Driving Cancer Research Forward Deep in the Heart of Texas

About a decade ago, John DiGiovanni was working as associate director of the Science Park–Research Division (SPRD) in rural Smithville, Texas, one of the world's foremost environmental science centers and a basic research arm of The University of Texas M.D. Anderson Cancer Center (UTMDACC). Around him, in research buildings clustered beneath sky-high pine trees, were dozens of multidisciplinary investigators making links between cancer and the human environment. DiGiovanni believed the Smithville program to be one of the most successful models of interdisciplinary research aimed at understanding the environmental causes of cancer and its prevention. "I couldn't name another program like ours in which so many people were focused, in a variety of investigative ways, on the environment and cancer development," says DiGiovanni. "Then I realized that we had naturally developed along the lines of an NIEHS center."

Backed by enthusiastic support from UTMDACC and The University of Texas (UT) at Austin, DiGiovanni and colleagues submitted a grant to the NIEHS to become one of what are now 22 Environmental Health Sciences Centers. In 1996, the Smithville Center for Research on Environmental Disease (CRED) was born with a five-year $2.5 million grant, and it was supported again in 2001 for another five years, at $1 million a year.

Outreach to action. The CRED Community Outreach and Education Program gets involved in helping citizens to understand the science behind local environmental health issues.

CRED is one of the few NIEHS centers that ties researchers from multiple institutions and campuses: SPRD in Smithville, the UTMDACC main campus, which is 130 miles to the southeast in Houston, and UT Austin, about 40 miles in the other direction. CRED is also perhaps the only NIEHS center almost completely devoted to the cancer–environment connection, says DiGiovanni, who today directs both CRED and SPRD. "We like to think of ourselves as the NIEHS center for research on environmental carcinogenesis and its prevention," he says. To create the substrate that can make such research possible, the center is divided into five research cores, seven facility cores (which provide tools to do research such as cell and tissue analysis and processing), and a very active outreach program.

The Hub of the Wheel

The link that CRED provides between three different research hubs allows scientists to choose from a complete menu of investigative efforts in which they wish to collaborate, and the researchers are encouraged to move between the cores to work with other investigators and to bridge the campuses with extensive use of interactive video conferencing. "The research cores are an improved method of fostering the kinds of interactions we have always had in hallways here," says CRED researcher Rodney Nairn, who is also a research core director.

Investigators can take an overview approach, starting with understanding cellular and molecular responses to environmental exposures, then the genetic basis for variability in these responses, and ending with population-based prevention studies. Or they might explore the reverse pathway, moving from an interesting human epidemiological finding to an animal model, then to basic genetic and protein work. Researchers might even select different parts of the investigative menu and work collaboratively together on some insight that has generated a novel and intriguing hypothesis.

"One of the really exciting things we are set up to do is to generate hypotheses from the outstanding epidemiology research done at the UTMDACC campus in Houston, then go to an animal model and try to prove the basic mechanisms," says DiGiovanni. "Or the preclinical chemoprevention strategies developed in animal models might then be translated back into human chemoprevention trials. So epidemiology feeds basic research and vice versa. That can ultimately lead to prevention models that help us identify high-risk individuals."

One broad example is the center's continuing work on the association between lung cancer and the p53 tumor suppressor gene. CRED investigators were the first to discover that benzo[*a*]pyrene, a carcinogen found in cigarette smoke, can cause mutations in the p53 gene and described in the 18 October 1996 issue of *Science* how that happens at the molecular level. In a study published in the 1 May 2002 *Journal of the National Cancer Institute*, they found that common polymorphisms of the p53 gene are associated with increased lung cancer risk. That work documented an association between ethnicity and high-susceptibility variants of the gene, with variant allele frequencies highest in African Americans (29.1%) and lowest in Mexican Americans (12.2%). These findings will now be explored in CRED's new mouse model of p53 variation. All of this work together may lead to prevention strategies aimed at those who are genetically more susceptible to lung cancer.

Different Spokes

The Mechanisms of Toxicity and Cell Death research core is largely staffed by UT Austin scientists and is headed by Jim Kehrer, a UT Austin professor of pharmacology and toxicology. It focuses on identification of the cellular and molecular mechanisms by which chemicals modulate programmed cell death, and the relationship between these effects and environment-induced diseases

Core researcher John Richburg of UT Austin is studying environmental causes of male infertility. Richburg's work is an example of research into how a toxicant—in this case, di(2-ethylhexyl) phthalate (DEHP), a common plasticizer easily recognized as the "new car" smell—can lead to cell death in testicular germ cells. DEHP is known to

