

SOUTHWESTERN NEWS

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UT SOUTHWESTERN DISCOVERIES ADVANCE BIOMEDICAL RESEARCH IN 2001

DALLAS – January 7, 2002 – Investigations into cell growth that may someday inhibit cancer; how a harmful Alzheimer’s disease protein functions in healthy brains; finding a means to combat the effects of cystic fibrosis; and how cocaine affects the brain at the molecular level, are some of the scientific discoveries at UT Southwestern Medical Center at Dallas during the past year.

Staying at the forefront of biomedical research is one of the key goals at UT Southwestern, said Dr. Robert Alpern, dean of Southwestern Medical School. “The discoveries made in our research centers and laboratories make a difference, not only for Texans today but also for millions of other Americans who will one day benefit from the knowledge this research brings to light.”

Here are some of the discoveries that illustrate how UT Southwestern advanced biomedical research in 2001.

PROJECT CHANGING WAY SCIENTISTS CONDUCT RESEARCH

Nobel laureate Dr. Alfred Gilman, chairman of pharmacology at UT Southwestern, is leading a \$10 million-per-year project allowing researchers around the world to pool their efforts in studying one of the most puzzling mysteries in biomedicine — how cells interact with, or signal, each other.

The Alliance for Cellular Signaling (AFCS) involves 20 universities and 50 participating investigators: 48 in the United States, one in Canada and one in the United Kingdom. The project’s research ultimately could lead to the development of a “virtual cell” that could be used to test new drugs.

STUDY SHOWS DRUG IMPROVES OUTCOME OF CHILDREN INFLECTED WITH MENINGOCOCCEMIA

Death and amputations from meningococemia were reduced when researchers used a cloned protein, similar to one that occurs naturally in the human body, to treat children who contracted the often-fatal or mutilating childhood bacterial disease, according to a study published in the British medical journal *The Lancet*.

Treating patients with a recombinant form of bactericidal permeability-increasing protein (BPI), Dr. Brett Giroir, associate professor of pediatrics at UT Southwestern and chief medical officer at Children’s Medical Center of Dallas, and doctors across the United States, Canada and England noted a 68 percent reduction in major limb amputation, a 28 percent reduction in blood transfusions and an improvement in functional recovery of children with this disease.

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TELOMERASE INHIBITORS MAY HELP PREVENT BREAST CANCER

Cell biology researchers at UT Southwestern found that attacking an enzyme called telomerase, which promotes indefinite cell growth, could prove helpful in preventing breast cancer. Their research is the first to demonstrate that telomerase is a target both for cancer therapy and prevention.

Dr. Brittney-Shea Herbert, a postdoctoral fellow working with Drs. Jerry Shay and Woodring Wright, professors of cell biology at UT Southwestern, and scientists from the National Cancer Institute, treated noncancerous breast cells for three months with chemopreventive and antitelomerase agents. They reported in the *Journal of the National Cancer Institute* that almost none of the cells began the infinite division process that signals the onset of cancer.

RESEARCHERS REAFFIRM USE OF PREDICTOR OF INFANT SURVIVAL

UT Southwestern researchers reaffirmed the value of the nearly 50-year-old Apgar score as a quick and easy predictor of 28-day neonatal survival. The research, published in *The New England Journal of Medicine*, was conducted at Parkland Memorial Hospital, the primary teaching hospital for UT Southwestern faculty physicians, which has a level III neonatal intensive care unit.

The study evaluated more than 150,000 infants born at 26 weeks or later over an 11-year period. Dr. Brian Casey, assistant professor of obstetrics and gynecology at UT Southwestern, was the principal investigator.

RESEARCHERS LINK BICARBONATE TRANSPORT TO CYSTIC FIBROSIS

Physiology researchers at UT Southwestern, working with Korean researchers, found an association between defects in the transport of bicarbonate and cystic fibrosis. The study was published in *Nature*.

Dr. Shmuel Muallem, professor of physiology, said the findings raised the question about whether delivering bicarbonate to diseased tissues can someday be used to lessen the effects of cystic fibrosis in patients and even extend their lives.

RESEARCHERS ATTACK RIDDLE OF COCAINE ADDICTION IN BRAIN

Dr. Eric Nestler, chairman of psychiatry, and other researchers at UT Southwestern and at Rockefeller University uncovered new information about dopamine-related activity in the brain that may lead to better understanding of the long-term brain-cell changes associated with cocaine addiction and addiction recovery.

The research targeted specific changes in two brain proteins following the administration of cocaine. The findings, published in *Nature*, provide important information about how the brain reacts to cocaine after repeated administration.

SCIENTISTS FIND GENE FOR INHERITED FORM OF HIGH CHOLESTEROL

Researchers at UT Southwestern located the gene that, when mutated, is responsible for an inherited form of high cholesterol. This disorder, which results in the development of premature coronary artery disease and accumulation of cholesterol in

skin and tendons, is rare, but understanding its origin may lead to the development of new treatments for high blood levels of cholesterol.

