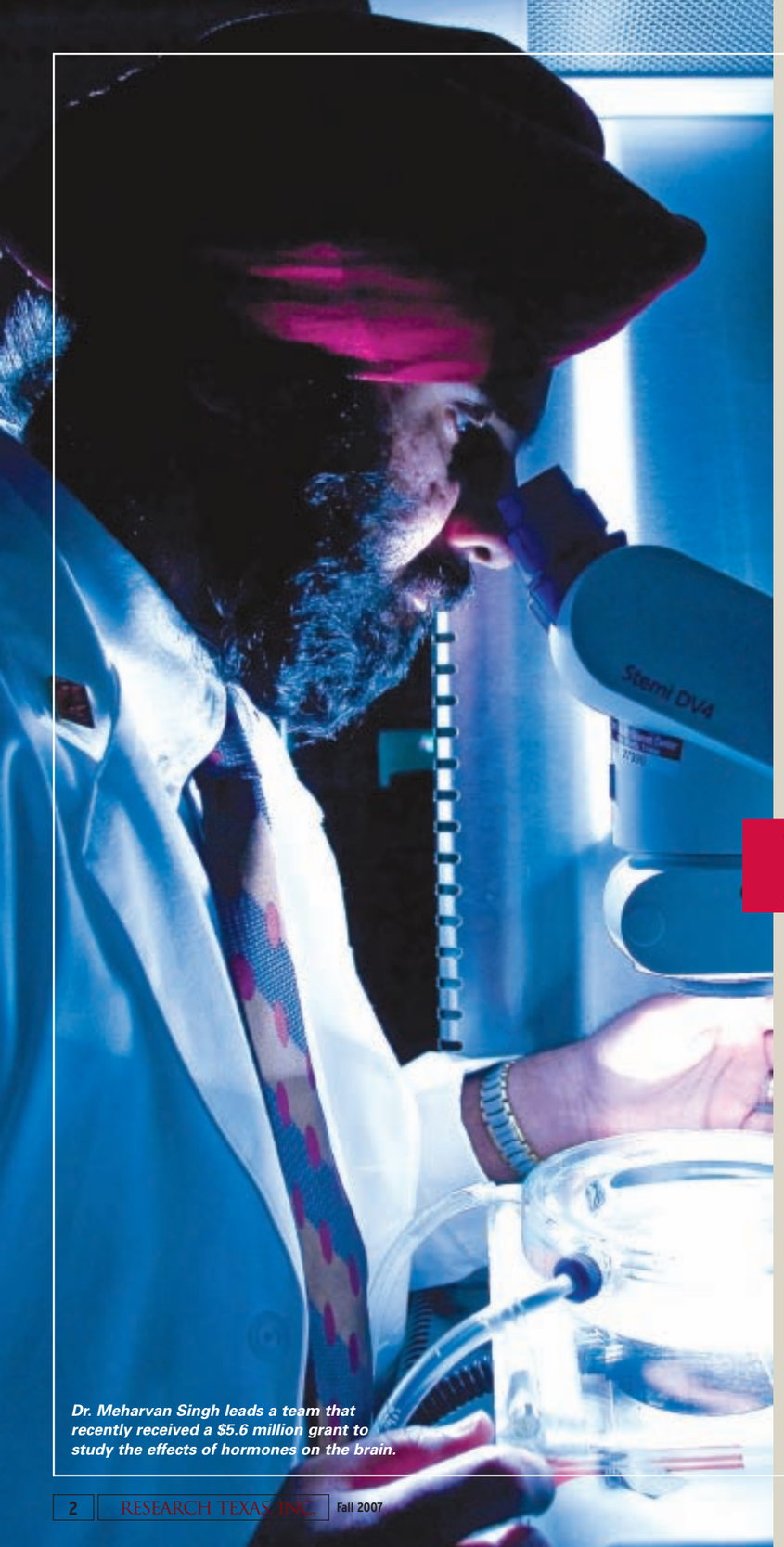


Dr. Meharvan Singh leads a team that recently received a $5.6 million grant to study the effects of hormones on the brain.

