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# NCRR Reporter

WINTER/SPRING 2009

CRITICAL RESOURCES FOR RESEARCH

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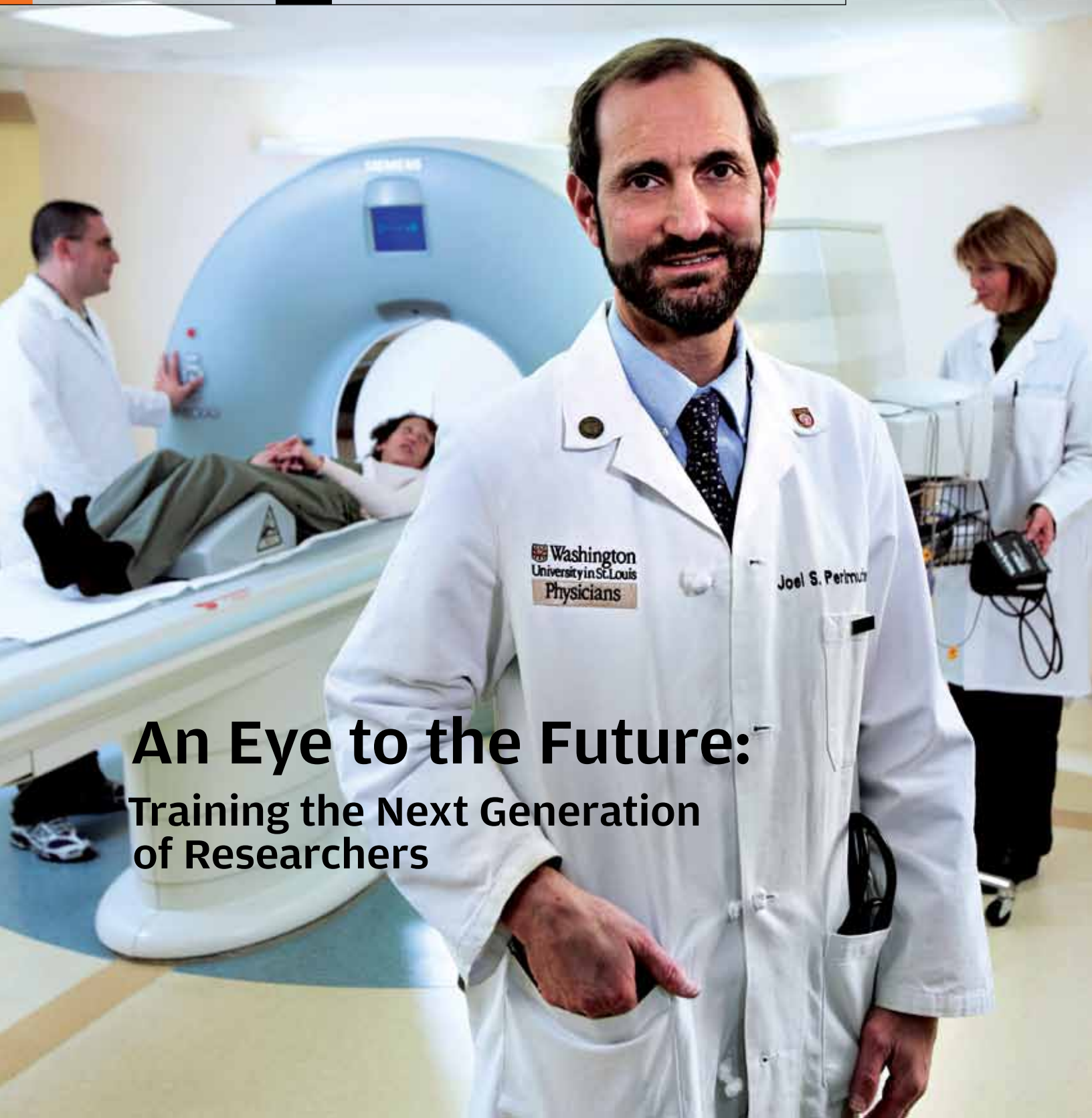


## An Eye to the Future:

### Training the Next Generation of Researchers

## FROM THE DIRECTOR

# Guiding Successful Careers to the Intersection of Basic, Clinical and Community Sciences

Translation of research advances to practices that will improve human health cannot occur without a cadre of well-trained translational and clinical researchers. Until recently, training for these researchers relied on one-on-one instruction by more senior mentors. However, the increasing complexity of biomedical research and the technologies used to carry out this research require a broad range of expertise that is difficult to acquire without structured programs.

To meet this growing need, NCRR's Clinical and Translational Science Award (CTSA) consortium is developing innovative approaches that give researchers the skills they need for successful careers at the intersection of basic, clinical and community sciences. The article that follows in this issue of the *NCRR Reporter* highlights examples of training programs offered at three CTSA institutions and the individuals who have benefited from them, charting their own paths to successful careers. Although clinical and translational researchers face many challenges, the stories you will read in the next few pages demonstrate that these challenges can be overcome with the right infrastructure and resources.

The training programs designed by CTSA grantees incorporate didactic courses, often leading to master's or doctoral degrees; hands-on experiences in the laboratory and clinic; mentorship; and, importantly, exposure to large, interdisciplinary teams. At the same time, these programs give participants sufficient flexibility to embark on individualized career paths, such as research on vaccines, Alzheimer's disease, nutrition or chronic kidney disease.

In addition to providing courses that benefit budding researchers at their own institutions, CTSA grantees are working together as a consortium to leverage the expertise from each site to increase the impact and reach of available programs. Through partnerships, collaborations and connectivity, CTSAs are sharing courses, curricula and best practices — working together to ensure advancements in clinical and translational research and better health options for all.

Barbara Alving, M.D.

**Barbara Alving, M.D.**
*Director, NCRR*

## INSIDE

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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:**
Translational research involves multidisciplinary research teams. No one knows that better than Joel Perlmutter (center), director of the Brain, Behavior and Performance Unit (BBPU) at the Washington University in St. Louis Institute of Clinical and Translational Sciences — a CTSA consortium member. The BBPU plays a critical role in the translation of basic research findings to patients by providing collaboration, consultation and training for clinical research studies of the nervous system. Here, Perlmutter is shown collaborating with scientists at another CTSA-funded resource, the Human Imaging Unit.

PHOTO BY SCOTT FERGUSON, FK PHOTO

## Informatics Pilot Projects to Aid Scientists Nationwide

NIH has awarded three contracts totaling an estimated $4 million for pilot projects to improve informatics support for researchers conducting small to medium-sized clinical studies. Each project represents collaboration at three or more CTSA institutions. One goal of the CTSA program, which is administered by NCRR, is to advance collaborations in clinical and translational research by interdisciplinary teams of investigators. Software resulting from these pilot projects will be freely available to biomedical researchers, educators and nonprofit institutions.

Full project descriptions, along with the partnering CTSA institutions, are available at www.ncrr.nih.gov/ctsa/informatics.

