how understanding the fundamental mechanisms that drive cancers may open up new opportunities for inhibiting many cancer-related enzymes and receptors,” said Dr. Sikic.

CML is caused by a single mutation, the translocation in the bcr/abl gene, but other cancers lack such a simple, universally expressed target, notes Dr. Sikic. Cancers of the lung, breast, prostate, or colon

Riggs Receives GCRC Award

At the 2003 GCRC Program Directors’ Meeting, Dr. B. Lawrence Riggs, a prominent researcher in the field of age-related bone loss, accepted the 15th Annual GCRC Award for Excellence in Clinical Research. A professor of medicine at the Mayo Medical School in Rochester, Minnesota, Dr. Riggs was the program director of the Mayo Clinic GCRC from 1991 to 2002. The award recognizes outstanding clinical investigators who have conducted studies in GCRCs within the previous decade.

Dr. Riggs is perhaps best known for having demonstrated that the slow phase of bone loss in postmenopausal women is caused by estrogen deficiency. Low estrogen levels result in less estrogen-induced calcium reabsorption in the intestine and kidney, leading to calcium loss. Reduced serum calcium levels, in turn, trigger the release of parathyroid hormone, which normalizes serum calcium by increasing bone resorption, or breakdown. Dr. Riggs also showed that estrogen deficiency was the major cause of bone loss in aging men, as well as women. He has been the first to evaluate many treatments for osteoporosis, the metabolic bone disease that causes bone fractures in the elderly. Among the treatments that he has tested are transdermal estrogen, vitamin D₃, and raloxifene, a drug that stimulates the estrogen receptor. Much of Dr. Riggs’ research over the last 30 years was conducted at the Mayo Clinic GCRC.

—Steven Stocker



require at least three oncogenic events for tumor development, which suggests that use of a single inhibitor may prove insufficient.

Dr. Sikic compares Gleevec's success in treating CML with the bumpier development of another drug, Iressa (gefitinib). Its target, epidermal growth factor receptor-1 (EGFR-1), is overexpressed in only 50 percent of non-small-cell lung cancers. In two nonrandomized Phase II clinical trials, gefitinib produced remission rates of 10 percent and 18 percent, with relatively low toxicity. The drug is now undergoing clinical evaluation at several sites across the country, including the GCRCs at Stanford, New York University, University of Colorado, and University of North Carolina.

Gefitinib was approved last year for treatment of non-small-cell lung cancer in Japan, where preliminary studies touted a 25 percent remission rate. However, some questions have been raised about the drug's safety. Beginning in late 2002, Japanese authorities have received reports of higher-than-usual rates of interstitial lung disease and possible deaths associated with the treatment.

In the United States, Iressa received FDA approval on May 5, 2003, as a single agent for advanced non-small-cell lung cancer in patients who previously had been treated with chemotherapy. Although Iressa clearly benefited some patients with advanced lung cancer, Phase III trials have found no increase in patient survival when the drug was added to two existing chemotherapy agents for the treatment of non-small-cell lung cancer. Still, Dr. Sikic notes, more favorable targets might eventually be found for this drug.

"The General Clinical Research Center at Stanford is a fundamental resource for translational research," says Dr. Sikic, echoing other speakers at the conference. "We have a highly trained research nursing force and

a wonderful biostatistical facility, all of which contribute to the quality of the science and the rigor of trials design."

—*Aaron Levin*

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Strengthening the Public's Trust in Clinical Research

by Dr. Elaine Collier
Assistant Director, NCRR Division of Clinical Research

Each GCRC has a multidisciplinary research team consisting of people with specialized positions, such as biostatistician, core laboratory director, and head nurse. In early 2001, NCRR added a new position to this list—the Research Subject Advocate (RSA). The RSA assists GCRC investigators, nurses, and staff

in the safe and ethical conduct of GCRC studies and represents the interests of research participants at the GCRCs. Most RSAs are physicians; however, some are nurses, pharmacists, or biomedical ethicists. Although relatively new, the RSA program already is having a measurable impact at the GCRCs.



