Synergy

Volume 3

2009 Research Annual Report

University of North Texas Health Science Center at Fort Worth

Welcome

Welcome to the third edition of the University of North Texas Health Science Center's annual research publication, *Synergy*. In 2008, the Health Science Center continued to expand and develop critical research programs that will lead to new treatments and therapeutics for a number of diseases and disorders. We recruited highly regarded scientists across the institution to join an already excellent group of faculty. The innovation and dedication of our scientists, combined with President Ransom's commitment to research, continue to lead to exciting new discoveries and have once again resulted in a record level of research awards.

In this issue of *Synergy*, we will introduce you to some of our new scientists and highlight the exceptional work of many experts who have been working diligently in the labs on a variety of biomedical research issues.

This year, our faculty collaborated with community partners to submit an application to the Centers for Disease Control and Prevention. This proposal to develop the North Texas Prevention Research Center should reduce and eventually eliminate health disparities in the diverse North Texas region. Involving the community in research is a high priority. See the story on page 8 for an example of how one of our new public health faculty members engages the community to solve problems at the grass-roots level.

We have initiated an exciting partnership with Cook Children's Health Care System that will increase our research efforts in a number of areas. We are particularly excited about enhancing translational research efforts for developing novel treatments of childhood cancer. In addition, the research of recently recruited senior scientists into our Physical Medicine Institute should lead to improvements in rehabilitation for those with injuries and disabilities.

We continue to build our excellent teams that are working to solve issues in the areas of infectious disease, vision, cardiovascular disease and nanophotonics. In addition, the new Brain Bank will help our world-renowned scientists focus on issues associated with aging and Alzheimer's disease, and rapidly translate discoveries made at the bench to clinical interventions.

This year, we also debuted our School of Health Professions via addition of a new degree program in physical therapy. Faculty recruited into this program will conduct research with members of the Physical Medicine Institute and the national Osteopathic Research Center, which is housed here at the Health Science Center. We look forward to their important research contributions.

Work in other areas continues to have an enormous impact. Our Institute for Human Identification (formerly the Center for Human Identification) continues to identify the remains of lost loved ones on both a national and international scale. These internationally recognized professionals continue to research improved methods of identification, so that this critical work can proceed even more efficiently.

The Health Science Center continues to support the fundamental discoveries of our researchers and maximize the possibility that discoveries made in the laboratory are translated into therapeutics and treatments for many diseases and injuries. For example, through our partnership with the local business incubator Tech Fort Worth, we launched the Acceleration Lab in March of 2008. The Acceleration Lab, located at the Center for BioHealth on our campus, is a commercial initiative that supports biotechnology-based companies. Companies that are accepted into the Acceleration Lab receive assistance with business development and access to state-of-the-art laboratory facilities.

This year was filled with new scientific discoveries at the UNT Health Science Center, and our scientists will continue to solve important clinical problems in 2009. New large-scale research programs and partnerships are being developed, and we look forward to sharing with you results from those and other efforts in next year's edition of *Synergy*.

Glenn H. Dillon, Ph.D.
Vice President for Research
gdillon@hsc.unt.edu

Inside

Cover Photo: *Trabecular meshwork glaucoma cells, which are involved in the build-up of pressue in the eyes of glaucoma patients.*

Welcome *to the third annual research report for the University of North Texas Health Science Center. Research is an integral part of the institution's mission, intimately associated with student training and our commitment to the advancement of knowledge. Our scientists lead cutting-edge research, analysis and treatment of diseases, and propel our discoveries from the bench to the bedside for the betterment of all people.*

Staff

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UNT Health Science Center Research Office

Vice President for Research
Glenn Dillon

Marketing & Communications
Vice President of Marketing & Communications
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Photographers
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Steel Shutter Photography

Writers
Dana Benton Russell, ABC
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Carl Bluemel
Fish & Mojo

Production Coordinator
Amy Buresh

Peering Into A Future Free from Glaucoma

Abe Clark's vision of the future is one in which the causes of glaucoma have been identified and treatments developed, thus saving the sight of thousands of people each year. Clark, who has a PhD in cell and molecular biology, joined the Health Science Center in April and recently was named head of the North Texas Eye Research Institute. The goals of this institute are to develop innovative vision research collaborations within the university, educate future visual science researchers (i.e., graduate students and post-doctoral fellows) and develop community outreach programs to address common ocular diseases.

Clark is leading a research team to better understand the molecular and cellular causes of ocular diseases, particularly glaucoma.

"Glaucoma is a leading cause of visual impairment and blindness in the world, affecting more than 60 million individuals worldwide," Clark explained. "My laboratory is using a wide variety of techniques to discover new pathogenic pathways that will lead to the development of novel disease-modifying therapies for the treatment of glaucoma."

Glaucoma is a group of eye diseases that gradually steal sight without warning. Vision loss is caused by damage to the optic nerve, which acts like an electric cable with more than one million wires. This nerve, located in the back of the eye, is responsible for carrying images from the eye to the brain. In many cases, the nerve damage is caused by increased intraocular pressure (IOP) in the eye due to a build-up of fluid. In glaucoma, there is poor drainage of the fluid from the eye. In addition to elevated IOP, other factors contribute to the development and progression of glaucoma. In fact, physicians don't know why some people suffer from the vision-threatening condition. And that's what motivates Clark and his team to unlock the secrets behind the causes of the disease so that appropriate, effective treatments can be developed.

"Current glaucoma therapy only indirectly treats a symptom of the disease — elevated intraocular pressure," Clark said. "New disease-modifying therapies hold the promise of directly intervening in the disease process and the possibility of reversing the disease process and restoring normal function."

Since joining the Health Science Center, Clark has been busy setting up his research lab and assembling his team of researchers. Working alongside Clark in the lab are post-doctoral fellow Weiming Mao, PhD, research associate in Cell Biology and Genetics, and graduate students Anirudh Sethi, Ashley Fitzgerald and Ankur Jain. In addition, Clark is collaborating on additional studies with fellow campus researchers Robert Wordinger, PhD, chairman of the Department of Cell Biology and Genetics, and Thomas Yorio, PhD, provost of the university and professor of Pharmacology and Neuroscience, on additional studies.

Prior to joining the Health Science Center, Clark was vice president of discovery research and head of glaucoma research at Alcon Laboratories in Fort Worth. While at Alcon, he served as adjunct professor in the Health Science Center's Departments of Cell Biology and Genetics, and Pharmacology and Neuroscience.

"I decided to become a researcher because I have always been interested in science and always had a driving curiosity about how nature works," Clark explained. "I became interested in ocular diseases when I joined Alcon Laboratories 24 years ago, and I have been working in the eye research field ever since. A major motivating factor for continuing to work in this particular research area is that our scientific discoveries can be directly applied to helping people with vision-threatening diseases like glaucoma."

Much of Clark's early work in his Health Science Center lab focused on generating and characterizing new ocular cell lines and setting up an ex vivo ocular perfusion culture model. This model, Clark explained, is unusual but a highly useful technique that will serve as a major research tool in his lab. The technique involves removing the front part of donated human eyes or cow eyes and placing them in specially engineered culture dishes. These cultures are perfused with a fluid to provide nutrients that allow the cells and tissues to survive in culture. The research team can moni-

Drs. Abe Clark, Robert Wordinger and Thomas Yorio focus on research to cure glaucoma and other diseases of the eye.

tor the effects of various agents on IOP using this model. This model has been valuable in helping to prove that the molecular mechanisms that Clark's team discovered in cultured glaucoma cells actually have a functional effect that mimics an important feature of glaucoma — elevated IOP.

Clark's research also focuses on studying trabecular meshwork (TM), tiny tissue located at the front part of the eye at the junction between the cornea (the clear outer coating of the front of the eye) and the iris (the colored tissue that forms the pupil of the eye). The TM is involved in draining the clear fluid in the front of the eye. In glaucoma, this drain becomes clogged, leading to a build-up of pressure in the eye that results in the loss of vision and blindness associated with glaucoma.