## Awards Fund Clinical Research Network Collaboration

Clinical Research Network Feasibility Awards went to six CTSA institutions in 2009, providing each with funding for one year. The awards are intended to support mutually beneficial, sustainable partnerships designed to break down research barriers. Working with existing government-funded and/or practice-based research networks, these newly funded projects will focus on research in translational science dissemination, cost-benefit and cost-effectiveness analysis, and community engagement.

For additional information, visit www.clinicalresearchnetworks.org/8.asp.

To access the clinical research networks database, visit www.clinicalresearchnetworks.org.

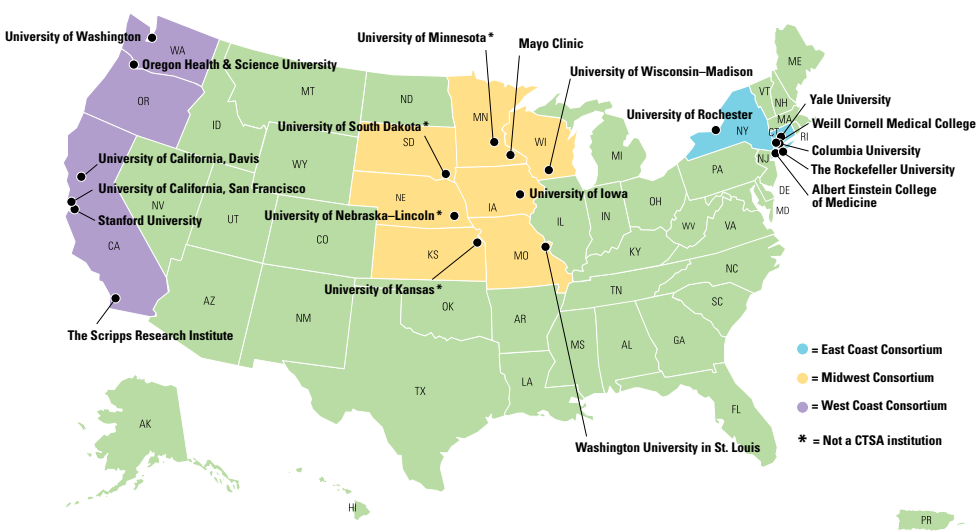
## West Coast Consortium Working to Accelerate Research

Many CTSA research institutions are now forming regional consortia. The evolving consortia are designed to find commonalities and complementary strengths to further accelerate clinical and translational research. The CTSA West Coast Consortium, comprising six research partners, is one example. Consortium members are sharing information, exchanging best practices, exploring opportunities to partner with other regional NCRR-funded programs and identifying potential candidates for inter-CTSA pilot and educational programs.

Through regular regional meetings, the West Coast Consortium members are moving forward and working together in areas and themes of common interest. At the group's December meeting, some of their recent collaborations were highlighted. Visit www.ncrr.nih.gov/ctsa/newsletter/currentissue/#article2 to learn more.

## New Google Search Feature on CTSAweb.org

A new search feature on the CTSA consortium's Web site, CTSAweb.org, provides access to content from CTSAweb.org and individual CTSA institution Web sites in one easy step. Using this search feature, CTSAweb.org visitors can retrieve information from across consortium institutions whose Web sites are available on the site. Find out about research activities, opportunities for collaboration, existing resources and other areas of common interest. Based on the Google search technology, the feature is available in the upper right corner of each page on CTSAweb.org. Visit the site, and try out the search. ■




■ CTSA regional consortia are leveraging strengths and increasing opportunities for collaboration.

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

# An Eye to the Future:

## Training the Next Generation of Researchers

*The CTSA consortium provides access to critical training opportunities for junior investigators.* **BY LAURA BONETTA**

In New York City, a physician treating patients infected with the hepatitis C virus learns to conduct laboratory research to gain clues about how the virus sabotages the function of blood cells.

In St. Louis, a graduate student developing computer-based tests to study how the brain controls movement begins to collaborate with nurses and physicians to translate her research to patients with Parkinson's disease.

Meanwhile, in Portland, Ore., a physician committed to serving underserved populations receives education and training for conducting community-based research so that she can better address the health care needs of her patients.

### CLINICAL AND TRANSLATIONAL SCIENCE AWARD CONSORTIUM

Creating a unique network of medical research institutions across the nation, the Clinical and Translational Science Award (CTSA) consortium is working to reduce the time it takes for laboratory discoveries to become treatments for patients. The consortium also is fulfilling the critical need to train the next generation of clinical and translational researchers through innovative advanced degree programs, mentoring, diverse collaborations and interdisciplinary teams. It brings together basic, translational and clinical investigators; community clinicians; clinical practices; networks; professional societies; and industry to develop new professional interactions, programs and research projects. Currently consisting of 38 research institutions, by 2012, when the program is fully implemented, the consortium will connect approximately 60 CTSA sites. The consortium is led by NCRR.

These three researchers represent the future of translational research — the translation of scientific and technical advances into tangible benefits for patients and communities. Each individual has benefited from the training and education provided through innovative programs at medical institutions across the nation with support from NCRR's Clinical and Translational Science Award (CTSA) program. Although the institutions' training programs have diverse strengths and goals, they share the common mission of providing junior investigators with the knowledge, skills and resources they need to conduct science that will improve human health.

"The things that bind all the CTSA institutions together are commitments to train the next generation of translational researchers, to share best practices and to work collaboratively," said Frederick J. Meyers of the University of California, Davis, chair of the Research Education and Career Development Key Function Committee for the CTSA consortium. "We expect to develop a fundamentally different group of researchers. They are still well-grounded in the discipline of science, but they also are knowledgeable of regulatory and ethical requirements, able to engage in team science and passionate about bringing discoveries to patients."

The training programs developed at each CTSA site span the entire spectrum of research, from basic to preclinical to clinical studies, providing future translational scientists with "core competencies," consisting of the necessary knowledge, attitudes and skills required to conduct interdisciplinary research. These

> "At least half of the students who go through our program are here because they want to learn how to do community-based research."
>
> —CYNTHIA MORRIS, DIRECTOR OF EDUCATION AND CAREER DEVELOPMENT AT THE OREGON CLINICAL AND TRANSLATIONAL RESEARCH INSTITUTE OF OREGON HEALTH & SCIENCE UNIVERSITY

competencies are taught primarily through didactic courses that lead to master's degrees in clinical research and, in some cases, doctoral degrees in translational and clinical research, tailored to an individual's career aspirations. In addition, these programs provide opportunities to expose future physician-scientists to interdisciplinary team science. Another important component of the training programs is the quality mentoring that participants receive from established scientists, who serve as guides and role models for the careers the junior investigators want to pursue.

Although many of these programs are still in their infancy — the CTSA program was just launched in 2006 — their effects can be seen clearly in the stories of individuals who have participated in them.

