Established in 1996, the Doris Duke Charitable Foundation seeks to improve the quality of people’s lives by nurturing the arts, protecting and restoring the environment, seeking cures for diseases, and protecting children from abuse and neglect. In addition to the Medical Research Program, the foundation awards grants in the following program areas:

- **The Arts Program** supports national and mid-sized presenting organizations, service organizations, the field of jazz, nonprofit theatres, public performing arts high schools and upper-division arts training institutions.
- **The Environment Program** supports forest and land conservation, the improvement of land-use planning, and conservation fellowships for graduate students at five universities.
- **The Child Abuse Prevention Program** supports early intervention efforts that are national in scope and supports the development of child abuse prevention services where large numbers of young children and their families are served.

The foundation’s activities are guided by the will of Doris Duke, who endowed the foundation with assets that now total approximately $1.2 billion. Additional information on the foundation is available at www.ddcf.org.

**From the Staff**

Elaine K. Gallin, Ph.D., Program Director  
Sylvie Le Blancq, Ph.D., Program Officer  
Erich K. Giebelhaus, MPP, Program Associate

This Bulletin provides us with the opportunity to update the clinical research community on our programs, share the work of our grantees, and, most importantly, to promote clinical research.

Now entering its sixth year, the Medical Research Program has awarded more than 160 grants totaling over $106 million. Our program focuses on supporting and strengthening clinical research. The foundation defines clinical research broadly, as research conducted with human subjects or material of human origin, or data about human health, disease, behavior, and health services. With this focus, the Medical Research Program seeks to develop leaders in clinical research, expand the frontiers of clinical research, and strengthen the clinical research infrastructure. Our research grants focus mainly on four disease areas: AIDS, cancer, heart disease, and sickle cell anemia and other blood disorders.

Three of our programs support physician-scientists at different stages of their careers: the Distinguished Clinical Scientist Award (for established clinical investigators), the Clinical Scientist Development Award (for clinical investigators at the beginning of their careers), and the Clinical Research Fellowship Program (for medical students). Profiles of some of our award winners appear on the following pages.

Two other competitive grant programs have been designed to help push the frontiers of clinical research: the Innovation in Clinical Research Award program, which we have funded for the past four years, and our newest grant program, the Clinical Interfaces Award Program, which is expected to award its first grants in mid-2003 and is described on page 6.

The Medical Research Program also supports a few special projects each year that fit within our programmatic strategies. In the past year, these projects have reflected the foundation’s commitment to support research that facilitates the care and treatment of AIDS patients in the developing world (see more about our international grants on page 2).

The year 2002 has been our busiest so far. Although 2003 promises to be a productive year, we will not be offering any new grant competitions until 2004 due to budget reductions. Nevertheless, we remain committed to working with our advisors, grantees, and the rest of the community to support activities that will speed the translation of basic research findings into the clinic.

We are proud of the continuing success of our outstanding family of awardees and fellows, and are pleased to highlight some of their work on the following pages.

Comments & Questions

We welcome your feedback! Please send comments or suggestions to:

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For details about the Medical Research Program, visit http://ddcf.aibs.org.
International AIDS Projects

In 2002, the Medical Research Program (MRP) continued to support projects that strengthen the clinical research capacity and conduct the clinical research required for effective treatment and care of HIV/AIDS patients in sub-Saharan Africa. The following are highlights of some of the MRP’s international AIDS grants.

ACRiA: Forging New Partnerships

Given the magnitude of the epidemic in sub-Saharan Africa, it is an extraordinary challenge to provide AIDS care and treatment (including treatment with antiretroviral drugs) to all those who need it. To help meet this challenge, the MRP has partnered with the Rockefeller Foundation to create and support a small grants program, known as the AIDS Care Research in Africa (ACRiA) program. ACRiA will award at least 10 grants of up to $80,000 each to junior African researchers to conduct clinical research on how to best care for and treat AIDS patients in their countries.

This project is unique in that it is led by an alliance of outstanding African AIDS researchers (several of whom are pictured below). Dr. Peter Mugyenyi of the Joint Clinical Research Centre and Dr. Elly Katabira from Makerere Medical School in Kampala, Uganda, are the program co-chairs. Grantees will be selected by peer-reviewed processes. Over 40 letters of intent were received in response to the first request for proposals. To receive information on the program, send an e-mail to acria@jcrc.co.ug.

Building Clinical Research Capacity in South Africa

The Nelson R. Mandela School of Medicine of the University of Natal in Durban is at the forefront of the fight against AIDS in KwaZulu-Natal, the South African province hardest hit by the AIDS epidemic.

