Forging a Path From Laboratory to Clinic

CTSA consortium accelerates the process of bringing research discoveries to patients. **BY LAURA BONETTA**

After administering two rounds of very intensive chemotherapy and radiation, followed each time by infusions of stem cells to help replace blood cells damaged during the course of treatment, Stephan Grupp and colleagues at Children's Hospital of Philadelphia can cure about half of their patients with neuroblastoma, one of the most common and deadly solid tumors among children. The success rate, much higher than that achieved by standard therapy without the stem cell infusions, "is better, but not nearly good enough yet," says Grupp.

To improve the outcome even further, he wanted to add another step to the therapy regimen by immunizing his patients against their cancer. Using a "cancer vaccine," Grupp could teach the patients' immune systems to seek out and destroy any remaining neuroblastoma cells, thus minimizing the chances of a relapse. But before embarking on this pioneering work, Grupp had to overcome one major obstacle: The immune systems of children who have undergone chemotherapy and radiation are severely weakened.

Grupp and colleagues, including Carl June at the University of Pennsylvania, tried "rescuing" the immune system by collecting blood cells from patients at the time of diagnosis and then coaxing the immune cells into dividing and multiplying outside the body. In a pilot clinical trial funded by the National Cancer Institute, the researchers transplanted the multiplied immune cells back into patients after they had received therapy. Preliminary data suggest that these transplanted cells are fully functional and allow a patient with a devastated immune system to mount an immune response to a vaccine.

To finish the current trial as quickly as possible and move on to testing the cancer vaccine, Grupp decided to enlist the help of a collaborating institution. That's when he came up against a mountain of administrative paperwork.

RECONFIGURING THE RESEARCH ENTERPRISE

Clinical trials, such as the one Grupp is conducting, are a critical step in translating scientific discoveries arising from laboratory, clinical, or population studies into practical applications that can improve human health. But researchers engaged in this "translational research" encounter numerous challenges on the path from bench-to-bedside testing. Unlike scientific research focused on a particular approach or discipline, translational research crosses boundaries between basic science and clinical applications, requiring intense interactions among investigators with diverse backgrounds and types of expertise and among members of both academic and industrial communities.

To strengthen and accelerate the process of bringing scientific discoveries to the community, the Clinical and Translational Science Award (CTSA) consortium, established by NCRR as part of the NIH Roadmap for Medical Research, strives to remove roadblocks and ease challenges in clinical and translational research. (See sidebar, "A Consortium for Transforming Clinical and Translational Research.")

■ Physician-scientist Stephan Grupp at the Children's Hospital of Philadelphia is testing a new therapy for neuroblastoma, a common and deadly cancer among children. Using resources provided through the Clinical and Translational Science Award at the University of Pennsylvania, Grupp was able to enlist the help of a collaborating institution to complete his study more rapidly.

For the most part, the current generation of clinical researchers could only draw on the resources of their own departments to carry out their work. "But as science has advanced, we need a set of tools and knowledge that transcends the structures of a typical clinical department," says Robert Califf, vice chancellor for clinical and translational research at Duke University Medical Center. "That is why NIH Director Elias Zerhouni decided we needed to provide a home for this kind of research." Califf, along with Lars Berglund, associate dean for clinical and translational research at the University of California, Davis, cochairs the CTSA consortium oversight committee.

The CTSA consortium, initiated in 2006 with 12 "homes" for clinical and translational research, is enhancing the nation's clinical research enterprise by encouraging and enabling transdisciplinary collaborations within and across research institutions, providing researchers with access to sophisticated technologies and expertise, offering assistance with regulatory and administrative tasks, and training the next generation of clinical and translational scientists.

Although the first 12 CTSAs are just starting to make the necessary facilities and programs available at their own institutions, many researchers are already realizing the impact that the new infrastructure will have on their current and future work.

SPEEDING THE DEVELOPMENT OF NEW THERAPIES

Through its CTSA, the University of Pennsylvania provided invaluable assistance to Grupp in negotiating an agreement to work on his neuroblastoma trial with colleagues at Dana-Farber Cancer Institute, considerably speeding up patient recruitment. "The collaboration will cut the length of the trial from eight to four months," explains Grupp.