"We have been able to culture TM cells from TM tissue carefully dissected from normal human donor eyes, as well as from donor eyes with glaucoma," Clark said. "Dr. Mao has established a cell-based assay in TM cells to study the Wnt signaling pathway, which we recently discovered is involved in glaucomatous IOP elevation. "

Clark's research also includes studying the optic nerve and retina, two additional tissues involved in glaucomatous damage.

Clark's association with Wordinger spans more than 12 years of studying the roles of growth factors in glaucomatous damage to the TM and optic nerve head.

"Dr. Clark and I work closely on the mechanisms leading to glaucoma," Wordinger said. "My research group is interested in the role of growth factors and growth factor receptors in glaucoma. We examine human cells isolated from the TM and optic nerve head. We are especially interested in the role of transforming growth factor beta 2 since this is elevated in the aqueous humor on the optic nerve head of glaucoma patients. Dr. Clark is a collaborator on my NIH grant, and he and I have published more than 25 peer-reviewed manuscripts, articles and book chapters together. Uniquely, we share research laboratories as well as graduate students and post-doctoral fellows. We have joint lab meetings and have integrated our research collaborations and efforts."

The collaboration between Clark and Yorio includes eight peer-reviewed manuscripts, as well as co-editing a book on ocular therapeutics. They also are co-principal investigators on a grant to explore the mechanisms responsible for the increase in IOP that occurs in some patients following the topical application of glucocorticoids.

"This increase in IOP occurs in 95 percent of glaucoma patients but only one-third of the normal population," Yorio said. "Our work is trying to understand why this happens. We have identified a receptor that appears to be associated with this phenomenon and have shown that when this receptor is lacking in ocular cells from glaucoma patients, there is an elevated response to glucocorticoids that may explain the increase in IOP that is seen in these patients."

Yorio is internationally recognized for his glaucoma research over the past 30 years and is involved in additional studies looking at cellular mechanisms that may be responsible for the optic nerve damage seen in glaucoma patients.

Several grants are funding the research being performed by Clark, Wordinger and Yorio, including the National Institutes of Health (NIH), National Eye Institute (NEI), the Texas Higher Education Coordinating Board's Advanced Research Program and Alcon Laboratories. In addition, Clark has just received a grant from Alcon Laboratories to examine the molecular mechanism of a new drug that is being tested clinically in glaucoma patients for intraocular pressure-lowering activity. ■

Dr. Abe Clark joined the Health Science Center in 2008.

In the News

From Popular Science *to the* Wall Street Journal, *UNTHSC researchers were featured prominently in the news in 2008.*

Dr. Rhonda Roby, who earned her PhD from Spain's University of Granada in September, was featured in a front-page article in the *Dallas Morning News* this summer. Reporter David Tarrant explained the role that Roby and the Health Science Center's Center for Human Identification (now the Institute for Human Identification) is playing in identifying victims of Augusto Pinochet's Chilean coup, which occurred in 1973. Thousands of Chileans went missing and at least 30,000 were tortured. Now, the government wants to verify the identities of many victims who were buried in graves marked "N.N." for "no name."

In April, Roby became the first woman inducted into Oklahoma's Wall of Fame for the Putnam City Foundation, whose mission is to enhance and enrich educational opportunities in Putnam City Schools. In addition, she was a keynote speaker for the Association of Women in Science and guest lecturer for the Dallas Regional Chamber of Commerce's Distinguished Women luncheon.

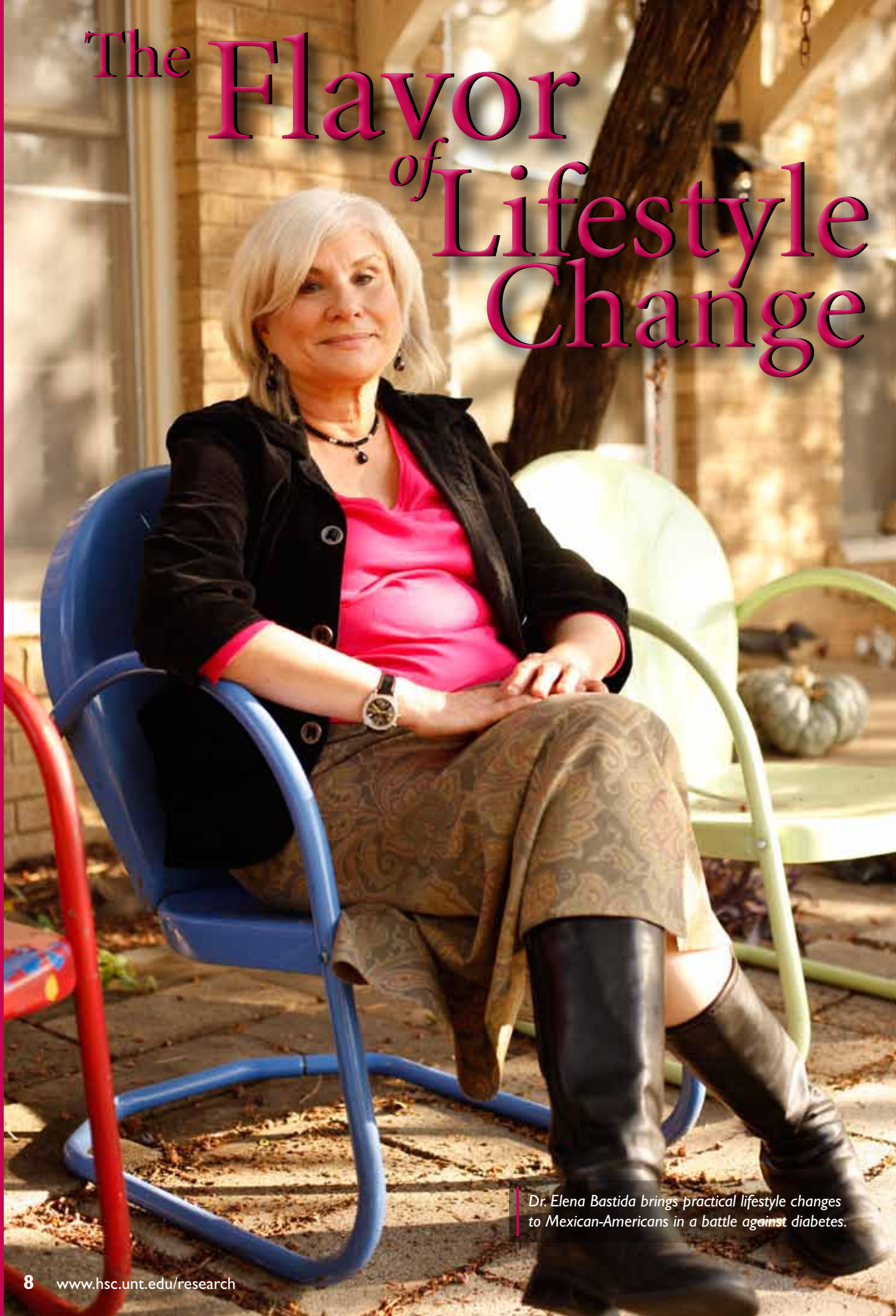
"This is my exciting year," Roby said.

With the economic disaster sweeping the country, **Harvey Brenner**, PhD, professor of social and behavioral sciences, was in demand from the top news publications across the country to comment on the physical and emotional stress and damage caused by the economic woes. *The Wall Street Journal*, *Newsweek*, *The New York Times*, Reuters and others ran articles quoting Brenner, who said that historically during recessions, with declines in national income and increases in unemployment, "you often see increases in mortality from heart disease, cancer, psychiatric illnesses and other conditions."

Three decades of research have shown a correlation between the condition of the economy and human health, including life expectancy.

With no end to the economic recession in sight, Brenner's expertise and knowledge likely will continue to be in high demand as the country learns how to cope with the reality and health issues associated with the economic downturn. ■

The Flavor of Lifestyle Change



Dr. Elena Bastida brings practical lifestyle changes to Mexican-Americans in a battle against diabetes.