Research Subject Advocate Theresa O'Lonergan (right) counsels a patient entering a GCRC-supported clinical study. (Photo by Tia Brayman, The Children's Hospital-Denver)

The role of the RSA still is evolving at each institution. In the first year, RSAs focused their efforts on areas of particular need at their respective GCRCs. In many cases, this involved assisting investigators in the establishment and development of data and safety monitoring plans for ongoing

A survey conducted by Theresa O'Lonergan, RSA at the pediatric GCRC at the University of Colorado in Denver and president of the Society of Research Subject Advocates, demonstrated that RSAs are succeeding in their goal of helping clinical investigators to comply with data and safety monitoring

RSAs currently have a very active electronic mailing list with wide-ranging discussions, which serve as a vigorous and deep resource to all RSAs as they solve human subject issues that arise at their institutions. In addition, the Society of RSAs has established several active committees. One of the committees is developing a survey to determine the activities performed by RSAs. Another is focusing on the potential for informatics systems to facilitate the activities of RSAs. The latter committee is in collaboration with the Association of GCRC Information Technology Professionals.

: *The Research Subject Advocate*
: *assists GCRC staff in the safe and*
: *ethical conduct of clinical studies.*

and new protocols. In addition, RSAs have been instrumental in fostering better communication and coordination among investigators, nurses, and their home institutions on issues related to protection of human subjects. A few RSAs counsel both research participants and potential participants regarding their important contributions to the conduct of research. Many RSAs have established policies and procedures that facilitate the application of appropriate human subjects protections in protocols, informed consents, and monitoring plans at their GCRCs.

requirements. According to the survey, 9 out of 10 RSAs have assisted investigators in development of data and safety monitoring plans at their institutions. Since the RSA program began, the number of such plans has increased threefold. Also, since the program began, the number of data and safety monitoring boards has similarly increased by three. These monitoring boards are required for any protocol that places participants at significant risk. In many cases, the RSA has been instrumental in establishing required data and safety monitoring boards.

The RSA program is active, interactive, and evolving. The current professionals serving as RSAs are committed to earning, improving, and maintaining the public's participation and trust in the clinical research enterprise.

Mentored Clinical Research Training: The K12 Program

**A conversation with
Dr. Anthony R. Hayward**

In fiscal year 2002, NCRR launched a pilot training program, the Mentored Clinical Research Scholar Program Award, the K12 award, to provide up to 5 years of institutional funding for a career development program targeted to physicians and dentists. The NCRR Reporter discussed the genesis and the future of the K12 program with Dr. Anthony Hayward, director of NCRR's Division of Clinical Research.

Why did NCRR become involved in the K12 program?

We already have a mentoring program in place for individual trainees that's been working well. It's called the K23, or Mentored Patient-Oriented Research Career Development Award. The K23 supports 3 to 5 years of supervised study that allows the grantee to develop independent clinical research skills. But the application process has a rather slow turnaround time. K23 applications are sent to NIH and undergo peer review. It can take up to a year from the time an application is submitted until funding is actually received.

But with the K12 program, we've enabled a much faster turnaround time, since we provide funding for up to three trainees directly to the institution. The institutions first must demonstrate that they have sufficient internal resources to evaluate candidates for training. By shifting responsibility for choosing trainees to an internal review committee, application turnaround time has shortened considerably. A three-month turnaround time is now possible for individual candidates.

How does the program work, once an institution receives its K12 award?

The director of the K12 program is able to use a training selection committee to choose among individual applicants. Funding is provided in year 1 for selecting up to three trainees. Applicants must work with a mentor who is involved in clinical research at that institution, and together they come up with a program proposal. The proposal is then submitted to the institution's GCRC Advisory Committee or some other institutional peer-review committee, which then ranks the various applications in terms of priority. The selected trainees receive a stipend of \$90,000 per year.

The K12 award can be used for up to 5 years. Our expectation is that K12 trainees will probably stay in the program until they're able to secure some sort of independent funding.

Are all recipients of NCRR's K12 grants associated with a GCRC?

Yes. All of the K12s we award go to institutions that have GCRCs.

How many K12 grants has NCRR awarded?

We received outstanding applications for the K12 award in FY 2002. Although we expected to award only 10 grants, the quality of the applications was so high that we ended up funding 11 institutions. An additional five centers were funded in FY 2003.