Getting another entity involved in the trial was far from easy. "This is an Investigational New Drug (IND) study, and Penn holds the IND," says Grupp. "So we had to develop procedures for Dana-Farber to participate. We had to write new standard operating procedures that could be exported to a different site." The payoff is that when the trial is completed in fall 2007, Grupp will have a chance to move forward with testing his new cancer vaccine. And if he and investigators at Dana-Farber decide to collaborate to test the new therapy, the groundwork has already been laid. "We now have a clinical trial agreement between the two institutions," he says.

Researchers are often not trained in complying with all the regulations set in place to ensure patient safety, and even if they have the necessary know-how, they cannot afford the time and effort to get through all the associated paperwork. CTSAs focus on freeing up the intellectual and creative talents of clinical

PHOTO COURTESY OF CHILDREN'S HOSPITAL OF PHILADELPHIA

> The CTSAs help researchers deal with the complexities of human studies. —LARS BERGLUND, UNIVERSITY OF CALIFORNIA, DAVIS

and translational researchers by providing regulatory support, clinical research coordinators, technology transfer assistance, and project management. "The CTSAs help researchers deal with the complexities of human studies," says Berglund. "At our university, we have individuals who are trained to take care of regulations. With increased use, their experience increases, and they become better and faster at the task."

MOVING RESEARCH FROM THE LABORATORY BENCH TO PATIENTS

Another challenge faced by clinical and translational researchers is that their work calls for a broad set of skills and expertise that is rarely found in a single laboratory or department. "In the long run, the consortium will make translational and clinical research more economical and efficient by providing access to important skills and technologies currently limited to defined disciplinary areas or specific labs," explains Berglund.

Institutions belonging to the CTSA consortium are establishing centralized facilities for specialized technologies, such as combinatorial chemistry and molecular therapies, imaging and informatics, as well as repositories of patients' samples. "These are institutional resources traditionally undersupported," says Califf. "All researchers can use them and have access to them more readily and at a lower cost than if they had to seek them out on their own."

In addition, CTSAs provide support for patient-oriented studies by providing access to patients and to trained medical personnel who can help researchers with medical evaluations, protocol design, review of clinical laboratory findings, and other competencies. This support is particularly critical to scientists in basic science departments, like Marc Flajolet at The Rockefeller University, who are not trained or do not have the resources to move important research findings to clinical applications.

In a study funded by the National Institute on Aging, Flajolet and supervisor Paul Greengard, director of The Rockefeller University Fisher Center for Alzheimer's Disease Research and a faculty member on the university's CTSA, reported that expression of high amounts of a particular enzyme increases the amount of amyloid beta, the rogue protein that accumulates within and around the brain cells of Alzheimer's disease patients.

■ Marc Flajolet, a researcher in the laboratory of Paul Greengard at The Rockefeller University, has identified a new set of compounds that can block the production of amyloid beta, a protein that accumulates in the brains of people with Alzheimer's disease.

On the other hand, inhibiting the activity of this enzyme—called casein kinase 1—reduces amyloid beta levels.

The results suggest that casein kinase 1 inhibitors could provide a new class of drugs for Alzheimer's patients. Such drugs are badly needed, because most current drugs being tested for Alzheimer's disease cause serious side effects in patients. The new compounds against casein kinase 1 might be safer because they use an entirely different mechanism.

Although the casein kinase 1 inhibitors look promising in the laboratory, more tests must be completed before they can be assessed in patients. For one thing, the compounds Flajolet

PHOTO BY GUY KLOPPENBURG, COURTESY OF THE FISHER CENTER FOR ALZHEIMER'S DISEASE RESEARCH

used in his study dissolve poorly in blood. He has, therefore, started to test similar molecules to find ones that are more soluble. Soluble compounds will then need to be tested in animal models of Alzheimer's disease to determine whether they improve symptoms.

But if these preclinical studies yield positive results, Flajolet might soon be in a position to test his compounds in clinical trials within the Rockefeller CTSA, which includes a hospital devoted exclusively to medical research. "We definitely have a lot of facilities here," says Flajolet. "We will do our best to take our findings through to studies in humans." The outcome may be a treatment for a disease that currently affects more than 5 million Americans; without effective treatments or cures, disease prevalence is expected to soar to 7.7 million people by 2030.