Flavor – it's the cornerstone and distinguishing characteristic of international cuisine, and integral to Mexican-American culture. However, few people would picture it as fitting into a healthy lifestyle.

In her recent epidemiologic studies, Elena Bastida, PhD, associate dean of research and professor of Social and Behavioral Sciences, noticed that populations of Mexican-Americans along the Texas-Mexico border presented high numbers of members with diabetes. She knew that there must be a way to incorporate the tastes and textures of Mexican-American food and the unique Mexican-American lifestyle into a program to lower the incidence of diabetes.

"One in four women 45 and older and one in five men in that age group had Type 2, or adult-onset, diabetes," Bastida said. "I asked myself, 'How do I bring about some changes?' That's how Sabor started. In Spanish it means 'flavor,' and it is an educational program that works well with the Latino culture — with what our people are already doing. It responds to entrenched cultural habits and behaviors."

Community members meet once a week with nurses, nutritionists, exercise experts and others to learn not only what to eat but how to incorporate dietary and physical activity changes into their existing lifestyles. The group shares recipes and dietary concerns, then participates in group exercises. But the program adds a unique twist — the members of the community classes choose what they learn, the recipes that they try, and even the types of exercises that they perform.

"Sabor teaches our participants how to prepare foods with the same flavor — that taste good — with less oil and fewer carbohydrates," Dr. Bastida said. "We work with nutritionists on the other side of the border to discover how best to keep cultural traditions intact, but make them healthier. And we ask the participants what they want to learn and know. If they tell us what they want to learn, they will be more involved."

Members choose everything from guided field walks and traditional slow-paced aerobics to ballroom and salsa dancing.

Participants of Sabor's pilot program were so enthusiastic about continuing their community-based education that they encouraged local leaders to pursue a new, $2.35 million grant from the National Institutes of Health that will continue the program, expanding it from 120 participants to 1,300. In fact, members of the pilot program wrote to Bastida, asking her to bring the program back to their neighborhoods when the project ended.

"First we would all like to start by giving you guys thanks for this awesome project brought to our neighborhood," wrote a group of participants from Sanchez Ranch, located in the town of Hidalgo, Texas, near the Mexico border. "Within this 10 weeks, we've learned a great amount of knowledge with all the themes brought to us. We are very interested that you guys keep us in mind in the future for upcoming projects. As a community, we feel like prolonging our aerobics classes as well as our healthy meal dieting."

The classes begin with an orientation session that includes assessments of participants' glucose and cholesterol levels, pulse, blood pressure, upper arm skin-fold measurement, waist-to-hip circumference and nutrition. Those measurements are repeated at 12 and 36 weeks to determine class effectiveness.

The program works to expose participants to every aspect of healthy eating, including shopping trips, during which they learn which ingredients to buy and how to check nutritional values of foods. The trip concludes with a meal at a local restaurant.

"We developed this program so that participants not only learn skills, but also build a foundation of social support," Bastida said. "Also we do not talk in abstracts like 'saturated fats,' and we keep the lectures short."

Add to this the close-knit communities that Sabor fosters in the neighborhoods in which the program has been introduced, and the project seems to be a success.

"We've noticed a great amount of changes within ourselves and our families," wrote the Sanchez Ranch group. "Just … to be able to spend quality time with our friends and family every Tuesday has made us more social and conscious about every person's need. The meetings themselves taught us a great amount about sicknesses that now we can prevent in the future." ■

"It's about the kids."

— Dr. Paul Bowman

New Partnership Means Hope for Kids with Cancer

In June, Paul Bowman, MD, senior pediatric hematologist/oncologist and chairman of the Leukemia and Lymphoma Program at Cook Children's Medical Center, was named department chair of Pediatrics, bringing his expertise in pediatric oncology to the UNT Health Science Center.

This exciting new collaboration between the exemplary care provided by Cook Children's Medical Center and the state-of-the-art research capabilities of the Health Science Center extends the depth of care and research that both entities provide, especially in Bowman's area of expertise, pediatric leukemia and neuroblastoma.

"This partnership will allow the pediatric oncologists at Cook Children's to use new drug and therapy discoveries immediately," Bowman said. "We already are working with leaders in molecular biology and immunology at the Health Science Center to identify opportunities for collaboration in pediatric cancer research (*see story on page 12*). A major initiative will be enhancing the understanding and treatment of children with high-risk neuroblastoma."

Currently, Cook Children's sees cancer patients in towns as far away as Midland and Odessa. In fact, the pediatric specialists treat children in 40 percent of the state. As the largest non-university pediatric center in the country, Cook Children's has a long history of leadership in the fields of oncology and hematology. Teaming up with the Health Science Center's new Institute for Cancer and Blood Disorders and its novel research on lipoproteins and the signaling protein RLIP 76, allows physicians access to innovative new treatments and helps researchers bring their solutions directly to the patients who need it — now.

"The partnership with the Health Science Center strengthens our academic credibility through research and helps us recruit top-level NIH (National Institutes of Health) researchers to work here," Bowman said.

"The timing is right," he continued. "With new leadership at both Cook Children's and the Health Science Center, the region's top pediatric hospital can collaborate with the Health Science Center's nationally recognized research capabilities to treat children here in Fort Worth and in many of the towns throughout West Texas. This partnership also enables us to develop graduate training that pairs research and clinical care."

The partnership has been formed in the right place at the right time to be a powerful influence on the health care of Texas children now and in the future.

"Long-term studies are needed," Bowman said. "We like to think that patients may emerge from treatments unscathed 25 years later, but that's often not the case. At this point, the goal is long-term remission with a minimum of recurrence. We now have an 80 percent survival rate, although many patients carry some baggage with them from the treatments."

The researchers hope to learn more about the causes of childhood leukemia; predictive, genetic and environmental factors that could influence childhood cancer; diagnostic and monitoring tests; and improved therapies. ■

Dr. Paul Bowman works with Emerson Espanet at Cook Children's Medical Center as she fights against the cancer that has invaded her system.

Fernando Franco and Daniel Johnson, shown here with Amy Bayles, CPNP , are two of Bowman's cancer patients at at Cook Children's Medical Center.

Researching ethnic Differences in Childhood Leukemia

Why are Hispanics more likely than other ethnic groups to get childhood leukemia? And why are African Americans, who typically experience a higher incidence of other cancers, the least likely to experience childhood leukemia?