UNT Health Science Center

Research could cool those hot flashes

Insomnia, hot flashes, irritability. Ask a woman over age 50 about the symptoms of menopause, and she'll recite them in a flash. But aside from these annoying symptoms, a woman's risk for diseases including heart disease, osteoporosis and Alzheimer's disease increase significantly after menopause. Since the levels of hormones such as estrogen and progesterone decline after menopause, does this decrease render the body more vulnerable to diseases commonly associated with aging? If so, can hormone therapy reduce such risks? And which hormones will benefit which individuals? That's what a team of scientists from the University of North Texas Health Science Center at Fort Worth (UNTHSC) intend to answer.

For years, physicians have prescribed hormone therapy to reduce the discomforts of menopause. But research efforts, including those at UNTHSC, suggest that such hormones also may reduce brain dysfunction and the risk of diseases associated with the aging process, including Alzheimer's disease.

A few years ago, results of a major clinical study (the Women's Health Initiative) concluded that hormone therapy was not effective and may create adverse effects. As a result, physicians and their female patients began to avoid hormone therapy for fear of causing more damage than benefit.

Dr. Michael Forster, Dr. Peter Koulen, Dr. James Simpkins, Dr. Meharvan Singh, Dr. Lazlo Prokai, Dr. Katalin Prokai-Tatrai (front row), Dr. Shaohua Yang and Dr. Michael Gatch are part of the research team.

In reality, the data did not warrant such broad generalizations, and, in an effort to clarify the apparent controversy, a team of researchers at UNTHSC, led by Dr. Meharvan Singh, is studying how estrogens and progestins affect the brain. Dr. Singh is the project director for the collaborative research team that received a $5.6 million grant from the National Institute on Aging (NIA), a division of the National Institutes of Health (NIH), in August to study the Novel Mechanistic Targets of Steroid Hormones in the Brain. This is the third NIH-funded program project grant awarded to the Pharmacology and Neuroscience Department, a feat achieved by few other departments in the country. This program of research takes a multi-pronged approach toward tackling issues relevant to our understanding of how hormones, particularly estrogen and progesterone, affect the brain.

The team of Drs. Singh, James Simpkins, Peter Koulen, Laszlo Prokai, Katalin Prokai-Tatrai, Shaohua Yang, Michael Forster, Michael Gatch and Shande Chen from UNTHSC, along with Dr. Dominique Toran-Allerand from Columbia University in New York, will address which estrogens or progestins are best at protecting the brain (for example, natural vs. synthetic progestins) and which may help the brain stay healthy.

"We work well together," Dr. Singh said. "This project is really a collaborative effort where the program as a whole is truly greater than the sum of its individual components.

"Through a better understanding of the biology of these hormones, we may understand the consequences of not having these hormones around after the menopause. Then, we can use this knowledge to develop safer and more effective means of treating diseases whose risks increase following the menopause," Dr. Singh said. "Through this research, we hope to give women more options, not rob them of choices."

In addition to the $5.6 million NIH grant, Dr. Singh also received a recent grant from the Alzheimer's Association to study the effects of progesterone on the levels and regulation of a family of proteins, called neurotrophins, whose function is altered in Alzheimer's disease. By understanding the basic mechanisms by which these proteins are regulated, Dr. Singh hopes to provide the foundation for new and innovative means of treating diseases like Alzheimer's disease.

Dr. Singh, together with Stan Hall, chief executive officer of G & H Medical Products International, also received a Small Business Technology Transfer (STTR) grant from NIA. This partnership was developed based on Dr. Singh's other research relating to how a class of hormones, called androgens (which include testosterone), affect brain health. The goal of this project is to develop a diagnostic test to define risk associated with androgen therapy. Dr. Singh hopes that this eventually will allow physicians to determine if a patient is a good candidate for androgen therapy.