As part of its strategy to enhance AIDS research and training capacity in southern Africa, the MRP has provided $1.8 million to help the Mandela School of Medicine build a new Medical Research Institute. The new institute, which will be named the Doris Duke Medical Research Institute, will officially open in July 2003. It will house both laboratory and clinical trials facilities.

Some of the new institute’s laboratory space will house the HIV Pathogenesis Program (HPP), a bilateral program between the University of Natal and Massachusetts General Hospital supported by a $2.25 million grant awarded by DDCF in 2002. In addition to researching the immune response to HIV, the HPP provides research training. Research findings from the HPP were presented at the International AIDS Meeting in Barcelona in July 2002, and included a presentation by Nolwandle Mngqundaniso (pictured at right).

Developing Inexpensive AIDS Diagnostics

Antiretroviral therapy for AIDS requires more than just drugs. It also requires laboratory tests to monitor the therapy. Currently, such tests are too costly and complex to be used in most local settings in developing countries. Inexpensive, simple, and accurate monitoring technologies are urgently needed to improve the medical management of antiretroviral therapy in developing countries. In June 2003, as part of the 2003 Innovation in Clinical Research Award program (see page 7), DDCF expects to award up to 12 new grants of $200,000 each to support the development of diagnostics for monitoring antiretroviral therapy specifically for point-of-care settings in developing countries.

Below: Fanny Kiepiela, Ph.D. (right), Head of the Pediatric Immunology Laboratory of the Nelson R. Mandela School of Medicine at the University of Natal, and Nolwandle Mngqundaniso (left), a member of the Pediatric Immunology Laboratory, pictured before Ms. Mngqundaniso’s poster presentation at the 2002 Clinical Scientist Meeting in Newport (see page 10).
CONSORTIUM TO EXAMINE CLINICAL RESEARCH ETHICS

Assessing the System of Participant Protection

Is the oversight of clinical research adequately organized and conceptualized to meet today’s challenges?

The Consortium to Examine Clinical Research Ethics (CECRE) was established in 2001 with a grant from DDCF to help answer this question.

As the first major non-government financed effort to reevaluate the system of oversight for research involving human participants, CECRE aims to improve our understanding of the landscape and oversight of clinical research. One of its principal objectives is to generate empirical data to improve the quality and efficacy of oversight reform efforts.

Assessing Proposed Reforms of the Clinical Research Oversight System

CECRE has begun its work by summarizing and analyzing recent and/or ongoing initiatives in order to identify gaps between proposed reform efforts and concerns about the oversight system. In this context, it examined recent accreditation efforts, the Institute of Medicine’s 2002 report, and changes to the National Human Research Protection Advisory Committee, as well as to the Office of Human Research Protection.

Mapping the Clinical Research Landscape

CECRE’s Landscape Project will develop a method to gather empirical information on clinical research, including data on the nature, funding, and organizational structure of research. This effort to characterize the “landscape” of clinical research and its oversight seeks to fill significant gaps in information, such as details on the cost of the review and oversight process, which can severely limit the efficacy of reform initiatives.

Information about the costs of protocol review, information technology, and staff and Institutional Review Board member education is essential to ensure that sufficient resources are invested in research oversight in the future. Data will be collected from academic and other sites where clinical research is conducted.

Reexamining the Concept of “Vulnerability”

The other essential component of CECRE’s efforts is to explore the ethical framework of clinical research. In that context, CECRE’s work thus far has focused on a systematic reexamination of the concept of “vulnerability” in clinical research subjects and its use in the oversight system. CECRE is exploring the idea that a new concept of “special scrutiny” is needed for the oversight of some research and is developing possible criteria for its use.

Developing a Distinctive Approach

CECRE’s work is distinctive in several respects. First, it brings together people with knowledge and experience from different disciplines and aspects of the clinical research enterprise. CECRE members are from public and private academic research institutions, government, the pharmaceutical industry, non-profit health organizations and others involved in clinical research, and they represent disciplines ranging from medicine, public health and pharmacology to business, law, history and philosophy.

Second, CECRE aims to generate ideas for reform that are based upon empirical data. Third, while CECRE members acknowledge the importance of informed, voluntary consent and the assumptions and conceptual frameworks that underlie the work of Institutional Review Boards, CECRE does not presume that the existing structure of the system for participant protection is the optimal one and will try to explore these issues from a novel perspective.

For more information about CECRE, please visit http://csmej.mc.duke.edu.

CECRE GOALS

1. Examine past and present reform efforts in the ethical oversight of clinical research to identify future needs.

2. Develop a method to generate previously unavailable data on the current characteristics of clinical research, including how it is conducted and overseen.