The program is still relatively new, but have you received any feedback from grantees?

Yes, we've asked the centers about the



number of individual applications they've received and about the quality of the candidates. We've found that interest in the program is strong. Each institution reviewed about 12 applications for the 3 vacant trainee positions in the first year. For each trainee appointment, there was at least one highly qualified applicant who did not receive funding.

What are NCRR's future plans for the K12 program?

Our next step is to evaluate the effectiveness of the program. The first meeting of the K12 program directors will take place in September 2003, and we will ask them to work with us to develop the best criteria for evaluating the success of the program. As soon as we have information as to how well it is working, then we will have some idea as to when we could reasonably try to set some funds aside and see if we've allocated enough funds to readvertise it.

• Critical Resources

The Microbe and Cell Superstore

At the American Type Culture Collection (ATCC), scientists can obtain everything from bacterial strains that came from Louis Pasteur's laboratory to the DNA segments of practically every expressed gene in mice and humans. Researchers also can choose among nearly 18,000 strains of prokaryotes, more than 57,000 strains of fungi and yeasts, and over 4,000 cell lines from more than 150 species.

From its humble beginnings in 1925, when its inventory consisted of only 175 microorganism strains, ATCC has grown into the largest and most diverse collection of biological materials in the world. Located in a 106,000-square-foot facility in northern Virginia, this nonprofit organization fills annual orders for about 235,000 items, including microbes, cell lines, and recombinant DNA materials. Income from these orders provides the bulk of ATCC's support, with the remaining funds coming from contracts and grants with NCRR, National Science Foundation, and other sources.

Although some people refer to ATCC as a biological repository, Dr. Raymond Cypess, president and chief executive officer, prefers to call it a biological resource center. "A repository is kind of a passive, museum-type organization," says Dr. Cypess. "A biological resource center collects and preserves items of biological interest, just like a repository, but there's greater emphasis on authentication, development of new tools and models, and knowledge management."

ATCC follows four basic steps in its handling of biological materials: acquisition, authentication, preservation, and distribution. In the acquisition process, ATCC scientists peruse the recent scientific literature and select new microbes, cell lines, and other items for the collection. They then ask the researchers who discovered or developed these items to send samples of their cultures to ATCC. "Not everyone in the scientific community understands the function of ATCC," explains Dr. Shung-Chang Jong, director of the Yeast Genetic Research Resource Center. "We write a letter to inform them that we have a contract to maintain this material and make it available to the scientific community. In some cases, researchers will send in unsolicited deposits because many scientific journals require that authors deposit their materials with a cell bank and list a cell bank accession number when describing their organism in the paper."

The next step—authentication—involves verifying that the culture contains the specified cell species or biological agent and that it performs as promised. The cultures also are tested for contamination with bacteria and fungi. The bacterial species mycoplasma, sometimes called the "crabgrass of tissue culture," is particularly troublesome. Unlike most fungal or bacterial contaminants, mycoplasma cannot be detected visually and often interferes with cellular studies without the scientist's knowledge. Testing performed by ATCC showed that an average of 16 percent of mammalian cell cultures are contaminated with mycoplasma.

After the cultures are shown to be authentic and uncontaminated, a sample is subjected to a "token freeze" and then unfrozen to confirm that the cultures can be recovered from cryopreservation. At this point, a few vials are selected for distribution and the rest, known as the "seed stock," are slowly frozen and then



An ATCC worker prepares to insert a "cane" into a liquid nitrogen tank. Each cane holds several ampoules filled with biological samples, and each tank can hold up to 10,000 samples.
(Photo by Greg Sykes, American Type Culture Collection)

stored at temperatures as low as -196°C inside stainless steel tanks cooled with liquid nitrogen. Freezing maintains the genetic information of the strains, which tends to change through random mutations if the cells are left to multiply. When the distribution samples are exhausted, a vial from the seed stock is thawed and grown for distribution. When the last seed vial is reached, it is grown and tested for authenticity and purity, just as if it were an original sample. If it passes the tests, a few vials are selected for distribution and the rest are frozen as more seed stock.