The UNT Health Science Center has the distinction of having one of only a few departments in the U.S. with three program project grants (P01) funded by the National Institutes of Health. In addition, the UNT Health Science Center's Pharmacology department is in the top 10 percent of research grant dollars per faculty member and the top 20 percent of total research grant dollars of all research centers.[1]

The NIH funds grants, cooperative agreements, and contracts that support the advancement of fundamental knowledge to meet the NIH mission of extending healthy life and reducing the burdens of illness and disability. Program project grants generally are awarded for three to five years for a discreet, specified, circumscribed research project.

[1]Based on 2005 Association of American Medical Colleges data for Pharmacology Departments.

Could the next big cancer breakthrough emerge from a UNTHSC research lab?

Father and son researchers Yogesh and Sanjay Awasthi are on a life-long quest – to find a new cancer treatment that won't harm the body but will kill cancers. They believe they are close to finding the gold at the end of that rainbow. Their quest, which has spanned some 25 years, has brought them to a likely suspect – a protein called RLIP76. It's this protein and its potential to "turn off" vital signaling processes within cancer cells that may hold the key to developing a revolutionary approach to cancer treatment.

The Awasthis' quest began in India, when Yogesh received his doctorate in natural plant chemistry and began to pursue his passion to reduce the toxicity of environmental cancer-causing agents. After moving to the United States, the elder Awasthi first identified the existence of the RLIP76 protein in 1983. What he didn't realize at the time was his son's keen interest in his research.

"When Sanjay was 14 years old, he began to secretly visit my research lab at night, "Yogesh said. "He would talk to fellow researchers and began some of his own experiments. That is what ultimately led to his identification in 1999 of RLIP76 as a multifunctional protein and transporter that responded to any stress applied to the cell."

In September, Sanjay joined the University of North Texas Health Science Center (UNTHSC) to continue the fight against cancer. Yogesh and his fellow researchers at the University of Texas Medical Branch at Galveston have been critically involved in supporting and furthering the work of Sanjay and his fellow Dallas-Fort Worth-based researchers. He is looking forward to moving to the Metroplex this fall and joining his son in the lab once more.

Dr. Sanjay Awasthi (front) and his team, Jyotsana Singhal, Dr. Sharad Singhal, and Dr. Sushma Yadav, joined the UNT Health Science Center this fall to pursue their cancer research.

Sanjay, a board-certified oncologist and researcher, compares RLIP76 to car exhaust stored in a tube on the side of the cell. When the cell is stressed, the tube attaches to the wall of the cell and pours out noxious chemicals. This biochemical change sends signals that result in inflammation and cancer cell growth. Interrupt that signaling process by reducing or eliminating the RLIP76 protein through the use of enzymes, and the changes in the cell stop. The cancer stops growing and dies. Ultimately the patient survives and returns to a healthy, normal life.

The Awasthis are buoyed by exhaustive animal trials that showed a reduction and ultimate elimination of tumors in mice that were given the protein inhibitor and in some cases that received complementary chemotherapy. That has led them to UNTHSC and the prospect of conducting clinical trials.

"My father and I are extremely excited about joining the UNTHSC family because the institution is highly recognized for its research biologists and its successful track record in sponsoring and conducting clinical trials," Sanjay said. "Our work is at a critical point, and our association with UNTHSC will help our research move forward to the next level."

"There are several groups around the world who are focused on this particular protein," Sanjay admitted. "We were the first to show that the protein was a transporter, and now we have demonstrated that by eliminating the protein, cancers die. This opportunity at UNTHSC has come along at just the right moment for us, for our research and for the cancer patients who may some day benefit from it."