3. Begin a reexamination of the ethical framework and the goals of clinical research ethics.

4. Recommend ways to ensure that human research participants are protected and clinical research is ethical.

5. Engage public policy makers in dialogue.

CECRE Participants (pictured left to right):
Alan Fleischman, M.D. (New York Academy of Medicine); Dale Hammerschmidt, M.D. (University of Minnesota); Ruth Faden, M.P.H., Ph.D. (Johns Hopkins University); Angela Bowen, M.D. (Western IRB); Lisa Eckenwiler, Ph.D. (Duke University Medical Center–Old Dominion University); David Coccheto, Ph.D. (GlaxoSmithKline); Carol Levine, M.A. (United Hospital Fund); Ezekiel Emanuel, M.D., Ph.D. (National Institutes of Health); Jeremy Sugarman, M.D., M.A., M.P.H. (Duke University Medical Center).

CECRE Participant Not Pictured:
Kenneth Getz, M.B.A. (CenterWatch).

CECRE Consultants and Staff Not Pictured:
Robert Califf, M.D. (Duke University Medical Center); Christine Grady, Ph.D. (National Institutes of Health); Robert Mayer, M.D. (Harvard Medical School/Dana Farber Cancer Institute); Joan Rachlin, J.D., M.P.H. [PRIM&R]; Carianne Tucker, M.P.H. (Duke University Medical Center).

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For more information about CECRE, please visit http://csmej.mc.duke.edu.
For Dr. Nina Bhardwaj, years of basic immunology research and medical training are coming to fruition with the advent of clinical trials of novel immune therapies that she helped develop. Her work with dendritic cells has the potential to shape therapies for diseases as diverse as AIDS and cancer.

Dendritic cells, first discovered in mice 30 years ago, act as patrol sentinels of the immune system: they take up foreign proteins (antigens) produced by pathogens, and display them to the “execution” arm of the immune system (T cells), greatly boosting immune responses. Bhardwaj’s research focuses on harnessing the immune-stimulating properties of dendritic cells to help the body identify and eliminate diseased cells.

Bhardwaj’s interest in immunology began in medical school at New York University, where she also earned a Ph.D. in cellular immunology, working with Dr. Jerry Lawrence. For her clinical fellowship, she chose to study rheumatoid arthritis, a disease in which the immune system functions improperly and attacks the body’s own tissues. Later, working at Rockefeller University with Dr. Ralph Steinman, a pioneer in the field of dendritic cell biology, Bhardwaj became interested in the basic biology of these powerful stimulants of the immune system.

Engineering Dendritic Cells to Stimulate Immune Response

Her interest led Bhardwaj to studies of antiviral immunity, in which dendritic cells are prominent. Bhardwaj and colleagues became adept at isolating these cells from human volunteers and growing and manipulating them in the laboratory. A key advance was the ability to “load” dendritic cells with a specific antigen and steriley inject them into human subjects. Put back into the body, these engineered dendritic cells helped direct an immune response to the antigen.

With these tools in place, Bhardwaj and others felt dendritic cells could offer an alternative to traditional chemical adjuvants, that is, agents that stimulate the immune system. Initial studies in healthy subjects indicated that lab-manipulated dendritic cells could be effective when put back into people. Actual proof of their therapeutic potential, however, would require validation in a clinical disease setting.

Bhardwaj soon encountered several potential obstacles to the translation of basic research to the clinic, including putting together the right team of clinicians, designing the study, applying for funding and regulatory approval, recruiting suitable patients, high expenses, and a great deal of paperwork. In this respect, she credits her 2001 DDCF Distinguished Clinical Scientist Award with helping her carry forward two clinical trials aimed at testing the potential of dendritic cell therapy as new vaccines against the HIV virus.

conducting Clinical Trials to Test Dendritic Cell Vaccines

The first trial testing these new vaccines will be done in HIV patients during the initial, or acute phase of infection. The trial’s aim is to boost patient immune responses to HIV and see whether the patient can control the infection, even when off anti-viral drug therapy. Patient dendritic cells are exposed to HIV proteins, and are then used to vaccinate the patients, who are subsequently taken off drug therapy in a controlled fashion. This trial is being carried out in collaboration with Dr. Bruce Walker at Massachusetts General Hospital, a 1999 DCSA recipient.

The second trial, conducted in conjunction with the pharmaceutical company Aventis, will be one of the first to test dendritic cell vaccines in chronic infection. Chronic HIV patients will be vaccinated with self-origin dendritic cells that have been treated with a canarypox virus vector expressing HIV proteins. The results will be compared with patients injected with the canarypox vector alone.

Such a “multiple-arm” study, where the experimental treatment is compared to one or more alternatives, is an essential component of Bhardwaj’s clinical research philosophy. As she puts it, “We are trying to ask the reasonable questions, and hoping to get good answers.”