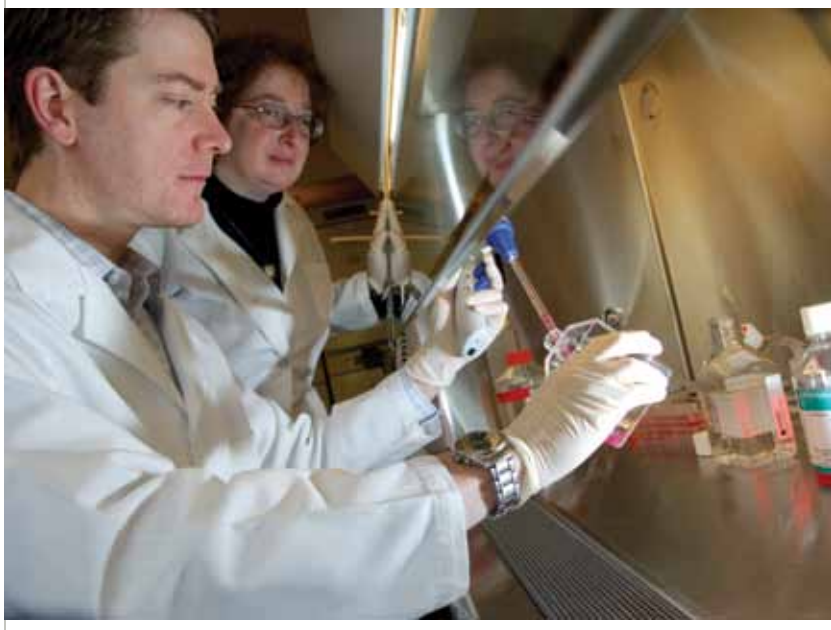
### BASIC DISCOVERY TO TRANSLATIONAL RESEARCH

Edgar Charles treated patients infected with the hepatitis C virus during his residency in internal medicine and fellowship in infectious diseases at New York University School of Medicine. This viral infection is one of the most common causes of chronic liver disease and organ transplantation in the United States. One of the many puzzling aspects of the disease is that some patients also develop an inflammation of the blood vessels, probably due to the presence in the blood of certain types of immunoglobulin. These molecules are normally produced by the plasma cells of the immune system to identify and neutralize foreign substances, such as bacteria and viruses, and in some diseases, they also can attack normal cells and tissues in the body. Additionally, some patients with hepatitis C infection suffer from a type of immune system cancer called non-Hodgkin's lymphoma.

Charles reasoned that more research was needed to fully understand the disease and, in particular, the role B cells of the immune system were playing in it. Although the two-year fellowship he had undertaken at New York University included a year of research, Charles said that "to do more research seriously, I would have to have more training." He was not, however, sure of how to go about getting that training.

After considering different training programs, he learned about the Clinical Scholars Program offered by The Rockefeller University's Center for Clinical and Translational Science — a member of the CTSA consortium. This three-year program, which leads to a master's degree in clinical and translational research, gives a junior investigator, typically a physician, the opportunity to join the laboratories of established scientists who provide mentorship for the scholar's research. The mentored research project is complemented by a curriculum that provides education in several core competencies, including the responsible conduct of research, biostatistics and standards for conducting clinical studies. "Once I looked into the program, it was a very clear choice for me to do it," Charles said.

In his early efforts, he arranged to conduct a research project to study B-cell function in patients with hepatitis C infection under the joint supervision of Charles Rice, a renowned virologist, and Lynn Dustin, a distinguished immunologist, at The Rockefeller University. Charles first had to



■ Edgar Charles performs experiments on blood cells from patients infected with the hepatitis C virus as mentor Lynn Dustin, an immunologist at The Rockefeller University in New York City, looks on. Charles undertook the research as part of the Clinical Scholars Program offered by Rockefeller's Center for Clinical and Translational Science, a member of the CTSA consortium. A recent graduate of the program, Charles has now received a coveted NIH Mentored Clinical Scientist Development Award to launch his career as a physician-scientist.

PHOTO BY ZACH VEILLEUX, THE ROCKEFELLER UNIVERSITY

■ Jennifer Semrau, a graduate student at the CTSA-supported Brain, Behavior and Performance Unit (BBPU) at the Washington University in St. Louis Institute of Clinical and Translational Sciences, monitors a Parkinson's disease patient's hand movements as he responds to visual cues on a computer screen. Semrau, who is conducting her doctoral research in a bioengineering laboratory, benefited from training and resources provided by the BBPU, which allowed her to apply her research to patients.

obtain blood samples from patients. For this aspect of the study, the assistance he received from the Center for Clinical and Translational Science was invaluable. The Center's staff helped Charles obtain approval for his proposal from his institutional review board (IRB) — typically a daunting undertaking — such that he was able to quickly start his research. (An institution's IRB considers ethical, policy and regulatory issues regarding patient research.) Nurses and other medical staff then helped Charles recruit suitable patients and collect samples.

In Dustin's laboratory, Charles began learning how to operate as a scientist. "Edgar was beautifully trained clinically, and he had done some bench work before, but when he first came to my lab, he was not yet able to function independently as a scientist," Dustin said. "I started out suggesting experiments for him and teaching him procedures. I also critiqued his writing for grant applications and papers." In the laboratory, Charles learned to carry out different sophisticated molecular and biochemical analyses on the B cells he isolated from patients' blood.

Through his research, Charles discovered that the hepatitis C virus causes certain B cells that produce a particular type of immunoglobulin to greatly increase in numbers. He published his findings in the prestigious scientific journal *Blood* in February 2008. Based on this work and a grant proposal he wrote describing future studies, Charles received a Mentored Clinical Scientist Development Award from NIH's National Institute of Allergy and Infectious Diseases. The award provides support for up to five years to help recipients transition from mentored research to an independent research position. "Developing the skills to become an independent clinical investigator is precisely the goal we set for trainees in our master's program, and so we are delighted with Dr. Charles' success," said Barry Coller, director of the Center for Clinical and Translational Science.

Charles started with a medical problem and used basic laboratory science to find possible answers for it. His findings are providing insights into what causes the disease symptoms associated with hepatitis C infection and may someday offer clues on developing treatments to alleviate such symptoms. The next step in the continuum of translational and clinical research is the translation of laboratory findings to patients — a step that requires its own set of competencies, as well as a dedicated infrastructure for clinical studies.

### ADVANCING RESEARCH FROM LAB TO PATIENT

The infrastructure needed for clinical studies exists in places like the Brain, Behavior and Performance Unit (BBPU) at the Washington University in St. Louis Institute of Clinical and Translational Sciences — a CTSA consortium member. "The BBPU really permits junior investigators to do patient-oriented research," said unit director Joel S. Perlmutter. "We provide support for getting the initial findings, so that they can use those results to apply to traditional sources of funding." Without this kind of support, applying basic scientific findings to human studies would be a much more challenging proposition. "The BBPU makes this kind of effort move forward in a much more efficient manner," Perlmutter explained. "It really enhances the chances of bringing research findings to patients."