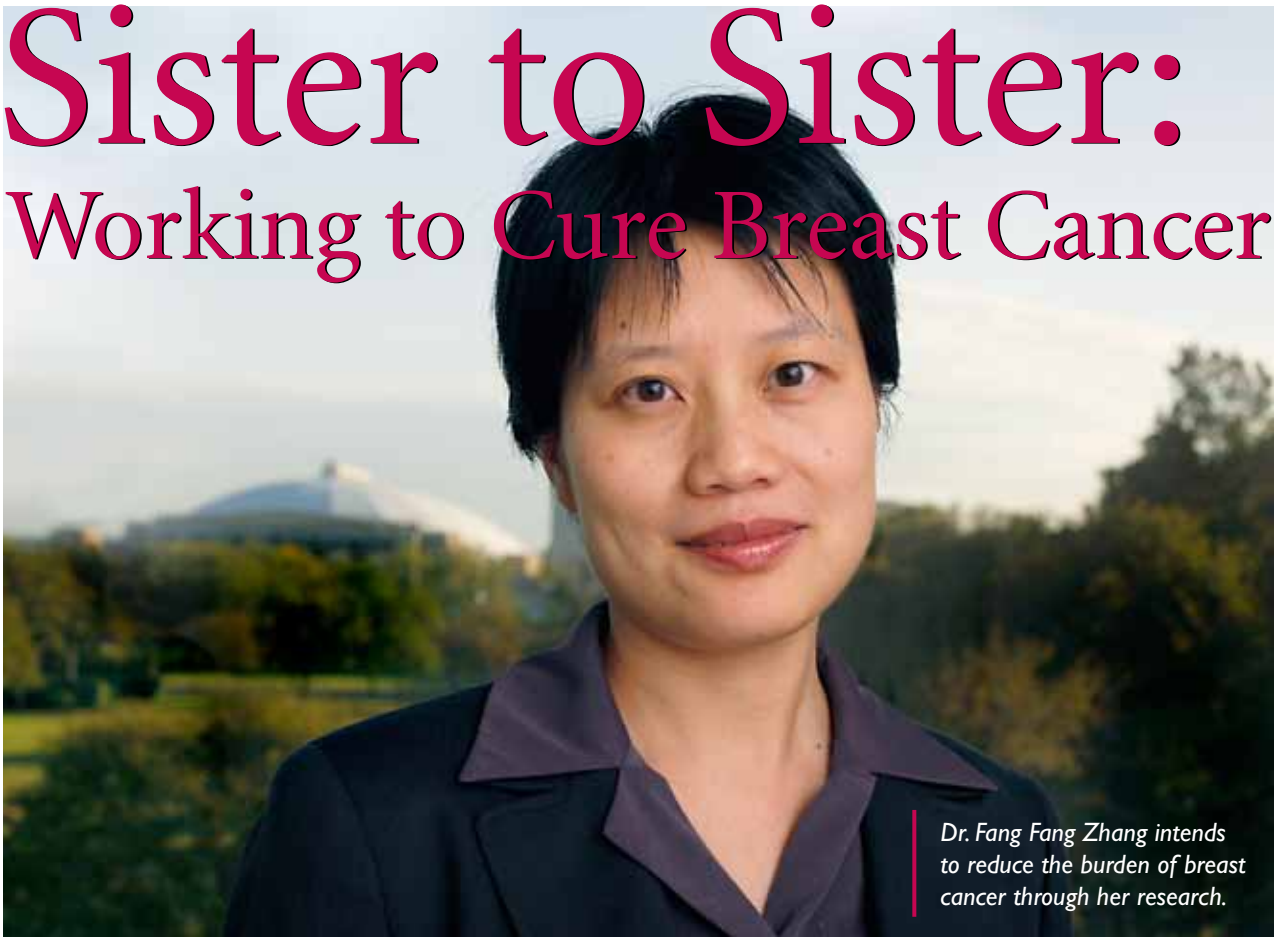
Finding answers to these intriguing questions is the goal of new research by Paul Bowman, MD, chairman and professor of Pediatrics, and the Health Science Center's Stephen Mathew, PhD, research assistant professor of Molecular Biology and Immunology; Fang Fang Zhang, PhD, assistant professor of Epidemiology; John Fling, MD, associate professor of Pediatrics; and Porunelloor Mathew, PhD, associate professor of Molecular Biology and Immunology.

These doctors and researchers are pooling their knowledge to determine if alterations in immune receptors enable cancer to escape, and if short-term environmental or chemical changes can "turn off" tumor suppressor genes. Could this explain the cause of disparities in childhood leukemia among different ethnic groups?

"Natural killer (NK) cells that are part of our white blood cells are the first line of defense against invaders such as viruses and tumors," Stephen Mathew explained. "In order for cancer to grow, it has to escape the first defense. These NK cells produce powerful chemical substances that bind to and kill tumor or virally infected cells. NK cells need signals from receptors on their cell surface to activate. We want to know how these signals are turned on. Is there an environmental, genetic or chemical trait in some people that influences the cell's ability to turn on or off?"

The collaborative effort will meld the clinical care and pediatric experience of Bowman and Fling with the scientists' insight and research expertise. By using the multidisciplinary brain power at the UNT Health Science Center, the team hopes to determine new treatment options that may improve the outcome for children with leukemia. ■

Sister to Sister:
Working to Cure Breast Cancer



Dr. Fang Fang Zhang intends to reduce the burden of breast cancer through her research.

Cancer is a puzzling and complicated illness, but at the UNT Health Science Center several researchers are working to better understand the mechanisms of various cancers and develop new treatments. Among them is Assistant Professor of Epidemiology Fang Fang Zhang, MD, PhD, who has received a grant of $243,202 from the Susan G. Komen Foundation for research on breast cancer. Zhang will use data collected from the Breast Cancer Family Registry, a NCI-sponsored international breast cancer registry, to determine if an integrated effect of diet, physical activity and body composition has an effect on breast cancer.

"Animal studies consistently show that energy restriction — usually a reduction in calorie intake — is associated with a reduced risk of cancer. However, such an association was not evident in human studies," Zhang explained. "We know that energy intake can be strictly controlled in animal studies whereas humans eat a variety of different foods. Moreover, it might be the balance between energy intake and energy output that determines the cancer risk, rather than energy intake alone."

Using the Breast Cancer Family Registry, Zhang will evaluate the association between energy balance and breast cancer risk in both population-based breast cancer cases and controls, as well as in pairs of sisters, one of whom had breast cancer and the other whom did not. She hopes to find behavior modifications and risk factors that can effectively reduce breast cancer risk in the general population and in high-risk families.

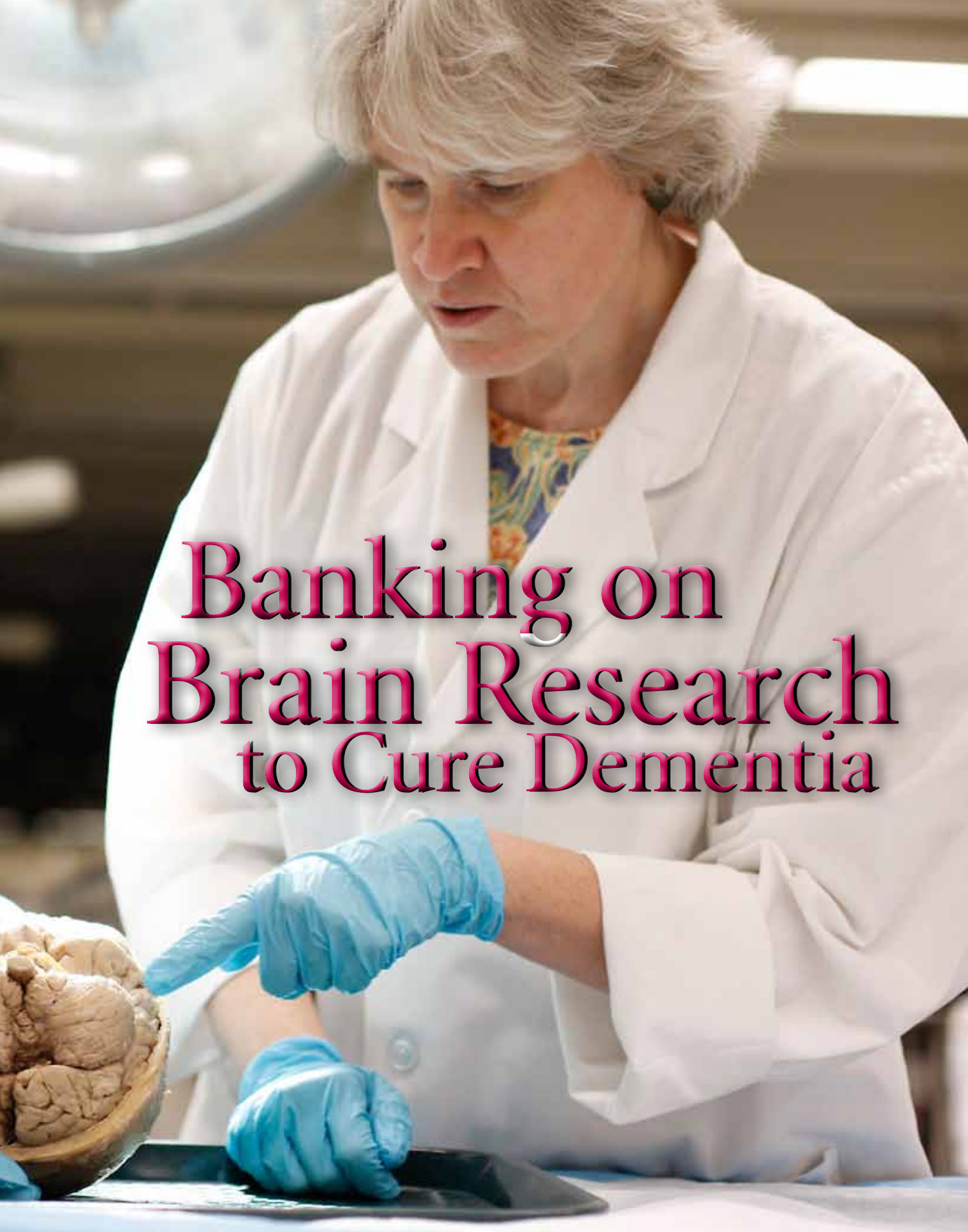
Her grant is part of the largest commitment of breast cancer research funding by a single nonprofit organization. The funding is targeted to 81 universities and hospitals in 27 states and five countries. These grants represent research with the highest likelihood of producing results for patients during the next decade.