Other Research Interests

Another research interest of Bhardwaj’s is immunotherapy of cancer. To this end, she has initiated another clinical multi-arm trial of dendritic cell therapy, this one for melanoma, at New York University. As she awaits the results, Bhardwaj continues to pursue basic research questions that might ultimately improve the therapies she is testing. For example, she is developing ways to recruit and activate dendritic cells in situ, thereby circumventing costly and painstaking cell culture. As the work goes forward, she envisions a continuing dialogue between basic and clinical research, aimed at eventually adding new tools to our arsenal against disease.
Despite being a highly respected scientist and board-certified adult cardiologist, Dr. Andrew Marks is not the typical recipient of a DDCF investigator award. Although he donates a portion of his time to the clinical cardiology service, the main focus of his work has always been in basic sciences. “I have not focused my efforts on clinical practice,” he explains. “My track record is in basic science. The support from DDCF has been so important because it has allowed me to develop the translational research aspect of my program on heart failure and cardiac arrhythmias.”

Linking the Ryanodine Receptor to Heart Disease

In many ways, however, Marks has the perfect credentials for translational research. For over a decade he has been working on a molecule that has turned out to be central to the development and treatment of heart failure. This molecule is the ryanodine receptor, the calcium release channel inside heart muscle cells that controls heart muscle contraction.

In the late 1980s, Marks first became involved in studying the ryanodine receptor during his research training at Harvard Medical School when he succeeded in cloning the gene encoding the receptor. At that time, there was no clear connection between the receptor and human disease, but Marks loved the excitement of molecular biology and he proceeded to study the molecular structure and function of the receptor in normal skeletal and heart muscle.

Marks reflects, “For me, it’s almost like a miracle to see the way things have evolved by sticking to my guns, so to speak, and studying a very fundamental aspect of how muscle contraction is regulated, and then to find unanticipated connections to heart failure and arrhythmias.”

Understanding the Role of the Ryanodine Receptor

Until recently, the role of the receptor in heart failure was unknown. But doctors have known for many years that patients with heart failure had extremely high circulating levels of adrenaline, and in fact those with higher levels tended to have a poorer outcome. This information prompted Marks to study the regulation of the ryanodine receptor by the adrenergic signaling system, and the results have been highly gratifying.

In the normal heart, adrenaline activates the ryanodine receptor, resulting in a stronger contraction. But in the failing heart, adrenaline overstimulation of the ryanodine receptor results in defective (“leaky”) channel function and an even weaker heart. These findings have direct clinical relevance, because they indicate that beta-adrenergic blockade (beta-blockers) should preserve function in the failing heart.

Previously these findings would have seemed counterintuitive, because giving beta-blockers to a normal heart decreases the function of the heart. “And in fact, there are now clinical studies that show that even in the sickest heart failure patient they do get an improvement in survival with beta-blockers, which is quite remarkable,” says Marks. “As recently as five or ten years ago you would have been brought up on charges if you tried to give your heart failure patient beta-blockers!”

Marks recognizes that there is still a long way to go in understanding the pathophysiology of heart failure and in developing improved therapies for heart failure patients. “We’re really at a very early stage in our work. So it’s very fortunate that there are currently available drugs that work and that can target this pathway,” he says.

In the near future, he plans to look at the genetic determinants of heart failure and its response to therapy. In the long term, he hopes to develop highly selective drugs that can regulate the ryanodine receptor without disrupting other signals in the cell.
Michael DeBaun: Attacking sickle cell disease on many fronts

Diagnosing Silent Stroke

Because sickle cell disease is genetic, care is a lifelong prospect. In addition to its hallmark painful episodes, the disease also carries a significant risk of neurological problems. The statistics are stark: before the age of 18, 11 percent of sickle cell patients will have an overt stroke, while another 22 percent will have a “silent” stroke, that is, an episode of insufficient oxygen delivery to the brain without overt symptoms.

These strokes tend to affect the frontal lobe, a region of the brain involved in executive function and attention. They can result in cognitive impairment and significant problems in school. Silent strokes can be insidious, because parents and clinicians may not be aware that brain damage has occurred.

In work supported by DeBaun’s 1999 Clinical Scientist Development Award, he and his colleagues showed that patients who have had silent strokes have cognitive difficulties similar to those seen in patients with overt strokes. They then demonstrated that a battery of easily administered and less-expensive cognitive tests can accurately diagnose when a silent stroke has occurred.

Reducing the Rate of a Second Stroke

For children with sickle cell disease who have had overt strokes, the conventional therapy is blood transfusion, which reduces the amount of the defective, “sickled” hemoglobin in the bloodstream.