The BBPU provides collaboration, consultation and training for clinical research studies of the nervous system. Kurt Thoroughman is one of many basic researchers taking advantage of these resources. A biomedical engineer interested in how the brain's complex wiring controls movement, Thoroughman has designed several experimental setups that give visual feedback to people as they perform certain movements. Such feedback tells them, for example, if they are moving a hand in the correct direction — if not, people automatically adapt the arm movement according to the feedback. "Over the years, we have come up with very precise tasks and tests of human performance," he explained. "Previously, it was thought that what you learn can change but *how* you learn it is fixed. But we discovered that both what and how you learn can change very quickly."

With graduate student Jennifer Semrau, Thoroughman decided to try the tests they had developed on Parkinson's



PHOTO BY SCOTT FERGUSON, FK PHOTO

disease patients. In particular, Semrau was interested in finding out whether the disease affects the brain's ability to adapt to a changing environment. With advice from staff at the BBPU, Semrau designed a protocol in which Parkinson's patients train on a computer to move a stylus from one point to another. After a while, the computer begins "tricking" them by giving them odd visual cues — for example, indicating that they are moving the stylus at an angle when in fact they are moving it in a horizontal line. The patients then adapt their movements to such cues.

A research coordinator helped Semrau obtain IRB approval, and a patient coordinator recruited suitable subjects with the aid of an extensive patient database. The BBPU has been instrumental in countless similar studies, providing training and assistance to scientists who would otherwise have little opportunity to work with patients. In parallel, the Institute of Clinical and Translational Sciences provides a number of didactic courses for translational researchers, including a master's degree in clinical investigation. "We don't try to reproduce those courses at the BBPU," Perlmutter said. "Instead we provide hands-on experience, as well as assistance with IRB applications, regulatory procedures and how to design a study protocol. We are really marrying the didactic with the practical."

Semrau had a unique opportunity to take findings developed in a basic research laboratory to Parkinson's patients. But once basic findings are translated to patient research, there is one more step in the continuum of translational and clinical science. If that research is to benefit human health, it has to reach out to communities.

### MOVING INTO PRACTICAL FIELD EXPERIENCE

The many roles of a translational researcher include bringing innovations into communities as well as determining the health needs of people in the community and how best to address them. This step, however, requires a set of skills that are not often taught in traditional courses. "In medical school, the focus is on the patient, on the one-to-one encounter between the patient and physician," said Cynthia Morris, director of education and career development at the Oregon Clinical and Translational Research Institute of Oregon Health & Science University — another CTSA consortium member.

The Master of Clinical Research program was designed to provide instruction to a broad spectrum of researchers — from graduate and medical students to full professors and practicing physicians. "Everyone has a different take on what they are learning based on their background and experience," Morris said. "That means that they all can learn from one another. They get used to the idea of working together in teams."

The unique aspect of the program is that half of it focuses on teaching core competencies, whereas the other half allows students to pick and choose from a variety of courses based on their interests and career goals. Many of these "electives" have a strong focus on community-based research. "At least half of the students who go through our program are here because they want to learn how to do community-based research," Morris said. "In other words, how to translate findings of lab research into practice and then into populations."

## CORE COMPETENCIES FOR CLINICAL AND TRANSLATIONAL INVESTIGATOR TRAINING

The task of CTSA education programs is to prepare the next generation of investigators to conduct clinical and translational research that will address the health care challenges faced in the United States. Creating a recognizable discipline centered on clinical and translational science will help build this workforce. To help establish the discipline, NCRR and the CTSA Education and Career Development Key Function Committee have drafted national standards for core competencies in clinical and translational science. The thematic competencies identify common, basic elements that should shape the training experiences of junior investigators by defining skills, attitudes and behaviors that can be shared across multidisciplinary teams of clinician-scientists. The overall goal is to create a competency-based education for training clinician-scientists that will define the discipline of clinical and translational science. Below are the training competencies for master's and doctoral candidates:

- Identify major clinical/public health problems and relevant research questions
- Critique the literature regarding the status of a health problem
- Design a study protocol for clinical and translational research
- Study methods, design and implementation
- Laboratory, clinical and population research methods
- Statistical methods and analysis
- Bioinformatics
- Conduct of responsible research
- Scientific communication skills and dissemination
- Population diversity and cultural competency
- Principles of community engagement in clinical and translational research
- Translational teamwork
- Leadership and professionalism
- Cross-disciplinary training and mentoring
- Advancement of knowledge

That was certainly the case for Rachel Solotaroff. After completing her medical degree and residency, she wanted to do research with underserved populations. "But I did not know how to go about it," she recalled. She initially enrolled in a master's program and took several courses in fundamental epidemiology and statistics — skills she was lacking. She also participated in an interactive course that taught her how to prepare a grant application. "That course was really fundamental," Solotaroff said. "I did not know how to formulate a research question. I was not trained to think like a researcher. It is not something that came naturally to me. But that course really taught me how to do it."

As a result, she was able to write a successful application to a fellowship that allowed her to study how patients with chronic diseases, such as diabetes, cope with self-managing their own health care with sporadic or no health insurance coverage. After spending two years on this research project, she became the medical director at Central City Concern, a social-service agency based in downtown Portland that provides medical, housing and employment assistance to a predominantly homeless population, including many individuals addicted to drugs.

## A SMORGASBORD OF COURSES

Thomas Pearson, co-principal investigator for the CTSA at the University of Rochester Medical Center in New York, is creating a database of courses that will be available to all students and researchers at any institution at the click of a button. "The CTSA consortium has done a nice job to create a core curriculum in clinical and translational research," Pearson said. But not every institution is able to provide high-level courses in specialized fields, such as proteomics or genomics. Such courses are not core competencies but are, as Pearson put it, "icing on the cake."

As a result, he has been collecting high-quality courses on important but more specialized topics developed at each CTSA institution. Once collected and reviewed by a panel of advisors, the courses will be posted on the Web as online lectures, Webinars, slide presentations and other Internet-friendly formats. "We are making a CTSA national consortium," Pearson said "This is just one way to become stronger than our parts."

In addition to making hundreds of courses available online, the Rochester CTSA has a pilot program to allow visiting professors to teach courses at different institutions as a "traveling show." Also, the program will provide scholarships for students to attend courses offered at different sites. "The idea is to give people at CTSA institutions more opportunities," Pearson said. "If I have a medical student interested in proteomics, I can tap the best teachers anywhere."

■ Cynthia Morris (seen here on the right) directs the Clinical Research Education program at the Oregon Clinical and Translational Research Institute (OCTRI) of Oregon Health & Science University (OHSU). In this photo, Morris is working with Melanie Gillingham, an early-career investigator who completed the Clinical Research Education program as a postdoctoral fellow at OHSU. Gillingham now has an OCTRI pilot grant and is also funded by the National Institute of Diabetes and Digestive and Kidney Diseases. She mentors medical students on their first research projects.

In her new position, Solotaroff is constantly confronted with a slew of questions related to the relationship between homelessness, addiction and health that she would like to systematically study. "Some of the questions I have come from things I see every day: 'How do you manage chronic pain in people with addiction?' Or 'How do you cope with the rapid weight gain and obesity in early withdrawal?'" She is confident she will be able to embark on such studies because of the training she received during her master's program. "I also made many contacts with researchers at Oregon Health & Science University," Solotaroff said. "I will be contacting some of those researchers to establish collaborations."