"There's a tremendous urgency to translate what we're learning in the lab into treatments for patients, particularly patients with very aggressive cancers who don't have years to wait," said Dr. Eric P. Winer, chief scientific advisor to Susan G. Komen for the Cure and director of the Breast Oncology Center at Dana-Farber Cancer Institute.

"We've revamped Komen's research program, challenging the best minds to solve the most difficult issues in breast cancer," said Hala Moddelmog, president and CEO of Susan G. Komen for the Cure. "These grants are geared to results — finding cures, tailoring treatments and resolving the issues that have stymied the search for a breast cancer cure."

"Breast cancer is the most common cancer in women, excluding non-melanoma skin cancer," Zhang said. "I want to help reduce this health burden for women." ■

Drs. Anuja Ghorpade and Rosalie Uht further research on Alzheimer's and other diseases by establishing North Texas' first immediate autopsy brain bank.



Banking on Brain Research to Cure Dementia

Alzheimer's disease. HIV-related dementia. Parkinson's disease. These are some of the most feared and most researched afflictions in the world. Many top researchers have studied patients who suffer from one of these neurodegenerative disorders and tested various treatments and preventive practices in lab animals.

However, primates are the only animals who appear to suffer from these neurodegenerative diseases, and it's difficult to study human brains.

"Although animal models are available to study dementing illnesses, there are limitations," said Anuja Ghorpade, PhD, vice chairman and professor of cell biology and genetics and co-director of the Brain Bank at the Health Science Center. "In the simplest of terms, a mouse is not a human. Thus, to determine the features of human dementia, the study of human brains is of great importance. Comparing human brain tissue donated by patients with dementia to those of non-demented individuals is the only way that the molecular basis of these devastating illnesses can be understood."

To address the need for more studies of the human brain, the UNT Health Science Center has brought two leading researchers, Ghorpade and Rosalie Uht, MD, PhD, on board to join Janice Knebl, DO, distinguished chair of Clinical Geriatrics and professor in Geriatrics, and James Simpkins, PhD, chairman of Pharmacology and Neuroscience and director of the Institute for Aging and Alzheimer's Disease Research. These top researchers are working to establish a program that will allow people to donate their brains to research at the UNT Health Science Center after they die. There will be no costs or compensation for donating, except the satisfaction of knowing that one could be contributing to the understanding and treatment of these diseases in the future.

Deciding to donate one's body can be a very simple or a very complicated decision. The brain is included as part of a general autopsy, unless specified otherwise. Conversely, an autopsy may be restricted to the brain only. In either case, specific paperwork must be filed by the individual or family prior to or immediately following death. And time is of the essence in retrieving brain tissue.

When a body is "donated to science," it is preserved by various processes. These processes often destroy the key aspects of the brain that need to be studied. In order to preserve the brain, it must be retrieved quickly and prepared for analysis. That's where Uht, a board-certified neuropathologist and associate professor in the Pharmacology and Neuroscience department, comes in. With the help of Kathleen Borgmann, the Brain Bank manager, who will be on call 24/7 to accept donation calls, Uht will ensure appropriate brain tissue recovery and processing. This around-the-clock coverage will permit collection of high-quality tissue through established processes in compliance with state and federal guidelines at several local hospitals.

In the case of HIV-related dementia, neurons and microglia will be analyzed by Ghorpade and her team. In the case of Alzheimer's disease or normal-aged patients, tissue will be available to members of the Institute of Aging and Alzheimer's Disease Research, one of the Health Institutes of Texas being spearheaded by the UNT Health Science Center.

Tissue from patients known to have exhibited symptoms of dementia from HIV, Alzheimer's or other neurodegenerative processes, as well as tissue from symptom-free individuals, will be needed for analysis. A unique contribution of this Brain Bank will be the systematic acquisition of brains from age-matched individuals. Without the ability to compare brains from demented to non-demented people, the pathogenesis of dementing illnesses will never be truly understood.

Individuals who enroll as Brain Bank donors will provide updated information regarding hospitalization records, any brain-related medical history or infections. These data and health histories will be used to help diagnose the ailments and piece together the research puzzle.

When tissue is collected quickly, viable cells can be studied in the laboratory, which provides a unique view of pathogenic processes that cannot be obtained in any other way.

Ghorpade and Uht came to the UNT Health Science Center this year to establish the Brain Bank. Ghorpade brings 10 years' experience in HIV-1 research and successfully established a similar program at the University of Nebraska Medical Center. Uht brings with her training in neuropathology obtained at the University of California-San Francisco and experience as an autopsy pathologist at the University of Virginia at Charlottesville.

Together, Ghorpade and Uht are a dynamic duo, and in the pioneering spirit of Texas, they hope to help blaze a trail to the cure of these devastating illnesses. ■

Where Are They Now?

Michael J. Cutler

Preventing sudden cardiac death

As a cardiology fellow in the prestigious Physician Scientist Pathway (PSP) program at the Heart & Vascular Research Center at Case Western Reserve University in Cleveland, Ohio, Michael Cutler, who earned DO and PhD degrees from the Health Science Center in 2004, spends most of his time in the research lab of David S. Rosenbaum, MD, an international expert in T wave alternans, studying the molecular mechanism of sudden cardiac death (fatal ventricular arrhythmias) in heart failure.

The PSP program is designed specifically to train physician-scientists and future leaders in academic medicine. The curriculum includes three years of dedicated mentored research, preceded by two years of internal medicine residency, and followed by two years of clinical cardiology training. Cutler is in the fifth year of the program and feels honored to have been chosen because only one or two applicants are selected each year from a pool of more than 1,000.

"Sudden cardiac death is the most devastating manifestation of heart failure, yet the mechanisms that lead to fatal heart arrhythmias in some patients, but not others, is not known," Cutler said. "Currently, the most common treatment for the prevention of fatal arrhythmias in patients with heart failure is the implantable cardioverter defibrillator. While quite effective at terminating a dangerous arrhythmia, this approach does nothing to treat the underlying cause of the arrhythmia.

"A subtle beat-to-beat fluctuation in a component (T wave) of the electrocardiogram may be one cause of dangerous arrhythmias. I hope to identify the causes of this phenomenon, which is known as T wave alternans."

Cutler's application of research to patients suffering from heart disease is significant. By studying and better understanding the molecular causes of dangerous arrhythmias, researchers will be able to identify targets for the development of therapies that can prevent sudden cardiac death, not by terminating the arrhythmias, but by treating the underlying cause.

"Recently, we demonstrated in an animal model that one of the heart's calcium-handling proteins (SERCA2a) is involved in the development of T wave alternans," Cutler explained. "Targeted gene therapy to increase the amount of SERCA2a in the heart improved T wave alternans and made the heart resistant to fatal heart arrhythmias. These findings prove the concept for a novel therapy that could prevent sudden cardiac death. The effectiveness of this therapy in humans will be determined by future clinical trials."

Cutler credits the experience of working with fellow researchers in the laboratory of Michael Smith, PhD, chair and professor of Integrative Physiology, during his time at the Health Science Center with helping him achieve his career objectives in cardiac electrophysiology and heart failure.