Joe Rodriguez/CRED

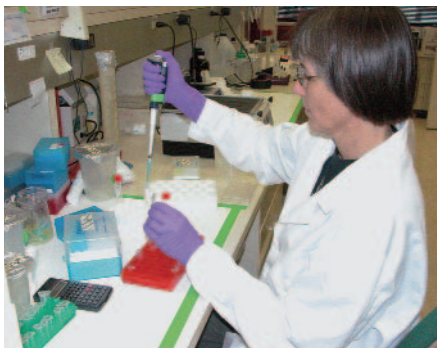
cause germ cell loss by damaging Sertoli cells in the testis. Sertoli cells help support germ cells, and so if Sertoli cells are not functioning properly, germ cell function suffers. The chemotherapy drug cisplatin is also thought to injure germ cells, but Richburg believes it may actually damage Sertoli cells, perhaps in the same way DEHP does. He is working out the molecular basis of that toxicity. While providing insights about cell death in general, the work furthermore describes how cisplatin leads to male infertility.

The Cellular Responses to DNA Damage research core has members from both SPRD and UTMDACC. These researchers seek to understand the relationship between formation and repair of DNA damage and carcinogenesis, with a particular focus on processes that occur soon after exposure.

Nairn's own research typifies the core's focus. He uses *Xiphophorus*, a family of colorful and popular aquarium fish that are genetically susceptible to melanoma, to understand the genes involved in the disease. Melanoma can form on areas of the human body that receive little sun exposure, and interspecies hybrids of these fish can develop melanoma either spontaneously or after exposure to UV radiation. Genetic analyses of melanoma-bearing fish have determined that there is a strong hereditary component in developing these tumors. Nairn has identified a *Xiphophorus* gene correlating to the p16 tumor suppressor gene in humans that seems to be associated with susceptibility to developing melanoma upon exposure to UV light. This work suggests a strong genetic component to melanoma, including several susceptibility genes and loss of a tumor supressor gene (which can occur through heredity or damage by sunlight).

"Next we'll examine whether the tumor suppressor gene is involved in other induced melanoma models that we've been studying," Nairn says. "Our hope is that this information will be particularly helpful for improved diagnosis as well as for prevention of melanoma with genetic testing."

Researchers in the Molecular Genetics and Environmental Carcinogenesis research core are primarily based at SPRD. They too use animal models to identify the genetic basis for variability in response to exposure to environmental carcinogens. For example, SPRD associate professor David Johnson, who directs the Comparative Mouse Genomics Center at CRED (one of five such centers in an NIEHS consortium), produced the first mouse model for natural variants of the human p53 gene. Another CRED investigator, Claudio Conti, has created a mouse model of variants of cyclin D1, a protein that regulates cell cycle proliferation. These variants can affect development of colon and breast cancers. The mice are born with germline mutations in certain genes, allowing researchers to study whether and how cancer develops, in contrast with other mouse models that are knockouts of specific mutations already known to cause cancer. "These unique mice will soon be made available to the [greater] scientific community," says Johnson.



The parts that make the whole. Three different research hubs allow investigators such as Rodney Nairn (above) and Judith Bergeron (below) to pursue individual research as well as benefit from scientific collaboration.

Susan Michaelson Roads/CRED

Core director Cheryl Walker, an SPRD professor, is using a rat model to determine if a link exists between environmental estrogen and cancer susceptibility genes. She is looking at uterine leiomyomas (benign fibroids), which affect up to 75% of women, and has found a three-day period very early in fetal development when a female rat is most sensitive to the environmental estrogen diethylstilbestrol. Walker theorizes that estrogen exposure during this sensitive period in fetal development reprograms uterine tissue, making it hyperresponsive to estrogen, which can then drive tumor development later in life.

Investigators in the Molecular Epidemiology and Ecogenetics research core are based primarily at UTMDACC and are focused on the study of gene–environment interactions in cancer etiology. Core director Melissa Bondy says that UTMDACC's strong program in population-based research is a plus for CRED, giving the researchers access to a wealth of patient data. "I think it is unique that the center is able to integrate a patient population into their studies of environmental carcinogenesis," she says.

For example, core investigators have linked organochlorine pesticide exposure to early-onset colorectal cancer through studies of Egyptians, who as a people have a high incidence of this disease. UTMDACC also maintains extensive tumor and tissue banks, with thousands of samples that are available to CRED faculty to validate theories developed in model systems, including animal models. "In this way, we are going from bench science to animals to human tissue models," Bondy says.

The Mechanisms of Disease Prevention research core has investigators from the SPRD and UTMDACC campuses whose research interests overlap somewhat with the other Smithville-based research core programs. Its director, SPRD professor Susan Fischer, is also a member of the Molecular Genetics and Environmental Carcinogenesis research core, and she is interested in the UV light work being done in the Cellular Responses to DNA Damage research core. Fischer has created a transgenic mouse model that overexpresses the enzyme cyclooxygenase-2, which synthesizes prostaglandins involved in inflammation and seems to play a role in basal and squamous cell skin cancers. The mouse develops many more skin tumors than wild-type mice when exposed to the carcinogenic combustion by-product dimethylbenzanthracene. Now Fischer is searching for which of four prostaglandin receptors on the skin mediates the tumor-promoting effect. "If you know which receptor that is, you may be able to make a drug that blocks that receptor," she says. She eventually hopes to turn to her colleagues to test whether such a drug, maybe in lotion form, could prevent cancer in sun-damaged skin.