### THE FULL RANGE OF TRAINING

Advances in biomedical research, computer science and informatics, and imaging and other technologies are providing unprecedented opportunities to improve human health. Yet transforming those advances into practical benefits for patients and communities requires a broad range of knowledge and skills specific to translational research. Such knowledge and skills are best acquired through carefully planned and innovative programs that incorporate didactic courses; hands-on experiences; mentorship; and participation in large, interdisciplinary teams. The training programs designed by CTSA institutions incorporate these components and give the new investigators sufficient flexibility to embark on individualized career pathways. ■

PHOTO COURTESY OF KENT ANDERSON

# The Business End of Translational Research

*University science and business faculties work together to advance science and medicine.* **BY DANA TREVAS**

Translational research — taking scientific advances from the bench to the bedside — often involves transforming great ideas into concrete products — devices, drugs, tools or processes. It must, of course, be financially feasible both to develop and to disseminate these products. Thus, there is a clear role for a business-minded approach that helps propel translational research forward. With its focus on multidisciplinary collaboration, the Clinical and Translational Science Award (CTSA) program creates an environment in which business principles can inform scientific development, speeding up the translational process. A number of CTSA grantees have forged relationships with business schools that take advantage of a natural synergy of resources. One example is the Institute of Translational Health Sciences (ITHS) at the University of Washington in Seattle.

At the ITHS, individual health scientists have been collaborating with business school faculty and students on isolated projects for some time. In crafting its CTSA proposal, faculty members learned that "the business school already had structures set up that were being used by some investigators, but nothing was institutionalized," said Nora Disis, who heads the ITHS. "People in both the business school and the law school had already been thinking about working with health scientists, so that began an easy synergy."

"The West Coast is a collaborative environment in general," Disis continued. "At the University of Washington, we have an entrepreneurial academic environment. Because we don't get very much money from the state legislature, we depend on each other for grants and infrastructure."

■ Nora Disis capitalizes on the collaborative environment and entrepreneurial spirit at the University of Washington. As head of the Institute of Translational Health Sciences, she paved the way for a group effort that brought together faculty and students in genetics research, bioengineering, business and law and resulted in a startup company that is pioneering a novel drug delivery device as well as other innovative approaches.

PHOTO BY CLARE MCLEAN, UNIVERSITY OF WASHINGTON

## GOING LEAN

The ITHS has instituted a number of programs that draw on the expertise of its business and law schools. Among the most significant steps taken may be the move toward implementing the principles of "Lean" production, the basis of the Toyota Production System. This method defines value from the perspective of the customer and seeks to eliminate waste — that is, anything that does not provide value to the customer.

Lean involves the distillation of a process down to its basic level to identify any redundant, counter-productive or otherwise wasteful steps within that process. Although the method may appear intuitive and simple to implement, it involves a tremendous commitment throughout every level of an organization to analyze complex systems, such as those found in health care and research facilities. Lean also involves dedication to continuous performance improvement (CPI) to ensure constant vigilance in waste reduction. The method is time-intensive and arduous, but when it works, it works well — as evidenced principally by cost reductions.

"Seattle is a hotbed for the Lean system," said James Hendricks, head of the Research Institute at ITHS partner Seattle Children's Hospital, which utilizes Lean. In the early 1990s, aircraft manufacturer Boeing, then Seattle-based, dramatically reduced its production costs when it implemented the system. Health care systems in the area picked up on the idea, and their success generated even more enthusiasm. The University of Washington's Clinical Research Center (CRC) and Seattle Children's Hospital are two cases in point, and Hendricks has spearheaded implementation of the concept at both institutions.

■ James Hendricks heads the Research Institute at Seattle Children's Hospital, an Institute of Translational Health Sciences partner and among the first medical centers in the country to apply the Toyota Motor Company's successful Lean management improvement methods to health care. Hendricks spearheaded a continuous performance improvement process that dramatically reduced the time it takes for research proposals to be reviewed and approved by cutting out unnecessary paperwork and redundant steps.

The hospital's Research Institute targeted the length of time it takes for research proposals to complete the institutional review board (IRB) process. IRBs consider the ethical, policy and regulatory issues surrounding patient research, but investigators often find that providing all the materials required for review and responding to IRB requests for information is complex and time-consuming. Rapid performance improvement workshops were aimed at streamlining the administrative tasks around IRB review without sacrificing patient safety. As a result, the Research Institute reduced the time from initial submission to final IRB approval from 86 to 46.5 days. The number of steps in the process decreased from 57 to 35. That's just one example. Hendricks said that despite the difficult economic climate, the Research Institute has guaranteed its staff that there will be no layoffs. "We can do that because we've pulled out the waste, and we are so much more productive now."

By bringing together everyone involved in the process for a multiday workshop, breaking the process down into steps, then analyzing the purpose of each step, the hospital was able to get rid of excessive hand-offs and backlogs. Furthermore, "involving the customer as well as the worker keeps people honest and helps them make hard determinations about what really is waste," Hendricks said. When you look closely at these processes, you find that "waste is cleverly disguised as work."

Hendricks worked with Havivah Schwartz of the ITHS to use the Lean system to improve the process of scheduling visits for CRC research subjects. Researchers had long expressed dissatisfaction related to scheduling, including the excessive lead time to schedule appointments and a high rate of no-shows. "We had been trying to address the issue for about two years with little success," Schwartz said. She stresses the importance of identifying areas for improvement that resonate with customers. Looking into the problem, she said, "We were under the mistaken impression that we needed to improve scheduling primarily for the benefit of the researchers. We came to discover very quickly that it was also of paramount interest to the staff" and will likely benefit patients, as well.

Success with CPI requires a tremendous commitment of time and resources. "We spent three months preparing for the

PHOTO COURTESY OF SEATTLE CHILDREN'S HOSPITAL

workshop," Schwartz said. "Collecting information about what to address, for example, via survey, is just the tip of the iceberg." Preparation includes interviews and evaluation to map out the targeted process at its most granular level. Staff and researchers contribute to the preparation process and take time out of their schedules for the workshop itself, which can last as long as a week. "There's no way we could get that commitment unless it was something that makes a difference to their work and life," Schwartz said.

By standardizing methods and implementing software and other tools to simplify and streamline processes, the CRC stabilized staffing assignments, making the workload more predictable and reducing overtime costs. It decreased the number of no-shows from 21 to 14 percent. The result is a more transparent system that allows unit managers to make more informed decisions. The increased efficiency among staff allows them to better meet the needs of researchers.

> A number of CTSA grantees have forged relationships with business schools that take advantage of a natural synergy of resources.

One key component of the Lean process is the "continuous" part of CPI. There is always more waste to cut. Hendricks noted, "My investigators are happy that we cut the IRB time in half, but it's been about a year and a half. And now, they want to know what we're going to do to pull out more waste."