• ***ATCC has grown into
the largest and most
diverse collection of
biological materials
in the world.***

Cultures are distributed either frozen in sealed ampoules or as growing populations. In addition to supplying the cultures, ATCC also provides background information, such as media formulations, applications, and key scientific references. For scientists who encounter problems with their cultures, ATCC has technical support staff to answer questions via e-mail or phone.

Besides its core collection of microbes, cells, and DNA, ATCC also houses special collections, such as the National Stem Cell Resource and the Yeast Genetic Research Resource Center, both supported by resource grants from NCRR's Division of Comparative Medicine. The stem cell resource currently has embryonic stem (ES) cells from mice and is seeking to acquire ES cells from a range of species, including nonhuman primates, zebrafish, and chickens. It also possesses tissue-specific stem cell and precursor cell lines, such as embryonic heart muscle cells from rats, and provides standardized media and selected reagents related to stem cell characterization and utilization. The yeast resource center manages about 25,000 genetically defined strains of *Saccharomyces cerevisiae* and other yeast species. Included in the collection are deletion mutations for every gene in the *S. cerevisiae* genome that encodes a protein.

In addition to acquiring and distributing biological materials, ATCC acts as a repository for biological materials submitted in connection with patent applications. "We're like a trust company in this regard," explains

Dr. Cypess. "We hold the material until the patent has been approved and then release it to the scientific community." Collecting the royalty, however, is the responsibility of the patent holder.

ATCC scientists also develop products that scientists can use in connection with their cultures. "One of our best products is our Mycoplasma Detection Kit," says Dr. Cypess. "It's probably the best kit in the world right now for detecting mycoplasma in cell cultures." The kit uses the polymerase chain reaction to detect DNA sequences in eight commonly encountered mycoplasma contaminants. The test is highly sensitive, detecting less than 1 colony-forming unit per 5- μl sample, and takes about four hours to complete.

Because of its size, nonprofit status, and careful authentication and preservation procedures, a biological resource center such as ATCC offers several advantages over other sources of biological materials, such as peer-to-peer networks, private collections, and for-profit biological supply companies. One advantage is the certification of research materials, which can prevent the widespread contamination of cell cultures that occurred in the past when researchers informally shared the cell lines that they had developed. Another advantage is the preservation of biological materials that may be of uncertain value. For example, *Thermus aquaticus* was a largely ignored bacterium that sat in ATCC's facility for about two decades before Dr. Kary Mullis paid \$37 for a specimen in the mid-1980s and used it to help invent the polymerase chain reaction. This technique, which rapidly amplifies selected sections of DNA, won Dr. Mullis the Nobel Prize in Chemistry in 1993.

"An infrastructure such as ATCC, which can authenticate and share biomaterial, is critical to the scientific community," says Dr. Cypess. "I think that we'd have a hard time conducting science these days without such an infrastructure."

—*Steven Stocker*

For more information about the American Type Culture Collection, visit www.atcc.org, or contact Dr. Jay George, Chief Scientific Officer, at 703-365-2736; fax: 703-365-2779; e-mail: jgeorge@atcc.org.

ATCC is supported in part by the Division of Comparative Medicine of the National Center for Research Resources. To learn more about other NCRR-supported comparative medicine resources, see www.ncrr.nih.gov/comparative_med.asp.

News from NCRR

Health Economist Joins NCRR's Advisory Council

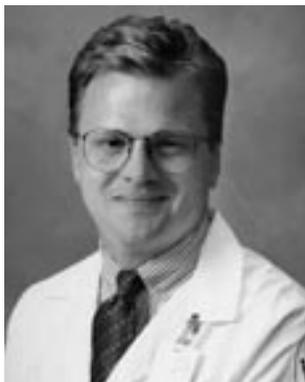
The newest member to be appointed to the National Advisory Research Resources Council—the body that advises NCRR on policies and programs, and performs second-level peer review of grant applications—is Dr. Thomas G. McGuire, professor of health economics at Harvard Medical School.



Dr. McGuire's research focuses on the design and impact of health care payment systems, the economics of health care disparities, and the economics of mental health policy. He is a member of the Institute of Medicine and a co-editor of the *Journal of Health Economics*.