As part of his DDCF grant, Dr. DeBaun formed a consortium of Pediatric Hematology Centers to address what risk factors, if any, were associated with subsequent strokes in 137 patients receiving blood transfusions. The study showed that although regular blood transfusions reduce the risk of a second stroke, over a ten-year period 23 percent of patients will still suffer a second stroke. The study also found that the best predictive factor for subsequent strokes was the absence of any medical complications (acute chest syndrome, infection) associated with the initial stroke.

Another aspect of DeBaun’s DDCF-funded work has been a Phase II clinical study to formally assess the feasibility, short-term efficacy, and compliance associated with regular blood transfusions for preventing subsequent neurological injury in children who have had silent strokes.

However, transfusion therapy has drawbacks that make adherence difficult for many, as treatments are time-consuming, and patients treated with transfusion long-term can develop immune reactions to imperfectly matched donor blood.

DeBaun believes the promise for curing sickle cell disease is stem cell transplant, and he believes that children with strokes should receive the best-matched blood possible, thus decreasing the rate of alloimmunization and other complications associated with transfusions.

To help address these needs, DeBaun is working with the St. Louis University Cord Blood Bank to recruit more African-American cord blood donors and with the American Red Cross to increase the number of African-American blood donors for children with sickle cell disease.

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Doris Duke Clinical Scientist Development Award

Established in 1998, the Clinical Scientist Development Award supports junior physician-scientists and research fellows as they begin their clinical research careers. This award recognizes that many clinical investigators need support at an early stage of their career development, when a researcher is transitioning from working in a mentor’s laboratory to setting up an independent research program. As of February 2003, DDCF has committed over $25 million to support 71 CSDA grantees working in cardiovascular disease, cancer, AIDS and blood disorders. The CSDA provides $100,000 each year for up to five years to junior faculty members and $65,000 each year to research fellows.

MRP Launches Clinical Interfaces Award Program

In September 2002, the Medical Research Program launched the Clinical Interfaces Award Program (CIAP), with the first awards to be made in 2003. The CIAP is designed to encourage outstanding researchers from different scientific disciplines (both basic and clinical) to collaborate on novel clinical research to address challenging questions in human health. The CIAP aims to catalyze activity by supporting new collaborations and by strengthening existing ones; demonstrating successful models for clinical research at the interface of multiple disciplines; and supporting interdisciplinary and inter-institutional endeavors that go beyond the program project mind-set. For more information, please visit http://ddcf.aibs.org/ciap.
Whereas much of biomedicine attempts to remedy existing problems, epidemiology attempts to identify populations at risk so that measures can be taken to prevent disease. A new collaboration between Dr. David Siscovick and Dr. Deborah Nickerson from the University of Washington aims to extend the power of epidemiological studies by applying the latest genetic variation technology. Their “proof-of-concept” project is one of the first to apply high-density analysis of genetic variation in human DNA to a defined study population, and could help pinpoint new risk factors for heart disease.

**Characterizing Lifestyle and Genetic Risk Factors Linked to Heart Attack**

Siscovick traces his interest in disease prevention to a lecture on preventative approaches to heart disease that he heard in his early medical training. With training in medicine and epidemiology, cross-disciplinary thinking comes naturally to him. For several years, Siscovick and colleagues have studied women in Washington state who have had heart attacks before the age of 59. This endeavor, covering three counties and 2.4 million people, aims to identify all such cases in the area. The idea is that by characterizing the circumstances of these rare, early-onset events, significant risk factors for heart attack can be identified.

Siscovick’s work showed that the disease population has a higher incidence of lifestyle risk factors, such as smoking, as well as genetic ones, such as inherited predisposition to form blood clots. But the techniques in use were cumbersome and tended to limit analyses to one variation in one gene. As a result, independent studies offered only glimpses into disease risk factors, making it difficult to compare results across studies or draw conclusions. Siscovick wished to broaden the scope by examining multiple variants in multiple genes at once. “High-throughput” genetic sequence analysis, such as that used by Deborah Nickerson, offered a technological solution to this problem.

**Identifying and Correlating Variants With Incidence of Heart Disease**

Nickerson’s work focuses on studying genetic variations known as single-nucleotide polymorphisms. Her group is particularly interested in the common patterns of variable sites that exist in the human genome for genes involved in blood clotting. Nickerson and Siscovick saw an opportunity to apply their expertise in identifying and quantifying traits in a new way to examine genetic risk factors for heart disease. In work supported by a 2001 Innovation in Clinical Research Award, Siscovick and Nickerson are analyzing a set of six “candidate genes” in the Washington state study. These genes are involved in control of blood clotting, and were chosen because Siscovick’s previous work had shown that a variant of prothrombin was associated with disease risk in this population. The early phase of the project will document the different variants and determine which are common in the population at large. As the data analysis progresses, they are evaluating the correlations among common human DNA variants into patterns with incidence of disease.