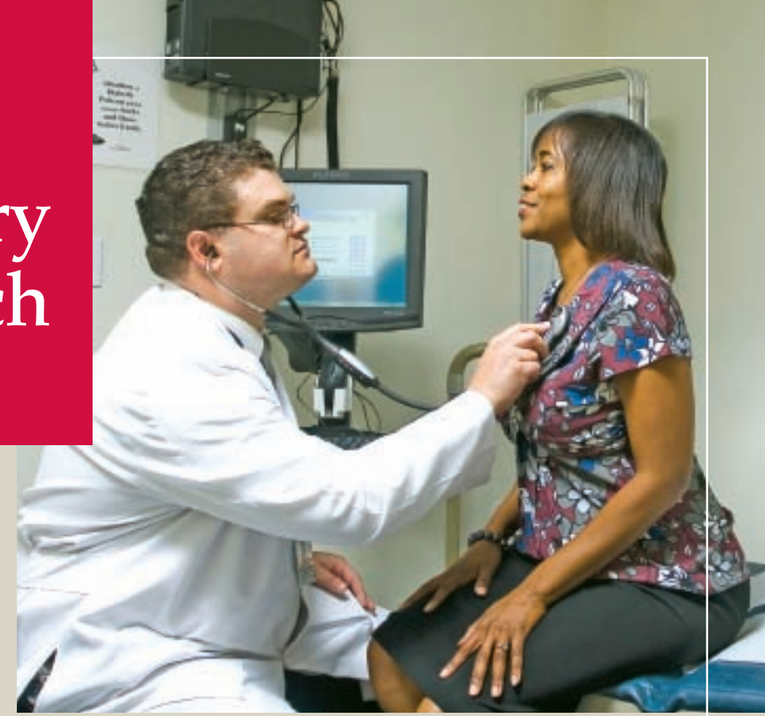
The Awasthis' lab at UNTHSC will include a team of experts to support their efforts. In addition, the lab will feature technology that will be critical to the researchers' efforts to demonstrate key characteristics of the RLIP76 protein.

"The technology and equipment we have at our disposal at UNTHSC will enable us to show in pictures that this is a protein that walks, shakes and moves – that it is a transporter," Sanjay said.

"In a way, this protein has brought my son and me full circle," Yogesh explained. "What began as my interest in plant toxicity and the environment has led us to work together in the lab in Fort Worth where we may be able to refine and introduce a completely new approach to cancer treatment."

UNTHSC forms Primary Care Research Institute

Collaboration will revolutionize primary care health research and treatment



Dr. Roberto Cardarelli is leading changes in the way doctors treat their patients through primary care research.

Imagine a health system designed so that primary care physicians can take what they learn about local health issues from treating patients in their neighborhood clinics and translate that information into solutions for those problems more quickly and easily. What if the results of research done in this manner were not seen only by the physicians, but also by the very people involved in the work – the patients who participated?

NorTex, the North Texas Primary Care Practice-Based Research Network, allows physicians and health researchers to do their work exactly this way – by recruiting actual clinic patients for studies, then disseminating their research findings in the local community through newsletters, churches and other avenues.

NorTex will lend its participating clinics and physicians' knowledge in this area to UT Southwestern by partnering in a pending $60-million, five-year Clinical Translational Science Award (CTSA) from the National Institutes of Health (NIH). By creating the new Primary Care Research Institute at the University of North Texas Health Science Center, NorTex will help revamp the way primary care research is done.

"We were approached by UT Southwestern and asked to be a partner because of our research network and the need for a practice-based research model as part of the grant," said Dr. Roberto Cardarelli, founder and director of NorTex and the new Primary Care Research Institute. "This large NIH grant will create an incredible infrastructure for all types of research and community resources and revolutionize the way we do primary care research in North Texas."

He said NorTex, through the formation of the Primary Care Research Institute, will continue to conduct clinic-based health research that affects primary care and public health, but it will now expand its ability to conduct this research throughout all of North Texas through a new partnership with Parkland Community-Oriented Primary Care clinics.

"Physicians in the Primary Care Research Institute will collaborate to conduct research in primary care and public health, including HIV/AIDS and preventive care research," Dr. Cardarelli said. "This allows us to do research in partnership with the community, not just gathering information from members of the community without sharing what we've learned with them."

The goal of the CTSA is to transform how basic, clinical and translational research is conducted to bring effective strategies and new treatments more quickly to health care workers and their patients. As a community engagement partner, NorTex will recruit research participants from the community and increase public trust in local research.