GCRC Researcher Wins Young Investigator Award

A researcher who developed a unique method of treating cancer has received the 2003 Young Investigator Award from the Society for Pediatric Research. The award recognizes physicians younger than 40 years of age who are conducting important research on pediatric diseases. This year's award, presented May 5 at the society's annual meeting in Seattle, went to Dr. Michael Jensen, director of the pediatric oncology



program at the City of Hope National Medical Center in Los Angeles. Dr. Jensen developed methods for genetically modifying cancer patients' own immune cells to attack their malignancies. He is now conducting clinical trials of these therapies at the NCRR-supported General Clinical Research Center at the City of Hope National Medical Center.

For treating some types of tumors, Dr. Jensen and his colleagues inserted genes into immune cells called

killer T cells, causing them to express a cell-surface protein that recognizes an antigen displayed on tumor cells. Thus activated, the killer T cell destroys the tumor cell. Dr. Jensen is now evaluating this experimental approach in the treatment of three types of cancer: lymphoma, neuroblastoma, and malignant glioma.

SEPA Grantee Receives National Academy Medal

The National Academy of Sciences honored Dr. Shirley M. Malcom with the Public Welfare Medal during the academy's 140th annual meeting, held April 28 in Washington, D.C. The award, presented annually since 1914, recognizes extraordinary use of science for the public good. As head of the directorate for education and human resources at the American Association for the Advancement of Science (AAAS), Dr. Malcom was honored for effectively bringing health-related information to young people and adults who are traditionally distanced from the world of science. A recipient of NCRR funding since 1991, Dr. Malcom has received two Science Education Partnership Awards (SEPA), which encourage collaborations between scientists, community groups, and other organizations to enhance public understanding of the life sciences.



Dr. Malcom's first SEPA grant supported the AAAS Black Church Health Connection Project, which developed and field-tested hands-on biology activities that were distributed to more than 500 churches for use in after-school programs and community events. Dr. Malcom's second SEPA-funded project, the Public Library Initiative, launched in 2000 and is ongoing. Under the initiative, plain-language booklets and toolkits related to the health sciences are produced and made available through public libraries in low-income African American and Hispanic American communities. The ultimate goal is to reduce health disparities among different segments of the population.

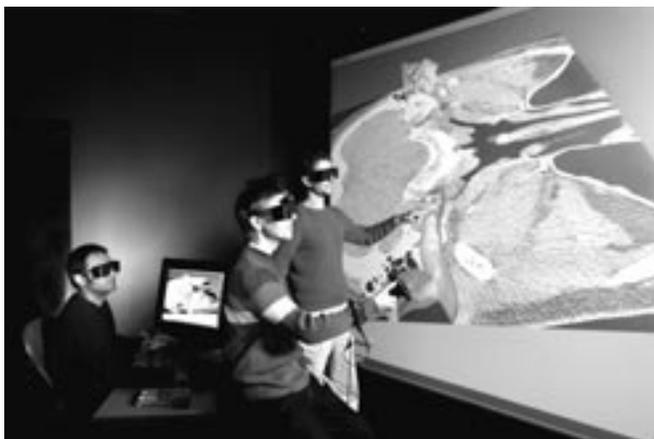
GCRC Studies Lead to FDA-Approved Therapy

The Food and Drug Administration (FDA) has approved the first treatment for Fabry disease, a rare genetic disorder in which a fatty compound accumulates in the cardiovascular and renal systems, leading eventually to kidney failure, heart disease, and stroke. The treatment involves intravenously injecting an enzyme—alpha-galactosidase A—that is missing in the patients. The development of this therapy depended on more than 30 years of clinical research by Dr. Robert Desnick, professor of gene therapy and molecular medicine at the Mount Sinai School of Medicine in New York City. Dr. Desnick conducted his studies at the General Clinical Research Centers at Mount Sinai and the University of Minnesota in Minneapolis. For more information about Fabry disease and Dr. Desnick's research, see the *NCRR Reporter*, Fall 2001, pages 5-7.

Real Recognition of Virtual Reality

The life sciences have made it to the big screen, in 3-D no less, at the University of Delaware's NCRR-funded Delaware Biotechnology Institute (DBI). The screen is in DBI's "visualization studio," and a host of molecules and compounds are the stars. In April, the DBI program received technology's version of the Academy Awards: the Computerworld Honors Medal of Achievement.