The results could lead not only to insights as to how disease occurs, but also to the development of a prognostic screening test for increased risk of heart attack. Armed with this information, they could take steps to move to larger population studies and test the ability of these findings to reduce disease risk.

Siscovick and Nickerson have recently extended their collaboration to researchers across the United States in the CARDIA Study, with particular emphasis on genes involved in inflammation pathways that are potentially related to the risk of early-onset coronary atherosclerosis.

For now, both studies are in progress, and definitive conclusions are still to come. But Siscovick and Nickerson’s collaboration could be among the first practical advances to be gained from the analysis of correlations of common ancient DNA polymorphisms in the human genome.

**Paul Ridker Recognized for Innovative Work on Predicting Heart Disease**

Like Siscovick and Nickerson, Dr. Paul Ridker is also working on ways to predict a person’s risk of heart disease. Ridker is a Professor of Medicine at the Harvard Medical School, Director of Harvard’s Center for Cardiovascular Disease Prevention, and a recipient of a 2000 Distinguished Clinical Scientist Award. The results of Ridker’s study and the work of his research team on the use of C-reactive protein as a tool in predicting cardiovascular disease appeared in the November 14, 2002 issue of *The New England Journal of Medicine*. As a result of this study, the U.S. Centers for Disease Control and Prevention and the American Heart Association changed their recommended guidelines for patient testing in January 2003.

**Doris Duke Innovation in Clinical Research Award**

Established in 2000, the Innovation in Clinical Research Award has supported novel clinical research projects in cardiovascular diseases, and sickle cell anemia and other blood disorders. The award recognizes that funds are often scarce for high-risk projects that employ innovative approaches and multidisciplinary collaborations. The award provides $100,000 per year for two years. As of February 2003, DDCF has committed $5.8 million to support 29 investigators or teams of investigators for the ICRA program. See page 2 for details on the focus of the 2003 competition.
Karen Kölln’s interest in otolaryngology was sparked by a two-week clinical rotation that she completed during her second year at the University of Iowa Carver College of Medicine. In her medical training, Kölln had never had the opportunity to do clinical research in this field, an integral part of the burgeoning specialty that involves the diagnosis and treatment of head and neck disorders ranging from cancer to hearing loss.

Luckily for Kölln, she was given the opportunity to complete a full year of clinical research as a member of the first class of fellows in the Clinical Research Fellowship Program. Kölln applied for and was chosen to work in the University of Iowa Molecular Otolaryngology Research Laboratory, an internationally known laboratory that researches hereditary hearing loss. Her mentor was Dr. Richard J.H. Smith, Sterba Hearing Professor of Otolaryngology.

“I really didn’t have much research experience before this, although I was interested in it. I was hoping to do something for more than just a couple of months, to see if I really enjoyed and might pursue a career in clinical research,” said Kölln, whose fellowship research focused on Forkhead (FOXI1) mutations and their relation to Pendred syndrome, an inherited disorder that accounts for as much as 10 percent of hereditary deafness.

Kölln worked with a team looking to identify deletions in the PDS gene (SLC26A4) as a possible cause of Pendred syndrome. “It was amazing, one of the best experiences of my life,” she says. In addition, the fellowship allowed her to spend three months at a lab in Sweden affiliated with the research project. “I would recommend this program to anyone, even if you’re walking in with no research experience like I did. It’s a great opportunity that most would never be able to do otherwise.”

Now finishing her fourth year of medical school, Kölln continues her connection with the research laboratory. She has also just designed and posted a Web site that will serve as a resource for people studying Pendred syndrome.

For Raymond Givens, the Doris Duke Clinical Research Fellowship was not only a chance to design and conduct research, but also a lesson in the social benefits of his work.

Givens, a third-year student at Duke University School of Medicine, completed his fellowship at the University of North Carolina at Chapel Hill (UNC) in June 2002. His fellowship research focused on the new area of pharmacogenetics, which examines how genetic variations, which often coincide with ethnicity, affect an individual’s interactions with medications.

“The fellowship expanded my vision of myself as a physician,” Givens said. “It helped me see myself not just as a genetic epidemiologist, but as a physician-scholar who also could serve as an activist.”

Working with his mentor Paul Watkins, M.D., director of UNC’s General Clinical Research Center, Givens studied genetic variations (polymorphisms) in a subfamily of the cytochrome P450 enzymes, which are involved in the metabolism of many therapeutic drugs. His project focused on a polymorphism that is more common in African-Americans and might be associated with differences in the clearance of certain drugs. If this were the case, there may be clinical ramifications for those individuals with the polymorphism in terms of the effectiveness of certain treatments. Givens also began collecting data to test whether this polymorphism is linked to blood pressure control.