Lean is a philosophy, not just a set of tools, and it requires buy-in from the entire organization, Hendricks stressed. But once you see the results, you see how valuable the philosophy can be. Hendricks said the goal of working with Schwartz and others at the ITHS to implement CPI processes is "to reduce the cost of doing clinical research so there's more money for informatics and other areas that are dollar-intensive and can contribute to better clinical research."

"When I first saw the results of the IRB process improvement at Children's, it was jaw-dropping," Schwartz said. "But at the time — even though we were told differently — we understood Lean as a set of tools to increase efficiency. Now, I see it as a philosophy, a broader approach that we can apply outside of workshops to our overall strategic development" at the ITHS.

Hendricks underscored the similarities between the principles of CPI and those of the scientific method: "The scientific method, like CPI, is based on gathering empirical and measurable evidence to formulate and test a hypothesis," he said. "In CPI, the hypothesis takes the form of opportunities for eliminating waste and adding value for the customer."

Disis noted that when the ITHS announced its intention to apply Lean principles to its infrastructure, "people came out of the woodwork" to get involved. "Two faculty members in the undergraduate engineering program who do research on industrial efficiency came to us to research our experience with Lean."

### R&D MEETS MBA

Facilitating research is just one side of the equation. Investigators whose work leads to promising techniques or devices face the daunting task of production and marketing. At the University of Washington, the Department of Bioengineering had funding from the Wallace H. Coulter Foundation to promote translational research and was seeking individuals with MBAs to assist with product commercialization. The ITHS created the needed link with the university's School of Business. Piggybacking onto the existing fellowship program of the School of Business' Center for Innovation and Entrepreneurship, the ITHS-Coulter Fellowship supports summer internships for second-year MBA students to work with scientists in moving their discoveries toward the marketplace.

This collaboration of people and funding across disciplines has already produced tangible results. At the University of Washington's DNA Sequencing and Gene Analysis Center, Center Director and Associate Dean Rodney Ho worked with John Hoekman, a doctoral student in pharmaceutics, to develop a novel pressurized olfactory drug delivery device that enables drug administration via the nose directly to the brain. The approach speeds up the drug delivery process while at the same time bypassing the potential for toxic systemic reactions that can be caused when high concentrations of drugs are delivered orally or intravenously.

With an ITHS-Coulter Fellowship, the scientists teamed up with MBA students Michael Hite and Peter Olagunju to conduct market analysis and develop a business plan. The effort earned the team $50,000 from the University of Washington TechTransfer's Technology Gap Innovation Fund and won the $25,000 grand prize in the university's annual business plan competition. The team licensed the technology from the university and spun off a company, Impel NeuroPharma, to further develop the product.

On the basis of the early success of the fellowship program, Kim Folger Bruce, director of research partnerships at the ITHS,

■ Seattle Children's Hospital, an Institute of Translational Health Sciences partner, is leading the way in applying continuous performance improvement methods long used by successful manufacturers to improve the basic building blocks of health care: quality, safety, cost, delivery and engagement. Continuous performance improvement brings together everyone involved in the system at every level. Here, staff at Seattle Children's Hospital are learning about day-to-day operations from a clinician's perspective so they can work together to find better ways to deliver the highest quality service and value to patients while removing wasteful practices.

anticipated increased investment and participation. "It seems like a natural fit, but someone has to establish the relationships," Bruce said. "The need is there, and there are many MBA students interested in medical applications. So, once you have those relationships, then it's just matchmaking."

During the past four years, ITHS Director Disis has put in place changes intended to make the CRC function in similar fashion to a commercial clinical trial research unit. She sought business expertise to determine appropriate fees for the center to charge researchers and turned to the School of Business. The school identified an MBA student to take on the task as an intern. The intern is conducting interviews and gathering information from investigators, commercial research units and other sources to create a business plan to ensure the financial success of the center.

## AN ENTRY POINT FOR ENTREPRENEURS

The Entrepreneurial Law Clinic (ELC) at the University of Washington offers faculty members legal consultations in such areas as commercial potential of a new technology, business planning, regulatory issues and intellectual property concerns. The ELC combines a traditional law clinic with an externship. Investigators are matched with a team of law and business students, attorneys, and successful entrepreneurs who provide confidential findings and recommendations at no cost.

"I do translational research, develop products and take them into clinical trials — but I had never heard of the ELC!" Disis said. With additional funding from the CTSA program, the ITHS established a direct link that helps health scientists take advantage of the ELC's services. Impel NeuroPharma did so before submitting its entry to the business plan competition. Sean O'Connor, who directs the ELC, said, "The primary initial service my ELC provides for start-ups is a due-diligence exercise similar to what real-life investors will do" when they consider a business plan. After the competition, the ELC assisted Impel with the regulatory support services provided by the ITHS. The company continues to work with the ELC on patent issues.

Investigators at the University of Washington can also take advantage of "From Invention to Start-Up," a free eight-week lecture series on entrepreneurial issues unique to high-tech start-up companies. Each session is videotaped and posted online at www.inventiontostartup.washington.edu, along with each speaker's slide presentation.

## IN GOOD COMPANY

A number of other CTSA grantees have expanded their relationships with academic business schools. For example, Harvard University's Linkages program integrates the skills and resources available within Harvard's Law School, Business School, School of Engineering and Applied Sciences, Kennedy School of Government, and Graduate Schools of Education and Design to support clinical and translational research innovation. Duke University has an active collaboration with the Health Sector Management program at the Fuqua School of Business, which addresses both health care and entrepreneurship. The University of California, Davis, has developed several programs to educate faculty regarding entrepreneurism, intellectual property and business development with an emphasis on biotechnology. As institutions break down the walls between their research and business communities, they pave the way for more and better collaboration and translational science. (For a detailed list, see the CTSA Web site at CTSAweb.org, under "Building Connections.") ■



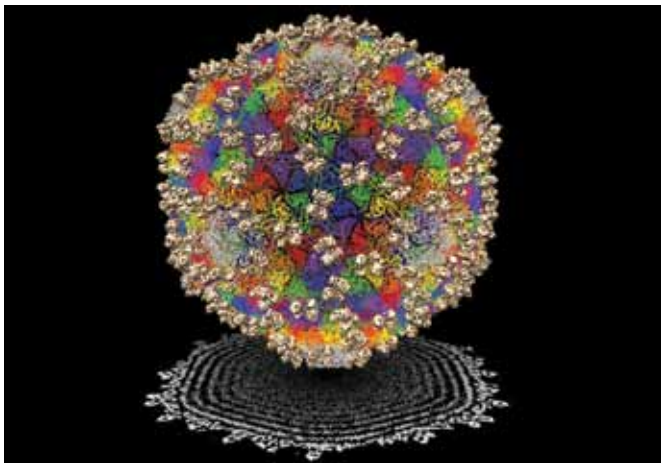
PHOTO COURTESY OF SEATTLE CHILDREN'S HOSPITAL

# Peering More Deeply into Proteins

A new protocol developed at the National Center for Macromolecular Imaging (NCMI) by Director Wah Chiu and his colleagues provides greater insight into protein structures, which might lead to the design of better drug interventions, ultimately helping to improve human health. Proteins are not only dynamic; they often form large complexes of multiple molecules, which are difficult — and sometimes impossible — to see using the conventional techniques that probe molecular structures at the atomic level, such as X-ray crystallography or nuclear magnetic resonance. Supported in part by NCRR, NCMI focuses on specimens that cannot currently be studied by these techniques. The center works on developing three-dimensional images and atomic models of complex molecular machines that can guide the design of drugs and vaccines for a variety of diseases.