The 100-square-foot screen comes to life with 3-D interactive images, supplied by researchers representing a cross-section of the life sciences.



Large enough for 10 people, the studio has allowed scientists and students to study much larger-than-life simulations of protein folding, 3-D images of the inner ear (pictured below left), and more. A computer network enables DBI's 29 laboratories and centers to feed data directly to the studio, which also is used by other colleges and a local hospital. As part of NCRR's Biomedical Research Infrastructure Network (BRIN) Program, DBI is expected to help coordinate research at Delaware institutions, says DBI associate director Dr. Karl V. Steiner. A description of DBI's visualization program is included in the Computerworld Honors Collection (www.cwheroes.org), which features more than 4,000 essays on award-winning information technologies.

NCRR-Supported Scientists Join National Academy

The National Academy of Sciences has elected 72 new members, including 4 who have made substantial use of NCRR-supported resources in their research. The National Academy of Sciences, located in Washington, D.C., is a private scientific organization that advises the federal government in matters of science and technology. Election to Academy membership is considered one of the highest honors that can be accorded a scientist or engineer. The NCRR-supported scientists are:

Dr. Dennis Carson, professor of medicine at the University of California, San Diego (UCSD). Using the resources of the General Clinical Research Centers (GCRCs) at UCSD and the Scripps Research Institute, Dr. Carson develops and tests the efficacy of antineoplastic agents in patients with cancers of the lymphoid system. One product of these studies is cladribine, a drug that is now the standard treatment for hairy cell leukemia.

Dr. Barry Collier, head of the laboratory of blood and vascular biology at Rockefeller University in New York City. While at the State University of New York at Stony Brook, Dr. Collier used that university's macromolecular analysis facility, funded in part by an NCRR Shared Instrumentation Grant (SIG), in his studies of platelet membrane receptors. From these studies came the development of abciximab, a drug that lessens the chance of a heart attack during a procedure that opens blocked heart arteries. Later, Dr. Collier utilized the GCRC at the Mount Sinai School

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of Medicine in New York City in studying the molecular mechanisms of Glanzmann thrombasthenia, a bleeding disorder.

Dr. Martha Ludwig, professor of biological chemistry at the University of Michigan, Ann Arbor. Dr. Ludwig uses X-ray crystallography to study the structure and function of enzymes, including enzymes involved in the control of homocysteine levels. Homocysteine is of interest because elevated levels of this compound have been found to be a risk factor for the development of cardiovascular disease. Throughout her career, Dr. Ludwig has used several NCRR-funded resources, including X-ray crystallography equipment purchased through the SIG program and synchrotron beamlines at Cornell University in New York and Argonne National Laboratory in Chicago.

Dr. Robert Stroud, professor of biochemistry and biophysics and of pharmaceutical chemistry at University of California, San Francisco (UCSF). Using X-ray crystallography and mass spectrometry equipment purchased in part through NCRR's SIG program, Dr. Stroud deciphers the structures of membrane proteins and channels. Then, using the computer graphics facilities at the NCRR-funded Resource for Biocomputing, Visualization, and Informatics at UCSF, he develops drugs that target these molecules. He is currently focusing on potential therapies for AIDS and cancer.

Brochure Links Animal Research to Human Health

A consortium of the eight National Primate Research Centers (NPRCs) released a 12-page color booklet, "Linking Research to Healthy Living," that highlights the importance of nonhuman primates to lifesaving advances in medicine. The NCRR-supported NPRCs, located in California, Georgia, Louisiana, Massachusetts, Oregon, Texas, Washington, and Wisconsin, created this brochure to offer the public a more comprehensive understanding of how nonhuman primate research ultimately enhances public health.

The publication outlines medical breakthroughs that depended on studies of nonhuman primates and ongoing NPRC-supported investigations related to women's health, infectious diseases, genetic medicine, and more. For links to the eight NPRC web sites, where you can download the brochure as a .pdf file or request a printed version, visit the NCRR web page at www.ncrr.nih.gov/compmed/cm_nprc.asp.



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