One unique aspect of his fellowship experience was the opportunity to submit a research protocol to an Institutional Review Board (IRB), a committee charged with overseeing research on human volunteers. “The IRB defense was new to me and something that most students don’t get the chance to do,” Givens said.

Givens’ research project went so well during his fellowship year that he decided to take additional time off from medical school to continue his work and pursue a Ph.D. at the UNC School of Public Health. During this time, he hopes to collect more data to test his hypothesis that the common expression in African-Americans of the particular cytochrome P450 variation is linked to the increased propensity for salt retention and higher rates of hypertension in African-Americans.

He credits the fellowship with being the springboard for his current interests. “Without the support which allowed me to conduct human subject research, these developments would not have occurred,” he said. Givens is now planning clinical and research careers in internal medicine and public health.

First CRF Meeting Held at Washington University

Kären Kölln’s interest in otolaryngology was sparked by a two-week clinical rotation that she completed during her second year at the University of Iowa Carver College of Medicine. In her medical training, Kölln had never had the opportunity to do clinical research in this field, an integral part of the burgeoning specialty that involves the diagnosis and treatment of head and neck disorders ranging from cancer to hearing loss.

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Now finishing her fourth year of medical school, Kölln continues her connection with the research laboratory. She has also just designed and posted a Web site that will serve as a resource for people studying Pendred syndrome.

For Raymond Givens, the Doris Duke Clinical Research Fellowship was not only a chance to design and conduct research, but also a lesson in the social benefits of his work.

Givens, a third-year student at Duke University School of Medicine, completed his fellowship at the University of North Carolina at Chapel Hill (UNC) in June 2002. His fellowship research focused on the new area of pharmacogenetics, which examines how genetic variations, which often coincide with ethnicity, affect an individual’s interactions with medications.

“The fellowship expanded my vision of myself as a physician,” Givens said. “It helped me see myself not just as a genetic epidemiologist, but as a physician-scholar who also could serve as an activist.”

Working with his mentor Paul Watkins, M.D., director of UNC’s General Clinical Research Center, Givens studied genetic variations (polymorphisms) in a subfamily of the cytochrome P450 enzymes, which are involved in the metabolism of many therapeutic drugs. His project focused on a polymorphism that is more common in African-Americans and might be associated with differences in the clearance of certain drugs. If this were the case, there may be clinical ramifications for those individuals with the polymorphism in terms of the effectiveness of certain treatments. Givens also began collecting data to test whether this polymorphism is linked to blood pressure control.

One unique aspect of his fellowship experience was the opportunity to submit a research protocol to an Institutional Review Board (IRB), a committee charged with overseeing research on human volunteers. “The IRB defense was new to me and something that most students don’t get the chance to do,” Givens said.

Givens’ research project went so well during his fellowship year that he decided to take additional time off from medical school to continue his work and pursue a Ph.D. at the UNC School of Public Health. During this time, he hopes to collect more data to test his hypothesis that the common expression in African-Americans of the particular cytochrome P450 variation is linked to the increased propensity for salt retention and higher rates of hypertension in African-Americans.

He credits the fellowship with being the springboard for his current interests. “Without the support which allowed me to conduct human subject research, these developments would not have occurred,” he said. Givens is now planning clinical and research careers in internal medicine and public health.

First CRF Meeting Held at Washington University

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Doris Duke Clinical Research Fellowship for Medical Students

The Doris Duke Clinical Research Fellowship for medical students, now in its second year, is designed to provide clinical research opportunities to exceptional medical students. Sixty-five fellows are participating in the 2002-2003 program. There were 42 students in the first class.

Fellows receive stipends of $20,000 plus health insurance and are matched with outstanding clinical researchers at the participating institutions. Students at any medical school in the U.S. who are U.S. citizens are eligible to apply.

The program is available at the following 10 medical schools:

- The College of Physicians & Surgeons at Columbia University
- Harvard Medical School
- Mt. Sinai School of Medicine
- University of California-San Francisco School of Medicine
- University of Iowa College of Medicine
- University of North Carolina Medical School at Chapel Hill
- University of Pennsylvania Medical School
- The University of Texas Southwestern Medical Center at Dallas
- Washington University School of Medicine in St. Louis
- Yale University School of Medicine

The national program leader is Allyn L. Mark, M.D., Associate Dean for Research at the University of Iowa Carver College of Medicine.

FELLOWSHIP PROGRAM

MATTHEW ALLEN

Matthew Allen began his college career with two diverse interests. He was intrigued by economics, particularly resource allocation and use. But he also had a strong interest in oncology, fueled by his personal experiences with his father, who died from cancer when Allen was 24.