"My interactions with these individuals made me a better scientist, clinician and, hopefully, person," Cutler said. "I have always viewed being a graduate of UNTHSC's Medical Scientist Training Program as a great honor. The medical and scientific training I received at the Health Science Center was world class and prepared me to successfully develop a career as a physician-scientist. I will always value and remember with fondness my time there." ■

Dr. Vicki Netjek interviews chronic drug users to determine if racial metabolic differences influence drug choice.

Metabolic Differences Indicate Drug Preference

When Vicki Nejtek, PhD, completed her five-year research project investigating medication efficacy in patients with bipolar disorder and cocaine or methamphetamine dependence, she had collected a goldmine of information. While finding quetiapine (Seroquel®) and risperidone (Risperdal®) not only treated mood symptoms but also reduced drug craving, she also discovered something new and revealing: racial metabolic differences may determine whether an individual prefers to use cocaine or methamphetamine.

Nejtek's initial study was designed to directly compare quetiapine and risperidone in treating patients with co-occurring bipolar disorder and stimulant dependence. More than 650 individuals — many on parole or probation — were screened for the study. As part of the study criteria, they were regularly screened for drug use via urinalysis. Nejtek's research showed that even if subjects continued to use cocaine or methamphetamines, treating their bipolar disorder with quetiapine or risperidone produced few or no interactive side effects. Matthew Avila, PhD, Marija Djokovic, MD, Alan Podawiltz, DO, Sejong Bae, PhD, and Kathryn Kaiser, doctoral candidate — all at the UNT Health Science Center — also contributed to the study.

"I find that many psychiatrists are reluctant to use pharmacotherapy to treat the bipolar symptoms in patients who are currently using illicit drugs as they are uncertain about the interactions the medication may have with the illicit drugs," Nejtek explained. "In fact, in the DFW Metroplex, roughly 50 percent of the patients suffering from these co-occurring disorders are untreated. We wanted to determine if it was safe to treat them in a real-world environment where daily or weekly illicit drug use is common."

In fact, the research found that both quetiapine and risperidone decreased drug cravings while improving mood symptoms. However, improving mood problems and reducing drug cravings did not translate into consistent drug abstinence.

This is the first double-blind, randomized study in the nation examining these medications in this population to show that both medications at low doses were effective for treating bipolar disorder and drug dependence symptoms such as craving. The low dosing strategy found effective in the study was substantially lower and had a slower titration than the recommended pharmaceutical guidelines. "The results from this study provide us some hope that developing medications to treat drug dependence is possible," Nejtek said.

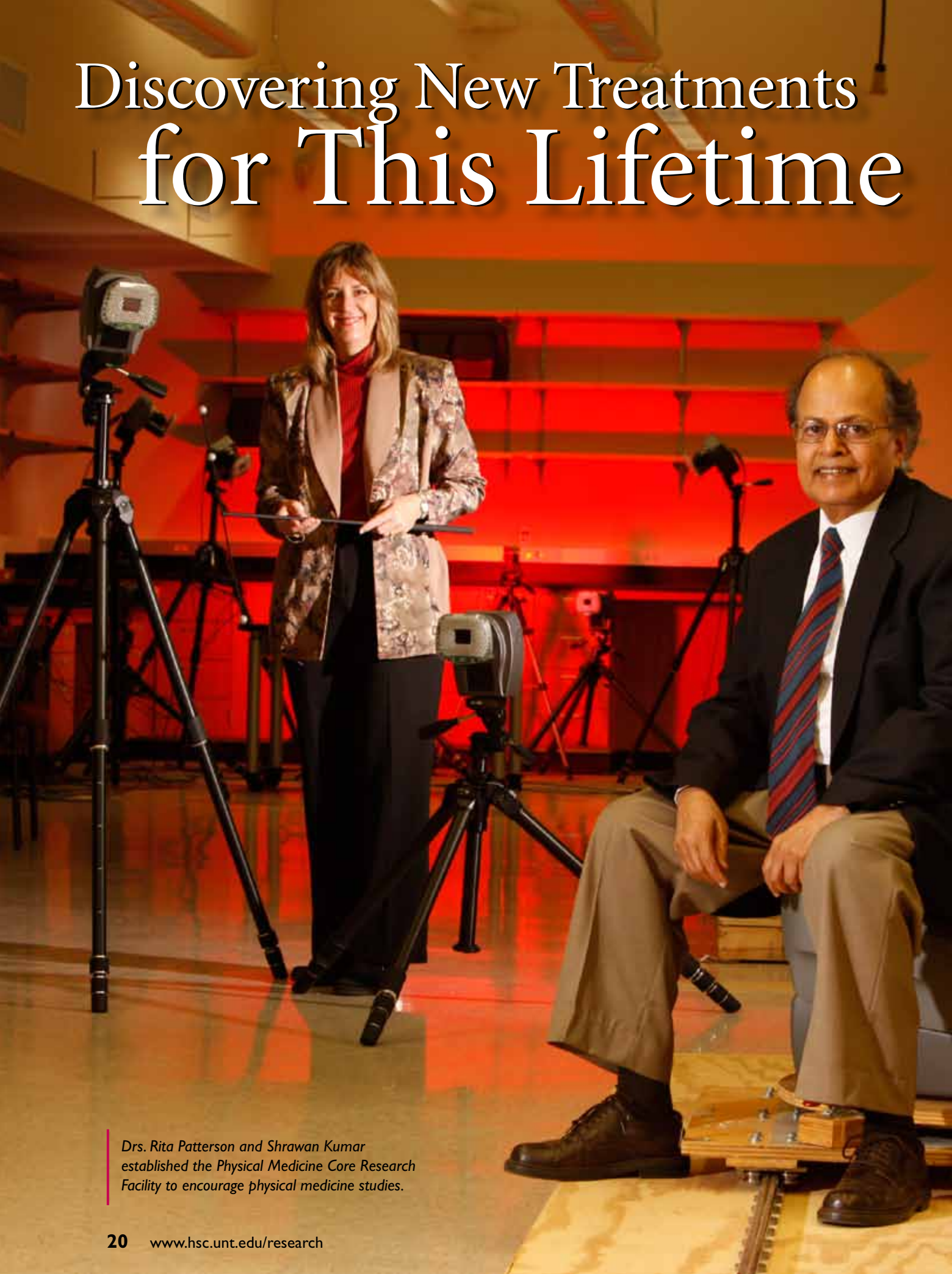
With a wealth of data from her subjects during her nine years of clinical trial investigative experience, Nejtek has begun looking at physiological reasons driving preferences for cocaine or methamphetamines. Nejtek was curious about why 99 percent of African Americans chose to abuse cocaine, while 50 percent of Caucasians chose methamphetamine and 50 percent chose cocaine.

While analyzing reasons for drug preferences and metabolic rates in the National Institutes of Health-funded EXPORT (Excellence in Partnerships for Community Outreach and Research on Disparities in Health and Training) grant, Nejtek discovered that African Americans reported more negative physiology, including anxiety, jitters, restlessness, a feeling of being "on edge", sweating, insomnia, racing heart, paranoia and agitation associated with methamphetamine use, and more positive physiology, including feeling alert, friendly, confident, sociable, stimulated, "on top of the world" and powerful with cocaine. Perhaps these physiological differences are related to the metabolic differences between cocaine and methamphetamine in the way that these illicit drugs are metabolized by African Americans and Caucasians.

Taking into account that the drugs' availability, price, and/or popularity could account for some drug preferences, Netjek's studies still showed that physiological differences were strong determinants in drug preference. "Further examining metabolic reactions based on the results from this study should be useful in medication development, giving physicians an option to treat drug users based on a patient's drug of choice and their metabolism," Netjek said.

Netjek plans to continue mining the data in hopes of determining even more effective ways of treating patients with co-occurring mood and substance use disorders. ■

Discovering New Treatments for This Lifetime



Drs. Rita Patterson and Shrawan Kumar established the Physical Medicine Core Research Facility to encourage physical medicine studies.