Where the Rubber Meets the Road

The job of translating the work of CRED into public health actions falls to the center's Community Outreach and Education Program (COEP). The outreach program has an unusually high degree of faculty participation, with more than 95% of staff joining in, says COEP director Robin Fuchs-Young, who is herself a basic researcher in the Molecular Genetics and Environmental Carcinogenesis research

core. The faculty give talks to lay audiences of all ages, lead field experiences, visit schools, mentor undergraduates and high school students in their labs, and participate in the annual summer training institutes for kindergarten through 12th-grade (K–12) teachers. Through the COEP, faculty have been involved in environmental issues arising in Austin, such as investigating the possible contamination of a favorite swimming hole with parking lot sealant. The COEP put together a well-attended community forum that gave the scientists the opportunity to explain the actual risks from the suspected carcinogen. They said that a year's worth of exposure to the chemical from pool use was less risky than the health hazards of eating one super-sized hamburger, and so the pool was reopened.

The COEP is helping to design a new K–12 educational model that incorporates environmental health science into all aspects of the curriculum. A successful COEP-designed K–12 science curriculum, the Student Cancer Research Education Assessment Module, or SCREAM, already teaches about gene–environment interactions. The well-received program, first issued on a compact disc and now slated to go on the web in 2004, puts a good deal of scientific information (for example, about DNA, mutations, and genetics) in the context of gene–environment interactions and genetic susceptibility. Another project includes an online curriculum for 4th- through 8th-graders called I'm In Charge Of My Own Health (**http://www.veggie-mon.org/**), in which cartoon characters including Veggie Mon and Sunspot educate students about healthy lifestyle choices that reduce disease risk.

The COEP is working now on a first-of-its-kind program to help high school students and young adults think about the ethical, social, and legal ramifications of genomics. "Genomic technologies are going to generate a tremendous amount of information about disease susceptibility, and this module will be a proven way for students and young adults to begin thinking about the implications of this kind of research," says Fuchs-Young.

Says DiGiovanni, "The center provides a remarkable framework for very strong and productive collaboration between scientists, scientists and the COEP, and scientists and the public." Coordination around a central hub of research goals partnered with far-reaching collaborations and outreach allows CRED researchers to move steadily forward as they seek to improve understanding of the environmental components of cancer and communicate that knowledge to the public. **–Renée Twombly**

Headliners | Pregnancy Effects

NIEHS-Supported Research

Federal Emergency Management Agency

WTC and Low-Birthweight Babies

Berkowitz GS, Wolff MS, Janevic TM, Holzman IR, Yehuda R, Landrigan PJ. 2003. The World Trade Center disaster and intrauterine growth restriction. JAMA. 290:595–596.

Heavy smoking by pregnant women and exposure to extreme air pollution have been linked to intrauterine growth restriction, low birthweight, and preterm birth, all recognized risk factors for certain developmental problems later in life. The collapse of the World Trade Center (WTC) in New York City on 11 September 2001 released a plume of toxic chemicals including soot, benzene, polycyclic aromatic hydrocarbons (PAHs), heavy metals, pulverized glass and cement, and alkaline particulates into the surrounding air. To evaluate whether this pollution produced similar pregnancy and fetal effects, NIEHS-supported researchers at the Mt. Sinai School of Medicine and the Bronx Veterans Affairs Medical Center tracked pregnant women who were living near the WTC at the time of the collapse.

The team recruited 187 women who were pregnant and present in the area of the WTC at the time of the collapse on September 11 or during the 3 weeks following. For comparison, the researchers tracked 2,300 pregnant women from elsewhere in New York City who delivered babies at the same time and who were not known to have been in lower Manhattan on September 11. For both groups, researchers measured demographic characteristics, gestational age, birthweight, and the presence of intrauterine growth restriction (birthweight of less than 10th percentile for gestational age), preterm birth (less than 37 weeks), and low birthweight (less than 2,500 grams).