NCMI uses the technique of single-particle electron cryomicroscopy (cryo-EM), in which large molecules are rapidly frozen to preserve them in their natural state, yielding snapshots of the dynamic processes these molecules might undergo. However, unlike X-ray crystallography, which can provide atomic resolution with the aid of protein crystals, cryo-EM has been unable to achieve such resolution.

Chiu and his colleagues are changing that. They have developed a new, five-step computational protocol to obtain a higher-resolution structural model from electron images of molecular machines without making crystals. First, with the image data recorded in a 300 keV electron cryomicroscope, they use their home-built software, EMAN, to combine tens of thousands of two-dimensional images of molecules in random orientations and generate a three-dimensional volume density map. Then, they use an application called SSEHunter to find regions of the cryo-EM map that might correspond to structural elements like alpha-helices or beta-sheets. Once they identify these elements, Chiu and colleagues use a shape-analysis technique called skeletonization to determine how the elements are connected. They next look at the primary amino acid sequence of the protein to predict how the amino acid sequence relates to these structural elements. Once they make these assignments, they can accurately reconstruct the topology of the entire protein.



■ The National Center for Macromolecular Imaging has used its new electron cryomicroscopy protocol to reconstruct a model of the epsilon 15 virus, which infects salmonella. This model also shows the virus' DNA inside the capsid, the shell of proteins that protect the DNA.

"We use all these pieces of information to pin down where the protein begins, how it winds through space and where it ends," Chiu said.

Using this new protocol, Chiu and his colleagues have built a three-dimensional picture of the epsilon 15 virus shell, which is composed of hundreds of proteins, at near-atomic resolution. They also have validated the protocol by using it to look at another molecular machine (GroEL) for which the X-ray crystallographic structure is known.

NCMI has teamed up with researchers from various institutions, including Purdue University; Stanford University; the University of California, San Francisco; Massachusetts Institute of Technology; and the University of Washington, to further refine the new protocol. This refinement will allow NCMI to reconstruct models of protein complexes at even higher resolution and accuracy.

Chiu's protocol can offer new insights into how proteins and viruses work and, ultimately, into ways to improve health. Epsilon 15 is a virus that infects salmonella. Many people across the United States have recently suffered from salmonella poisoning related to peanut products.

"Bacterial viruses might not normally be viewed as medically relevant," Chiu said. "But understanding the structure of epsilon 15 and how it is destructive to salmonella bacteria could lead to the design of an intervention for salmonella poisoning. That's down the road, but thinking about translational

PHOTO BY MATTHEW BAKER FROM WEN JIANG ET AL., COURTESY OF *NATURE*

potential is natural with technology developed at a Biomedical Technology Research Center."

—FRANCES MCFARLAND HORNE

**TO GAIN ACCESS:** The National Center for Macromolecular Imaging (NCMI), funded in part by NCRR, is one of 52 NCRR-supported Biomedical Technology Research Centers (BTRCs). Investigators at NCMI collaborate to resolve structures of large, complex molecules. All mature image-processing software is freely available on the Web at http://ncmi.bcm.edu/ncmi/test_software. NCMI is also working with researchers at Washington University in St. Louis to develop a graphical toolkit to help other investigators use the new structure mining protocol. For more information about this and other BTRCs, visit www.ncrr.nih.gov/btrc.

**ADDITIONAL READING:** Ludtke, S.J., Baker, M.L., Chen, D.H., Song, J.L., Chuang, D.T., Chiu, W. De novo backbone trace of GroEL from single particle electron cryomicroscopy. *Structure* 16:441–448, 2007.

Jiang, W., Baker, M.L., Jakana, J., Weigele, P.R., King, J., Chiu, W. Backbone structure of the infectious epsilon15 virus capsid revealed by electron cryomicroscopy. *Nature* 451:1130–1134, 2008.

# A New Way to Preserve Fish

Some fish species, like zebrafish and medaka, have become important models for human disease research and developmental biology studies. For 15 years, Terrence Tiersch's laboratory at the Louisiana State University Agricultural Center has been preserving fish species by freezing their sperm to facilitate the sharing of these animals among researchers. With the thousands of mutant and transgenic fish lines created around the world, as well as U.S. Customs restrictions on shipping live animals, freezing fish sperm is an easier and more cost-efficient way to maintain and share the lines. Now, Tiersch's group has received funding from NCRR to standardize the freezing process and expand it to a wider scale.

■ For 15 years, Terrence Tiersch of the Louisiana State University Agricultural Center has been preserving fish species, such as the zebrafish shown here, by freezing their sperm. Currently, Tiersch and colleagues are creating a standardized, high-throughput process that the NCRR-supported Zebrafish International Resource Center and similar facilities can use to maintain fish lines.

PHOTO COURTESY OF TERRENCE R. TIERSCH

Currently, there is no standard process for freezing zebrafish or medaka sperm. Individual investigators find their own way, but these methods are often slow, laborious and inconsistent. "People have homemade recipes and borrow technologies from other animal models," said Michael Chang, program director at NCRR.

Indeed, for the past 10 years, Tiersch's group has been using a nearby commercial facility that freezes bull sperm. The facility allows Tiersch access to its equipment, but he has to use the same process for fish that is used for bulls, which is not ideal. Also, being very small, zebrafish and medaka might yield only three microliters — no more than a tiny drop — of sperm sample at most. And even though zebrafish and medaka are similar in size, they are different species, living in different environments, and their sperm behave differently. That means the conditions and requirements for freezing their sperm also differ.

Tiersch's group and three collaborating laboratories are creating a standardized, high-throughput process that stock and resource centers, such as the NCRR-supported Zebrafish International Resource Center, can use to maintain fish lines. The first phase of this work will go beyond freezing alone. The group will identify all the steps on the path, from the state of the fish before sperm collection, to the coding and databases needed to keep track of specimens, to the final distribution of samples to investigators. This work will generate a "first draft" process, which will be fine-tuned in the second phase in collaboration with the resource centers. The final draft will be a process that allows resource centers, which once needed a day to freeze a small number of sperm specimens, to freeze thousands of samples in a shorter period of time.

"We're not just developing a technique or saying things are feasible," Tiersch said. "We're past that. The small scale is already there. We're coming up with the industrial scale."