ENABLING PRECLINICAL STUDIES AND THEIR TRANSLATION TO PATIENTS

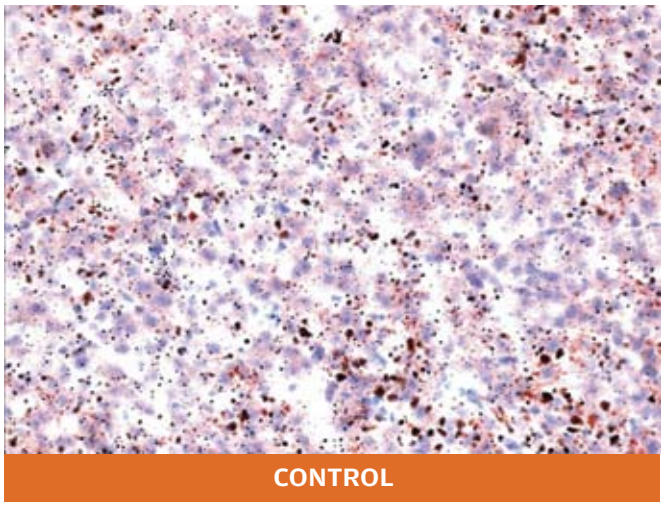
Whereas many clinical insights come from basic studies in the laboratory, others have their roots in observations in animal models. Daniel Marks of Oregon Health & Science University received a pilot grant from the university's CTSA to collaborate on a project initiated five years earlier by Kevin Grove at the NCRR-funded Oregon National Primate Research Center. "The pilot grant was so important, because I have not published in this field before," says Marks, whose medical training was in pediatrics. "It is hard to apply for an R01 grant if you have no publication record."

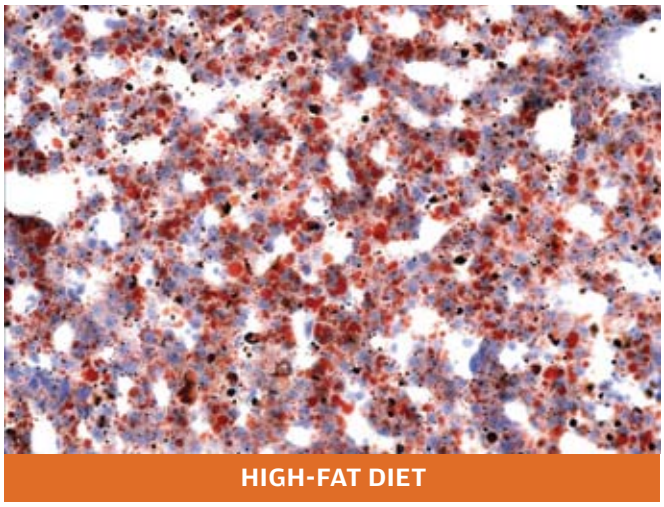
Grove had established a model of obesity in Japanese macaques by feeding them a diet consisting of 35 percent fat, the proportion of fat in the average U.S. diet. When given to pregnant monkeys, the diet invariably caused abnormalities in different organs in the developing fetuses. Marks documented an accumulation of fat in fetal liver cells associated with varying degrees of inflammation and scarring, a picture reminiscent of the liver disease typically observed in alcoholics. "To see this in the developing fetus is very alarming," says Marks. "If the results are confirmed in humans, they would have profound implications in light of the current obesity epidemic."

To examine this question, Marks started collaborating with physicians at the neonatal intensive care unit of the university's affiliated hospital to examine the livers of human fetuses by ultrasound. "To set up a study like this, you must draft consent forms for the parents, in English and Spanish in this case, draft a procedure that details exactly what you want to do with the patient, the risks and benefits, how the data will be managed, how we will protect patient privacy, and so on," Marks elaborates. He is receiving invaluable assistance from his institution's CTSA in fulfilling these requirements.

TRAINING THE NEXT GENERATION OF TRANSLATIONAL SCIENTISTS

In addition to supporting Marks' research, Oregon Health & Science University's CTSA has provided training opportunities for a graduate student and medical student in his lab to become "card-carrying translational researchers," says Marks. The CTSA offers several courses through its Human Investigations Program to train health care professionals who want to make clinical research a substantial part of their long-term career goals.