Of the few differences observed between the two groups, the most striking was that 8.2% of babies in the WTC group were in the lowest 10% of birthweight for gestational age, compared to only 3.8% in the control group. The authors assert that the study shows a strong effect even with a small number of participants. They speculate that the cause could be *in utero* exposure to particulate matter or PAHs. Possible long-term effects on the development of these children are unclear and will require continuous followup. **–Jerry Phelps**

PILGrimage to New York

For more than a decade, the NIEHS has strived to enhance community participation in the research-setting agenda. Under the leadership of Kenneth Olden, the institute has established a number of mechanisms by which representatives of community organizations with a variety of interests can voice their concerns, ideas, and recommendations for making environmental health research more responsive to community needs. One of these mechanisms is the Public Interest Liaison Group (PILG), which met 4–5 September 2003 with NIEHS leadership and the directors of five institute-funded research centers in and near the New York area to discuss ongoing studies and outreach efforts.

The PILG is composed of leaders representing 29 nongovernmental organizations that advocate for disease-specific interests or at-risk populations. These leaders meet with NIEHS staff and NIEHS-supported researchers to help develop a research agenda that is responsive to public constituents. As Olden said at the meeting, "The public wants to be included at the onset of research, and the researchers are also looking for the community's advice in setting priorities." The PILG provides a mechanism to achieve both.

An example of how public interest organizations have collaborated with the NIEHS on setting research agendas is represented by the work of breast cancer advocacy groups. Karen Joy Miller, founder and president of the Huntington Breast Cancer Action Coalition, and other members of the PILG and the breast cancer advocacy community were instrumental in providing input into planning the new NIEHS Breast Cancer and the Environment Research Centers to be opened around the country, and in requesting that the NIEHS include new Community Outreach and Translation Cores within these centers. "It is a real sign that NIEHS truly listens," said Miller.

The September meeting included the directors and many research staff of five NIEHS-funded environmental health sciences and children's environmental health centers. Represented were the Mount Sinai School of Medicine, New York University, Columbia University, the University of Medicine and Dentistry of New Jersey, and The Johns Hopkins University.

The center directors and staff presented highlights of the research being conducted at their institutions that contributes to the state of the knowledge of how environmental factors may affect a variety of diseases and effects. For example, Regina Santella, director of the Center for Environmental Health in Northern Manhattan at Columbia University, relayed information on a new study using meconium as a biomarker of fetal exposure to pesticides. George Lambert, a researcher at the Environmental and Occupational Health Sciences Institute at the University of Medicine and Dentistry of New Jersey–Robert Wood Johnson Medical School, described a program in its second year of funding to examine new evidence linking an increasing incidence of autism with environmental factors such as exposure to lead, methylmercury, and ethanol. Members of the PILG had the opportunity to discuss these research findings with the center directors and NIEHS staff, and to make recommendations on current and future research directions. "Priority setting is what this event is about," said Olden.

Members of the PILG with expertise in autoimmune and respiratory disease presented the work that their organizations are doing in advancing research and advocacy. Several of the presenters focused on supporting research through new funding mechanisms, including partnering and collaborating with the NIEHS.

Other presenters focused on communication to the public and translation of research results. Patricia Green, director of development for the Allergy & Asthma Network Mothers of Asthmatics, presented her organization's efforts to bring disease management tools to asthmatic children through innovative web-based educational programs. One of these is Breatherville, USA, a website located at **http://www.breatherville.com/breatherville.htm** where parents and children can find tips for managing child asthma and allergies, including advice on coexisting with pets, reducing allergens at home, and dealing with classmates and teachers who may not know about asthma. In another outreach initiative, Allen Dearry, director of the NIEHS Division of Research Coordination, Planning, and Translation, announced the development of an interagency meeting that will collect the expertise of the scientific and advocacy communities to devise best practices for asthma interventions, research, and prevention.

Closing the meeting, New York senator Hillary Rodham Clinton spoke of her support of the work that the NIEHS has done in making sure that research outcomes are responsive to public concerns. She remarked that the PILG members are "people who have taken their own personal experience of disease and translated it into action on behalf of a better environment." **–Luz Claudio**

Public Interest Liaison Group Member Organizations




- Allergy & Asthma Network Mothers of Asthmatics
- Alliance for Healthy Homes
- The ALS Association
- Alzheimer's Association
- American Autoimmune Related Diseases Association
- American Lung Association
- American Osteopathic Association
- Association of Women's Health, Obstetric and Neonatal Nurses
- Asthma and Allergy Foundation of America
- Barbara Balaban (Long Island, New York, breast cancer advocate)
- Birth Defects Research for Children
- Children's Environmental Health Network
- Children's Health Environmental Coalition
- Communities for a Better Environment
- Cure Autism Now Foundation
- DES Action USA
- Environmental Defense
- Greater Phoenix Chapter, Autism Society of America
- Huntington Breast Cancer Action Coalition
- Learning Disabilities Association of America
- Lupus Foundation of America
- National Breast Cancer Coalition
- National Center for Environmental Health Strategies
- National Prostate Cancer Coalition
- National Uterine Fibroids Foundation
- Parkinson's Action Network
- Platelet Disorder Support Association
- Society for Women's Health Research
- World Wildlife Fund

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