—FRANCES MCFARLAND HORNE

**TO GAIN ACCESS:** The new protocol for freezing zebrafish sperm will be available through resource centers, such as the NCRR-supported Zebrafish International Resource Center (http://zebrafish.org), which stores and maintains more than 1,000 different zebrafish lines. The new protocol will also be available to other resource facilities and research institutions that breed zebrafish and medaka.

# New Institutional Development Awards for Health-Related Research

NCRR is providing funds — up to an estimated $64 million — to establish six new Institutional Development Awards (IDeA) over the next five years. These awards support multidisciplinary centers — each concentrating on one general area of research — that strengthen institutional biomedical research capability and enhance research infrastructure. Designed to improve the competitiveness of investigators in states that historically have not received significant levels of competitive NIH research funding, the IDeA program supports the following new centers:

- University of Hawaii at Manoa — to study reproductive biology;
- University of Kentucky — to identify mechanisms linking the epidemic of obesity to cardiovascular disease;
- University of Louisville Research Foundation, Inc. — to study the cardiovascular causes and consequences of diabetes and obesity;
- University of Nebraska Medical Center — to research nanomedicine, drug delivery, therapeutics and diagnostics;
- The Mind Research Network, a nonprofit research organization in Albuquerque, N.M. — to study the neural mechanisms of schizophrenia; and
- Montana State University — to study cellular mechanisms to better understand how to overcome disease.

"By bridging the research funding gap in IDeA states, we are building innovative research teams, leveraging the power of shared resources, and enhancing the science and technology knowledge of the states' workforce," said NCRR Director Barbara M. Alving, M.D. "It is through this focused and innovative approach that we are producing a pipeline of researchers who will become future leaders working to improve the health of diverse populations throughout the nation."

# NCRR Funds Two New Biomedical Technology Research Centers

NCRR is providing up to an estimated $11 million over the next five years to establish two new Biomedical Technology Research Centers (BTRCs) designed to provide researchers nationwide with access to specialized research tools, training and state-of-the-art equipment. One center at the Northern California Institute for Research and Education, Inc., in San Francisco will develop innovative imaging techniques designed specifically to better diagnose and treat diseases, such as Alzheimer's. A second center at the University of California, San Diego, will create cutting-edge software for identifying and analyzing sets of interacting proteins that are important in a wide range of diseases, such as cancer.

Each center creates critical and often unique technology to apply to a broad range of basic, clinical and translational research. Serving as test beds for solving complex biomedical research problems, BTRC research projects combine the expertise of multidisciplinary technical and biomedical experts both within the center and through collaborative partnerships. These efforts result in innovative solutions to today's health challenges, which are then actively disseminated to promote rapid adoption and achieve the broadest possible impact.

The advanced techniques developed at the new Northern California Institute for Research and Education BTRC will offer researchers and clinicians who work with neurodegenerative disorders improved image clarity, more reliable and precise methods for capturing anatomical data, more efficient and accurate reconstruction methods, and improved image processing capabilities.

The new center at the University of California, San Diego, will bring creative

## NEW MOBILE SCIENCE LAB

The University of Pittsburgh's Clinical and Translational Science Institute unveiled a new mobile science lab that includes 26 work stations and sits inside a 70-foot tractor trailer. The result of collaboration between two NCRR-funded programs – a Clinical and Translational Science Award and a Science Education Partnership Award – the new lab will provide pre-college students in western Pennsylvania with hands-on opportunities to learn about the latest science research while using state-of-the-art lab technology.


PHOTO COURTESY OF UNIVERSITY OF PITTSBURGH

mathematical approaches to mass spectrometry and will build a new generation of reliable open-access software tools that will catalyze exchange and collaboration among experimental and computational researchers in proteomics, furthering advances in this critical field of research. The center will also focus on training the scientific community in the use of the technologies it develops.

To learn more about the two new BTRC awardees, visit www.ncrr.nih.gov/btrc/2008. For more information about the BTRC program, visit www.ncrr.nih.gov/btrc.

## New Animal Model Resource Planned

Scientists who work with animal models can look forward to a new Web site and database being designed to increase research efficiency, improve collaboration and ultimately help bridge the gap between basic science and human medicine. With funding from NCRR, the "Linking Animal Models to Human Disease Initiative" (LAMHDI) will integrate data and information about animal models and make them available to health researchers throughout the world. This new resource is being developed to make it easier for the biomedical research community to locate, identify, apply and build upon the most useful animal models for research.

"LAMHDI will give biomedical researchers worldwide access to a simple, yet comprehensive Web-based resource that will enable scientists to quickly find the best animal models for their research studies," said Harold Watson, LAMHDI project officer, NCRR Division of Comparative Medicine. "Critical tools such as these can help accelerate the research process, ultimately leading us to faster treatments."

The initiative grew out of an August 2008 meeting on Animal Models: Informatics and Access. At this meeting, animal research and informatics experts explored ways to remove research barriers and to develop frameworks for effective computation on existing animal models data to facilitate medical progress. To learn more about this meeting, visit www.ncrr.nih.gov/publications/comparative_medicine/animal_models_informatics_and_access.asp.

The $1.57 million NCRR-funded project will be supported by a contract to Turner Consulting Group, a government technology, strategy and IT firm.

## RCMI International Symposium on Health Disparities

Focusing on the theme of *Research Outcomes Accelerating Discoveries for Medical Applications and Practice,* the Eleventh RCMI International Symposium on Health Disparities was held December 1-4, 2008, at the University of Hawaii, John A. Burns School of Medicine. The symposium was sponsored by NCRR's Research Centers in Minority Institutions (RCMI) program, which enhances the research capacity and infrastructure at 18 minority colleges and universities that offer doctorates in health sciences. With 490 attendees and more than 300 scientific sessions, the symposium highlighted basic, clinical and translational research on the biological, environmental, cultural, socioeconomic and bio-behavioral bases of health disparities in cancer, cardiovascular disease, HIV/AIDS, infectious diseases, obesity and metabolic syndromes, and neuropsychiatric disorders.

In recognition of World AIDS Day, the 2008 symposium opened with a keynote address on overcoming the scientific challenges in HIV prevention given by Lauren V. Wood, senior clinical investigator in the Vaccine Branch at the National Cancer Institute. Other keynote speakers included Barbara Alving, NCRR director; J. Donald Capra, president emeritus, Oklahoma Medical Research Foundation; John E. Maupin, Jr., president, Morehouse School of Medicine; and Sidney McNairy, Jr., director, NCRR Division of Research Infrastructure. Emma Fernandez-Repollet, vice president of research and technology and professor of pharmacology at the University of Puerto Rico Medical Sciences Campus, received the Frederick C. Greenwood Award for her commitment to the training of minority scientists, her leadership and accomplishments in research administration, her long-standing service and dedication to the RCMI community, and contributions to biomedical research.

Also featured were keynote and plenary lectures by individuals who have made significant and seminal contributions to research on health disparities, improving health care access and delivery, and partnering with vulnerable populations and marginalized communities to eliminate health disparities.

Additional information about the presenters and their research can be found at www.mpi-evv.com/2008RCMI/research-path/default.htm. ■