Primary care research helps lower hospital rates and health care costs. Most primary care is delivered in the outpatient setting, and it has the potential for the greatest impact on the public's health. During primary care visits, physicians can diagnose and treat health problems before they become chronic or turn into emergent situations.

Primary care research also decreases health disparities – inequalities in the health status, access to health care and health risk factors among the racial and ethnic minorities and the general population – and NorTex is one of the few practice-based research networks in the nation that focuses its research on health disparities.

"We have to understand disease processes and factors that impact the progression of disease in a population – in a primary care outpatient setting – in order to know how we can prevent, diagnose, and treat that population to the best of our abilities while taking into account their cultural beliefs and values," Dr. Cardarelli said.

NorTex also conducts research in pediatrics, family medicine, epidemiology, health management and policy, and social and behavioral sciences as part of a new partnership with Cook Children's Physician Network. Its research focuses on primary care and public health issues in Tarrant County.

"NorTex is now growing into the Dallas region so it can fulfill its role for the CTSA," Dr. Cardarelli said. "That is, to collaborate with primary care and public health partners so we can do research with whom it affects the most – the clinicians and the communities."

Preventing Alzheimer's before boomers succumb to the epidemic

As baby boomers – the generation born between 1946 and 1964 – age, more and more members of this population are experiencing the debilitating symptoms of Alzheimer's disease. By 2050, the number of individuals age 65 and over with Alzheimer's could range from 11 million to 16 million unless science finds a way to prevent or effectively treat the disease. If advanced therapies and treatment for Alzheimer's aren't created, huge financial problems could develop within 20 years as families struggle to look after loved ones who may have forgotten who they are and need constant care.

Alzheimer's is a neurodegenerative disease related to aging with onset generally occurring in the late 60s, although some people experience symptoms as early as 30 years old. It is the most common form of dementia, a general term for the loss of memory and other intellectual abilities serious enough to interfere with daily life.

At the University of North Texas Health Science Center (UNTHSC), Dr. Peter Koulen and his team of researchers are developing therapies intended to mitigate or even prevent Alzheimer's disease by preventing damage to certain cells that are affected by Alzheimer's. In 2004, through several national and international multimillion-dollar grants, Dr. Koulen studied chemical and plant compounds for treating Alzheimer's sufferers, as well as gene therapy to protect healthy or repair damaged genes.

"What exactly goes wrong when someone develops Alzheimer's disease? Why do brain cells die? How can I protect them? We all want to answer these questions in time for our children to benefit from our work. I hope to produce results during my parents' lifetimes."