With a dozen tripods and cameras focusing on one subject, Rita Patterson's lab looks more like a movie studio than the typical microscope-and-beaker labs at the UNT Health Science Center. The technology that she uses to evaluate wrist movement is the same type used to film the movie "The Matrix" and "The Lord of the Rings," and the little FOX football-bot flex across the TV screen.

Just as animators do, Patterson, PhD, co-director of the Physical Medicine Institute's Core Research Facility established at the UNT Health Science Center earlier this year, attaches little electrode dots to the skin, then uses the cameras to track the movements of the hand and wrist on the computer. By watching the "animated" motions, she can determine which movements are easy and which may be hindered.

Patterson's research has focused on wrist and hand movements, but the new lab that she and Shrawan Kumar, PhD, professor of Manipulative Medicine, are building will be available to scientists, researchers, teachers, clinicians, physicians and community partners who want to champion, study and explore physical medicine, or how the body moves.

"We are creating a place where clinically applied research can be conducted, so that the results will be applied in my lifetime," said Patterson. The new research facility was created to provide both a research brain trust and facilities to explore research in physical medicine. "This is a wonderful opportunity to establish and grow a premiere physical medicine lab in the U.S. doing orthopedics, rehabilitation, manipulative medicine and cell biology, all in the same place.

"The invitation to establish the Core Research Facility here at the Health Science Center was really a perfect storm for me," she continued. "I'm a native of Irving, and this gives me the opportunity to return home, and also the chance to see the results of my research applied. I really get a kick out of applied research."

Collaboration is a key to the success of the PMI. Patterson and Kumar recently completed a project with Kris Chesky, PhD, director of Education and Research at the University of North Texas at Denton, where they evaluated the challenges of musicians with small hands who experience pain and discomfort playing the piano, cello and other instruments. By narrowing the size of the piano keys, Patterson and Chesky were able to prove that the musical tone wasn't compromised by making the musician more comfortable.

In fact, making daily living activities less taxing and preventing injuries are some of the goals of Kumar, co-director for the PMI. Kumar joined the Health Science Center to create an institute nationally recognized for meaningful original research and to enhance the quality of life for people with disabilities and physical problems.

His past research includes work on low back pain, whiplash, spinal problems, rheumatoid arthritis and gait rehabilitation. He is developing a device to help rheumatoid arthritis sufferers manage household chores. He has invented several devices and patented one to help people with spinal problems, including the therapeutic spinal mobilizer that measures spinal stiffness for treatment of back pain, and the axial rotation tester that tests spinal rotation capacity.

In the new lab, Kumar studies cervical motion and its effect on the jaw joint using a specially designed track, complete with a seat with an automobile-like seatbelt. By studying the motion of the machine and the way the cervical spine reacts, he can better understand the impact on the jaw.

The Instituional Review Board recently approved Kumar's research proposal to study Temporal Mandibular Joint (TMJ or jaw) research in collaboration with John Zuniga, DMD, PhD and chair of Oral Surgery and Gaylord Throckmorton, PhD and professor of Anatomy, at UT Southwestern Medical Center. His most recent grant from the Oral MaxiloFacial Surgery Foundation will help him identify new ways to assess jaw problems.

Another study in collaboration with Tom Mayer, MD, clinical professor of Orthopedics at UT Southwestern Medical Center, and Robert Gatchel, PhD, professor and chair of Health Psychology at the University of Texas at Arlington, focuses on lower back pain.

"My next goal is to establish funding to recruit graduate students to contiribute to the research," Kumar said. "That's the next critical step in further establishing the institute."

Both Patterson and Kumar are eager to collaborate with other researchers who want to use the knowledge gained in the Physical Medicine Institute to treat patients in need — here and now. ■

Intermittent 0xygen Deprivation *May* Strengthen Heart

For many people who have a history of heart problems either in their family or their own past, a healthy heart is always on their minds. Maintaining a healthy lifestyle and regular visits to the doctor are two things that an individual can do to stay heart healthy.

Many of the athletes who competed in last summer's Olympic games understand the benefits of training at high altitudes, then competing at lower altitudes. The benefits of high-altitude training have been clear for decades, which is why the American cycling team trains in Colorado, where less oxygen in the air makes the heart work harder.

Now, researchers at the UNT Health Science Center have demonstrated that depriving the heart of oxygen actually may strengthen it. These recent discoveries by research team Robert Mallet, PhD, associate professor of Integrative Physiology, Fred Downey, PhD, Regents Professor of Integrative Physiology, and Myoung-Gwi Ryou, who earned his PhD at the Health Science Center last summer, were reported in the June 2008 issue of *Experimental Biology and Medicine* and may lead to a new paradigm in protecting the hearts of patients at risk of coronary disease.

Hypoxia (the lack of oxygen) historically has been considered harmful to the heart. However, this new research has demonstrated that a 20-day program of brief, repetitive, moderate reductions in the amount of oxygen in arterial blood help increase the heart's resistance to heart attack.

"Intermittent hypoxia treatment may be a powerful adjunctive therapy for patients at risk of heart disease," Downey said. "The brief periods of moderate hypoxia are easily tolerated by most people, require neither surgery nor expensive medications, and can be administered by the patient at home or work using available devices. Indeed, intermittent hypoxia has been used for several decades in Eastern Europe to treat heart and neurological diseases and high blood pressure."

Patients spend up to 20 minutes per day in a hypoxicator — a clear chamber — that reduces the amount of oxygen in the air to an equivalent of 16,000 feet in altitude. Then the oxygen is increased to normal levels.

"It's like coming down from Pike's Peak, only much faster," explained Mallet. "The cyclical hypoxia regeneration apparently helps strengthen the heart muscle, making it more resistant to heart attack and dramatically reduces damage from an attack."

Maximum effect is reached after 20 days of cyclical hypoxia. The next phase of testing will determine how long the effect lasts, if it actually wears off. Eventually, the treatment may be tested on people who are at high risk of heart disease in order to condition the heart before a debilitating attack. ■

Below, Drs. Myoung-Gwi Rou, Robert Mallet and Fred Downey review results of oxygen deprivation on heart performance.

Going Clean and Green

Hang around the boat docks enough, and you'll learn that boat bottoms often collect mussels, barnacles and other crud that cause drag on the craft, dilute its performance and increase fuel and maintenance costs. Keeping the bottom clean while protecting the environment creates issues, too, as many cleaners and solvents pollute the water and kill fish and plant life.

Now, an interdisciplinary research team led by John Schetz, PhD, associate professor of Pharmacology and Neuroscience at the Health Science Center, has discovered an environment-friendly way to control aquatic biofouling.

The biofouling problem is estimated to cost about $6 billion annually for the maritime industry. Coupled with the pressure of pending or enacted legal moratoriums on effective, but toxic, antifoulants, and the lack of new alternatives in the pipeline, the timing is right for bringing this innovative technology out of the laboratory and applying it to the real world.

Schetz and his colleagues at the University of Texas at Arlington plan to utilize green chemistry to develop cleaner antifoulant coatings for use in marine environments. The collaboration was supported in part by a competitive joint institutional seed grant program between the Health Science Center and UT Arlington — the first of its kind for UNTHSC — and has resulted in more than a 16-fold return on the initial investment of federal grant dollars, a patent filing, a biomedical spin-off award, peer-reviewed publications, a doctoral student's dissertation, a Sigma Xi Distinguished Lecture and other invited lectures at various institutions.

The antifouling technology fits into a number of efforts aimed at energy, reducing energy costs, the environment and limiting humans' environmental footprint. It also should reduce the introduction and growth of nuisance species such as zebra mussels and quagga mussels. ■

Dr. John Schetz evaluates water purity associated with biofouling and its effect on mussels at Port Aransas, Texas.

New Research Faculty

The University of North Texas Health Science Center is providing a healthier future for a changing world with new discoveries through research. Below are new faculty recently added to the School of Public Health.