■ Daniel Marks and colleague Kevin Grove at the Oregon Health & Science University have been studying the effects of a high-fat diet on developing organs using a nonhuman primate animal model. These photographs show the livers of monkey fetuses whose mothers had been fed either a regular, low-fat diet (control) or a diet high in fat and calories. The livers were treated with a compound (oil-red O) that specifically stains fat deposits red. Many more fat deposits can be seen inside liver cells of fetuses in the high-fat diet group—a picture reminiscent of the fatty liver disease typically observed in alcoholics.

IMAGES COURTESY OF OREGON HEALTH & SCIENCE UNIVERSITY

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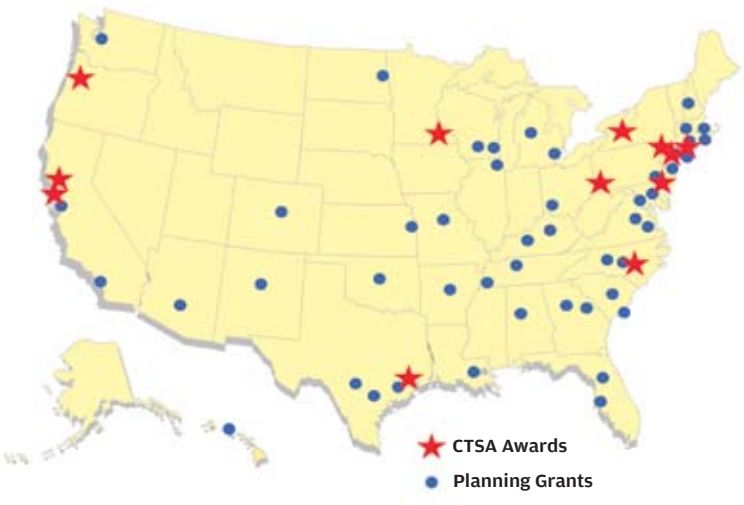

Twelve institutions participate in the CTSA consortium.
An additional 52 institutions have received planning grants to help them prepare applications to join the consortium.

Through this program, students can attend such courses as "Introduction to Clinical Research," "Clinical Research Design," and "Biostatistics and Protection of Human Subjects" as part of certificate, master's, and non-degree tracks. These courses provide training in clinical research from the initial trial design to data analysis and presentation, equipping students with the necessary expertise to pursue an independent career in this field.

Such training programs were established at Oregon and other CTSA institutions due to a realization that the scope of knowledge and expertise needed to be an effective translational or clinical scientist can no longer be acquired on the job as was done in the past (see "CTSAs in Focus," page 3). "We now offer different programs suited to different needs," says Berglund.

The three studies at Rockefeller, Oregon, and Penn span the continuum of clinical and translational research—from studies in the laboratory that may lead to new drugs, to animal models of disease that give important insights into human conditions, to new therapies tested in patients. They are just a few examples of the countless advances to be facilitated through the programs and resources established through the CTSA consortium.

As this initiative continues to expand with different CTSAs collaborating and sharing resources, it will help speed the course of translational and clinical research, ultimately benefiting the nation's health. "When we first got funded, I just wanted to focus on getting our own programs off the ground," says Berglund. "But the consortium has since become the most important part of our efforts. We are coming together at every level and really starting to work as a unit." ■

A CONSORTIUM FOR TRANSFORMING CLINICAL AND TRANSLATIONAL RESEARCH

The Clinical and Translational Science Awards (CTSAs) established a new consortium to transform how clinical and translational research is conducted, ultimately enabling researchers to provide new treatments to patients more efficiently and quickly. Launched on October 3, 2006, the consortium includes 12 academic health centers located throughout the nation. When fully implemented in 2012, about 60 institutions will be linked together. "Different CTSAs have different strengths," says Robert Califf, vice chancellor for clinical and translational research at Duke University Medical Center. "Our job is to create some common goals by sharing ideas and different expertise."

Representatives from all CTSAs meet several times a year to share experiences and establish best practices in a range of areas, including the following:

- Biostatistics and epidemiology
- Research design
- Communications
- Clinical research ethics and resources for research participants
- Participant and clinical interaction resources
- Regulatory knowledge
- Pediatrics
- Informatics
- Community engagement in clinical research
- Education and career development
- Institutional and national evaluation
- Translational research in traditional academic settings and in public-private partnerships
- Translational research

Information about the committees responsible for these areas and their activities is available at the consortium's Web site at http://ctsaweb.org.