Dr. Peter Koulen
University of North Texas Health Science Center

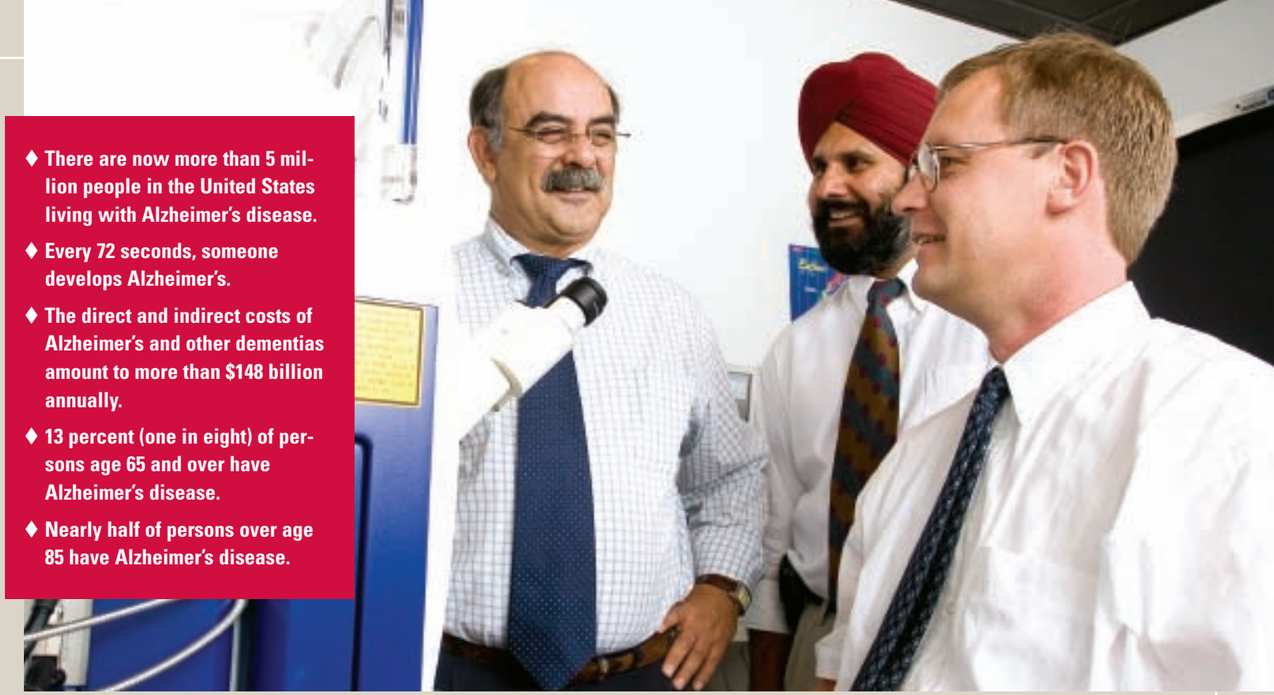
"If we can prevent cell suicide early, we hope to rescue brain function," Dr. Koulen said. "If we can delay the severe degeneration of cells, we can improve quality of life by improving or at least maintaining the current level of brain function."

The first group of compounds is close to being patented. The next step will be to introduce it in clinical trials with Alzheimer's patients. These compounds include naturally and artificially occurring chemicals, herbs and other botanic substances that appear to improve cell degeneration related to Alzheimer's.

What makes one person develop Alzheimer's and not another? While the answer isn't clear – yet – research has shown that women are more likely than men to develop the disease, as are those who have suffered a stroke. In fact, in 80 to 90 percent of cases, the cause of Alzheimer's onset is unknown.

Dr. Koulen's team works with other researchers to pool their knowledge, including Dr. Kent Chapman, a biochemist at the University of North Texas, who is helping to develop chemical and plant compounds. At the UNTHSC, collaborative efforts among Dr. Koulen, Dr. James Simpkins and Dr. Meharvan Singh studying the role of hormones in brain protection have provided new avenues for Alzheimer's therapy development. Dr. Simpkins is professor and chair of the department of pharmacology and neuroscience, and Dr. Singh is associate professor of pharmacology and neuroscience.

- **There are now more than 5 million people in the United States living with Alzheimer's disease.**
- **Every 72 seconds, someone develops Alzheimer's.**
- **The direct and indirect costs of Alzheimer's and other dementias amount to more than $148 billion annually.**
- **13 percent (one in eight) of persons age 65 and over have Alzheimer's disease.**
- **Nearly half of persons over age 85 have Alzheimer's disease.**



Drs. James Simpkins, Meharvan Singh and Peter Koulen collaborate on their research at the University of North Texas Health Science Center at Fort Worth.

Through almost $6 million in national and international grants, Dr. Koulen has contributed new findings on neuroscience and cell biology through the discovery and analysis of neurotransmitter receptors, novel ion channels and their accessory proteins. These discoveries allowed him to recognize that intracellular calcium channels and their associated regulatory proteins are responsible for controlling cellular signaling, including processes leading to cellular degeneration. Recently, he identified intracellular calcium channels as promising therapeutic targets for preventing neurodegenerative diseases of the eye and central nervous system.

Koulen also has proven that certain plant lipid compounds protect brain cells from death. Once he determines how the lipids work, he plans to develop a compound to treat Alzheimer's disease by protecting brain cells from dying. Koulen has initiated patenting of a group of compounds that could protect cells from degenerative diseases of the nervous system including Alzheimer's disease, stroke, glaucoma and macular degeneration. Two more Koulen patents are pending on potential drugs for the treatment of Alzheimer's disease.