Christine A. Moranetz, PhD

Associate Dean for Curricular Enhancement and Associate Professor of Social and Behavioral Sciences

Dr. Moranetz comes to the Health Science Center from the University of Kansas School of Medicine in Kansas City and Wichita, Kan., where she served as adjunct associate professor of Family Medicine and Preventive Medicine and Public Health, and director of special projects. She also served on the university's advisory board for the Community Health Project — a public health internship program for health professions students — and co-directed an HIV/AIDS prevention program. She earned her PhD in Education/Exercise Physiology and Nutrition from the University of Kansas at Lawrence.

David A. Sterling, PhD

Professor and Chair of Environmental and Occupational Health

As professor and division director of Environmental and Occupational Health at the Saint Louis University School of Public Health in St. Louis, Sterling earned a strong reputation as a principal investigator on projects related to air quality and disease. He also served as co-investigator of the Centers for Disease Control-funded Control Asthma in American Cities Project in St. Louis, a $4.5 million investigation of asthma prevention in children. In addition, Sterling is a lead investigator studying the effects of lead mining on the health of residents in Peru's mountainous regions.

Carlos Reyes-Ortiz, MD, PhD

Associate Professor of Social and Behavioral Sciences

Dr. Reyes-Ortiz served as researcher at the Sealy Center on Aging and as assistant professor of Rehabilitation Sciences at the University of Texas Medical Branch at Galveston. Prior to that, he was assistant professor of family medicine at Valle University in Cali, Colombia, and served as a geriatrician and physician in various locations in Colombia. Reyes-Ortiz earned his MD from Valle University at Cali, Colombia, and his PhD in Preventive Medicine and Community Health from the University of Texas Medical Branch at Galveston.

Subhash Aryal, PhD

Assistant Professor of Biostatistics

Dr. Aryal has served as instructor and research assistant of Biostatistics at the University of Illinois at Chicago, where he also earned his PhD in biostatistics. At the conclusion of his studies, he was selected as the outstanding student in Biostatistics and Epidemiology at the Illinois School of Public Health at the University of Illinois.

Hsueh-Fen Chen, PhD

Assistant Professor of Health Management and Policy

Dr. Chen came to the Health Science Center after serving as an instructor and research assistant at Virginia Commonwealth University in Richmond, Va., where she earned her PhD in Health Administration. Her research focuses on how hospital finances affect quality of care.

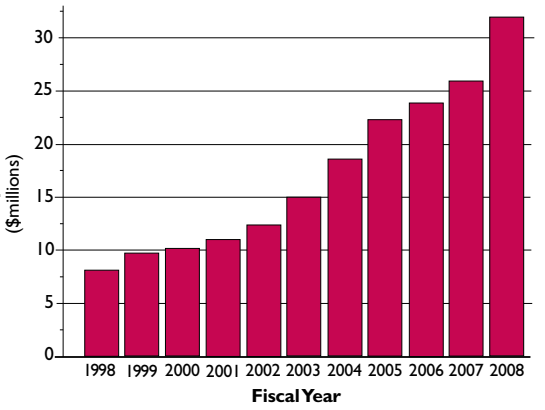
Christine A. Moranetz | David A. Sterling | Carlos Reyes-Ortiz | Subhash Aryal | Hsueh-Fen Chen

Research 2008

Research expenditures at the Health Science Center grew to an all-time high in 2008, to more than $32 million. Since 2003, our research expenditures have increased by more than 100 percent, the largest rate of growth of any health science center in Texas. In the past year, our faculty submitted grant proposals requesting more than $190 million to support their research.

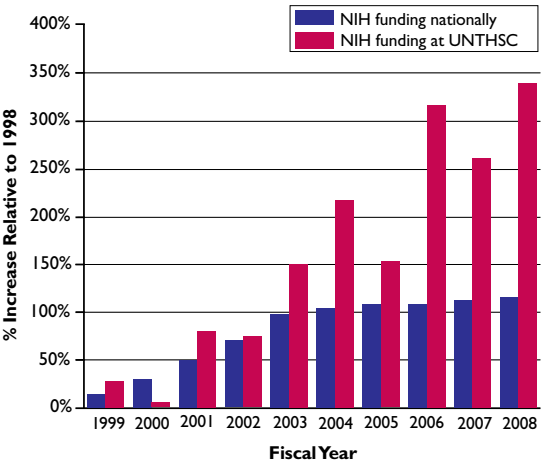
But submitting proposals to support research is only part of the equation — only the best proposals are approved for funding. The majority of research funding at UNTHSC is awarded from the National Institutes of Health (NIH).

The research activity of most health science centers increased along with the doubling of the NIH budget from 1998 - 2003. Since 2003, NIH funding nationwide slowed considerably, and, in fact, has not kept pace with inflation. In contrast to the overall national trend, NIH funding received by UNTHSC scientists has continued to grow at an exceptional pace. Whereas NIH funding in general has increased about 115 percent from 1998 levels, NIH funds to Health Science Center scientists have increased by roughly three times that level. Even in the face of flat levels of research funding at NIH, our faculty have continued to secure funding for the important research they are conducting. This, more than any other fact, is evidence of the exceptional, cutting-edge research being conducted by investigators at the Health Science Center.



UNTHSC Research Funding

We are committed to improving the health of our citizens through research. Our world-class research teams are focused on critical unmet medical needs, including aging, Alzheimer's disease, cancer, health disparities, vision loss and infectious diseases. In addition, our approach to translating the bench discoveries of our scientists into real solutions for clinical and public health problems is proving to be remarkably successful. The research discoveries of our faculty will continue to help improve the health and lives throughout the world.



Change in NIH Funding

Hope in Interesting Times

As I reflect on the fascinating research endeavors highlighted in this third-annual issue of *Synergy*, I was reminded of the expression, "May you live in interesting times." Supposedly of ancient Chinese origin, this little saying serves as both proverb and curse, and got me thinking about the remarkably brilliant people and modern technologies of our time, arrayed against a host of implacable diseases both old and new.

Consider the work being done to improve quality of life for those with rheumatoid arthritis and other disabling illnesses and injuries. As recently as 50 years ago, these individuals were relegated to life's sidelines. But at the Physical Medicine Core Research Institute, recent investment in cutting-edge lab equipment is leading to advances that will open new doors to more active, contributing lives. Who would have thought that the same powerful imaging technology that went into making movies like "Lord of the Rings" and "The Matrix" could be used to study the complexity of wrist movements and create new devices to improve dexterity, as well as quality of life?

Dementia, whether caused by Alzheimer's disease, Parkinson's disease, injury or other sources, remains one of the most well-researched yet feared afflictions in human history. But the tireless study of human brain tissue at our Brain Bank will yield clues to understanding, on a molecular level, possible causes and treatments. And a new focus on glaucoma and eye disease could lead to breakthrough research in these areas.

Likewise, exploring cancer's insidious reach into society is under way as we strengthen our partnership with Cook Children's Health Care System, where cancer research is central to our focus. Why is the incidence of childhood leukemia higher in Hispanic child populations than African American? Do genetic differences among sisters make one more likely to develop cancer than another? How important are environmental and lifestyle influences in developing or preventing cancer?

These and other big scientific questions can only be answered by researching the unknown. In this quest, we extend the frontiers of knowledge to encompass new discoveries that lead to new hope for patients in our community.

Driving this quest during these interesting times is an ongoing challenge of enormous proportions. That's why I can speak for all of us at the UNT Health Science Center as I welcome the leadership of Glenn Dillon, PhD, as our new vice president of research, as Dr. Thomas Yorio assumes the role of provost for the Health Science Center. Dr. Dillon's energy, effective leadership and commitment to our university are important attributes to helping us attain world-class recognition as one of America's most innovative research facilities.

Scott B. Ransom, DO, MBA, MPH
President
University of North Texas Health Science Center

UNIVERSITY of NORTH TEXAS
HEALTH SCIENCE CENTER
AT FORT WORTH

3500 Camp Bowie Boulevard
Fort Worth, Texas 76107
817•735•2000
www.hsc.unt.edu

Drs. Shrawan Kumar and Rita Patterson test the effects of motion on Research Engineer Sam Durham at the UNT Health Science Center's Physical Medicine Core Research Institute.