After receiving his bachelor’s degree in economics from the University of California at Los Angeles and completing his first three years at Harvard Medical School, Allen wanted to find a way to combine his interests in oncology and economics. The Doris Duke Clinical Research Fellowship allowed him to accomplish this. His study, “Decision Analysis on Tamoxifen as Chemoprevention for Breast Cancer in Young Women Treated with Radiation Therapy for Hodgkin’s Disease,” was completed at Harvard Medical School with guidance from his mentor, Dr. Peter Mauch.

“The mentoring I received was a benefit of the fellowship,” Allen said. “The contacts I made are not only role models but also are people who can make a difference in my career.”

The study looked at the pros and cons of using tamoxifen, a pill that inhibits breast cancer growth, in women who received radiation therapy before the age of 30 for Hodgkin’s disease, a type of cancer affecting the lymphatic system. Nearly one in four of these women will develop breast cancer by the age of 50 as a result of the radiation therapy. Allen’s study suggested that tamoxifen treatment was beneficial and cost-effective when started as early as 10 or as late as 15 or more years after radiation therapy.

“It seems to be very cost-effective and possibly cost-saving,” Allen said. “It’s a win-win situation. It improves the survival as well as quality of life and also appears to save money.”

The study is being submitted to the Journal of Clinical Oncology. Allen said he will continue research in this area, exploring whether prophylactic mastectomy might be an option for women who cannot take tamoxifen and whether breast MRI screening and a new class of drugs called aromatase inhibitors may provide further options. Currently, Allen is applying for residencies in either oncology or radiation oncology.

“This was a fantastic opportunity,” Allen said. “There are very few opportunities for medical students who want to do clinical or translational research because most grants that are available are for basic science research, so the Doris Duke program opened up a new door for many of us.”

CRF Program Leaders Meet at the 2002 CRF Annual Meeting (from left to right):

Peg Nopoulos, M.D. (Univ. of Iowa); Abhimanyu Garg, M.D. (Univ. of Texas Southwestern); Joel M. Palefsky, M.D. (Univ. of California, San Francisco); Daniel D. Federman, M.D. (Harvard Univ.; 2001-2002 CRF National Program Leader); Dennis A. Ausiello, Jr., M.D. (Harvard Univ.); Donald W. Landry, M.D., Ph.D. (Columbia Univ.); Karen Zier, Ph.D. (Mount Sinai School of Medicine); Paul B. Watkins, M.D. (Univ. of North Carolina at Chapel Hill); Daniel P. Schuster, M.D. (Washington Univ. in St. Louis); Michael J. McPhaul, M.D. (Univ. of Texas Southwestern); Debbie French, Ph.D. (Mount Sinai School of Medicine).

Not Pictured: Anil K. Rustgi, M.D. (Univ. of Pennsylvania); John N. Forrest, Jr., M.D. (Yale Univ.).
The third Doris Duke Clinical Scientist Meeting was held in Newport, Rhode Island, on November 9-12, 2002. The opening dinner, which was hosted by the DDCF President Joan Spero, featured a jazz performance by a talented group of young musicians from The Artists Collective, a grantee of the foundation's Arts Program.

Scientific sessions began on November 10 with a keynote address by the Medical Research Program's Scientific Advisory Council (SAC) Chair David G. Nathan, M.D., President Emeritus, Dana Farber Cancer Institute. Over the next three days, over 80 grantees presented their work in poster and platform sessions, which allowed attendees and guests to learn about the research being supported by the foundation. Scientific sessions were chaired by members of the SAC and Doris Duke Distinguished Clinical Scientist Award winners.

Special guests included Richard P. Lifton, M.D., Ph.D., Yale University School of Medicine, who presented his work on using human genetics to understand normal biology and disease pathogenesis. In addition, Allyn L. Mark, M.D., University of Iowa Carver College of Medicine, chaired a roundtable discussion of the Clinical Research Fellowship Program for medical students (see pages 8-9), and Alan R. Fleischman, M.D., New York Academy of Medicine, presented an overview of the DDCF-funded Consortium to Examine Clinical Research Ethics (see page 3).

Many participants took a break from the meeting to tour Rough Point, Doris Duke’s family mansion. ♦

Gottfried Schlaug, M.D. (pictured at right), a 2001 CSDA recipient from Beth Israel Deaconess Medical Center, discusses his poster presentation with Elaine Gallin, Ph.D., Program Director for Medical Research.

Doris Duke Clinical Scientists exchange ideas in Newport

650 Fifth Avenue 19th Floor New York, NY 10019

medical research program bulletin

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