"Alzheimer's is an epidemic," Koulen said. "Some people call it a silent epidemic, because it's not obvious like bird flu or AIDS. An individual can look healthy, but their brain is slowly degenerating.

"Alzheimer's creeps into the lives of families," Koulen continued. "It starts small and increases over the years. Alzheimer's sufferers lose themselves, their lives, their identities and their memories. It's the most debilitating of all diseases imaginable. Individuals suffer tremendously because they see their life slipping away, and there's nothing they can do about it. Physically they're fine. An individual can go out and walk the dog, but she doesn't recognize her husband of 50 years when he walks though the door."

With the new ongoing research that Koulen and his associates are pursuing, some day Alzheimer's no longer may wreak havoc on the lives of individuals and their families.

UNTHSC alumnus helps in national investigation of TB patient

Dr. Patrick Moonan, a 2005 graduate of the University of North Texas Health Science Center's School of Public Health, played a key role in the recent U.S. Centers for Disease Control (CDC) investigation of Andrew Speaker, the Atlanta attorney who traveled from Atlanta to Europe and back again while infected with what was believed to be an extensively drug resistant strain of tuberculosis (XDR TB). Speaker was ordered into involuntary medical isolation in May after he and his bride took the two transatlantic flights against doctors' orders, then drove across the U.S.-Canada border to return to Atlanta.

Dr. Moonan, a senior epidemiologist for the Division of Tuberculosis Elimination at the CDC, was the supervising investigator on the Speaker incident. His expertise in infectious diseases also garnered Dr. Moonan an interview for a report that aired on National Public Radio on June 13. The segment that aired on "All Things Considered" included an explanation of how TB genotyping is used locally.

In addition to his duties as part of the CDC's outbreak investigation team, Dr. Moonan co-ordinates the U.S. National Tuberculosis Genotyping Service. He has been with the CDC for two years.

What is the status of Speaker? His diagnosis was reclassified as multi-drug resistant tuberculosis (MDR TB) in early July. He underwent surgery in mid-July to remove the infected lung tissue. Speaker was released from the hospital nine days after his surgery.

"Treatment for Mr. Speaker went very well, and we were able to release him more quickly than we originally anticipated," says Gwen Huitt, MD, in a National Jewish Medical and Research Center news release. "Although we believe there are still a few tuberculosis bacteria in his lungs, ongoing antibiotic therapy should kill those. We expect him to return to a full and active life."

New TB drugs could save lives

Recent tuberculosis (TB) concerns have brought an old disease into the news, but TB research isn't new to the University of North Texas Health Science Center at Fort Worth (UNTHSC). The Center has partnered with Dallas-based Cumbre Pharmaceuticals to develop a series of new experimental antibiotic drugs for that may help treat TB patients.

UNTHSC's relationship with Cumbre started four years ago when Cumbre began a research program to develop a new antibiotic designed to treat serious bacterial infections that can develop in people with internal medical devices, including heart valves, catheters and artificial joints. After Cumbre looked at several different labs in the area to test the experimental antibiotic, the UNTHSC proposed that the company could use its facilities and technicians until Cumbre developed its own testing facility.

"When Cumbre began working with us four years ago, it was an interim project until it established its own testing facility," said Dr. Jerry Simecka. "Once they saw the quality of our work and cost effectiveness, Cumbre determined that the Health Science Center could provide the advanced testing services that were needed as well as or better than they could if they built their own facility."

Building on this successful collaboration, Cumbre again turned to UNTHSC last fall upon initiating a program focused on the development of new agents for the treatment of TB in collaboration with the Global Alliance for TB Drug Development. Prior to selecting any compounds for testing in human clinical studies, the UNTHSC team performs advanced tests to determine how the experimental TB drugs are tolerated, as well as the length of time they stay in the body.

Cumbre Pharmaceuticals is a research-based specialty pharmaceutical company that discovers, develops and markets anti-infective products for the treatment of serious and life-threatening infections, particularly those caused by antibiotic-resistant pathogens.