Dr. Helen Hobbs, senior investigator of the study and chief of clinical genetics, and her colleagues at UT Southwestern located the gene and found six mutations. The results of the study were published in *Science*.

THREE STATIN DRUGS FOUND TO REDUCE NEW MARKER OF HEART DISEASE

Three common cholesterol-lowering drugs significantly reduce a relatively new, independent marker of inflammation in the coronary arteries called C-reactive protein (CRP), researchers at UT Southwestern discovered. Inflammation in the coronary arteries has only recently been shown to be a major cause of heart attack and stroke.

More than 70 percent of the participants in the study, the results of which were published in *Circulation*, noted average decreases of 23 percent in CRP levels while on at least one of three statin drugs, said Dr. Ishwarlal Jialal, lead author and professor of pathology and internal medicine.

STUDY FINDS BETA-BLOCKING DRUG REDUCES HEART FAILURE IN BLACKS

Researchers led by Dr. Clyde Yancy, medical director of the UT Southwestern/St. Paul Heart Transplant Program, have found that the beta-blocking drug carvedilol reduces the symptoms of mild to moderate heart failure and the risk of death in black patients as well as it does in nonblack patients.

The study, reported in *The New England Journal of Medicine*, was the first to evaluate whether race influences the response to the relatively new beta-blocker carvedilol as a treatment for heart failure, a disease that affects 3 percent of all black adults in the United States.

ANTACIDS AS EFFECTIVE AS SURGERY FOR SEVERE HEARTBURN

A study by UT Southwestern physicians in *The Journal of the American Medical Association* suggested that anti-reflux surgery is no better for treating severe heartburn than antacid medications.

Dr. Stuart Spechler, professor of internal medicine, and his colleagues conducted a follow-up study of patients who had been treated 10 years earlier for gastroesophageal reflux disease, or GERD, to determine whether those who had surgery for the disease fared better than those who took prescription medication.

BETA-BLOCKER INEFFECTIVE FOR ADVANCED HEART FAILURE

A promising beta-blocker did not prolong survival of patients with advanced heart failure, according to a study conducted by researchers at UT Southwestern. The study was published in the *New England Journal of Medicine*.

The investigational medicine bucindolol, which in preliminary trials has been shown to be safe, effective and well tolerated, did not reduce death from moderate-to-severe heart failure in 2,708 patients who took part in the Beta-Blocker Evaluation of Survival Trial (BEST). Patients with less-advanced heart failure did, however, show

improvement with bucindolol. Dr. Eric Eichhorn, professor of internal medicine, co-authored the study.

STUDY REVEALS PROTEIN ESSENTIAL TO HEART FORMATION

UT Southwestern researchers found a protein that controls the development of the heart, a discovery that could contribute to novel methods of creating heart cells which could be used in the treatment of various cardiac conditions.

In *Cell*, researchers led by Dr. Eric Olson, chairman of molecular biology, reported that the protein myocardin is expressed in cardiac muscle cells and turns on cardiac genes. Without this protein, formation of the heart is eliminated in frog embryos.

SCIENTISTS MAP HOW ALZHEIMER'S DISEASE PROTEIN FUNCTIONS

Researchers at UT Southwestern have discovered how a harmful Alzheimer's disease protein functions in healthy brains – a finding that puts researchers one step closer to defining the pathogenesis of the disease.

Dr. Thomas Südhof, director of UT Southwestern's Center for Basic Neuroscience, reported in the medical journal *Science* that the protein called amyloid precursor protein (APP) — a protein that all people have in their brain cells — promotes gene expression. Understanding how the protein functions under normal conditions is a critical step in understanding Alzheimer's.

DISCOVERY SHOWS HOW HDL PROTECTS ARTERIES

Scientists at UT Southwestern discovered that high-density lipoproteins (HDL) — the “good cholesterol” — trigger a process that keeps arteries clean and flexible. It's a discovery, researchers believe, that could lead to new strategies to prevent or treat vascular diseases such as atherosclerosis, commonly known as hardening of the arteries.

Dr. Philip W. Shaul, professor of pediatrics, senior author of the study published in *Nature Medicine*, found that nitric oxide is a potent signaling molecule that keeps arteries from clogging and constricting, processes that restrict blood flow and lead to high blood pressure, strokes and heart attacks.

PHYSICAL EXAMINATIONS PLAY ROLE IN PREDICTING HEART FAILURE

Two common findings from a traditional physical examination can provide important information for the 5 million Americans diagnosed with heart failure, researchers at UT Southwestern found.

In a retrospective analysis of a large heart-failure trial, published in *The New England Journal of Medicine*, researchers led by Dr. Mark Drazner, assistant professor of internal medicine, found that patients with either a third heart sound or elevated jugular venous pressure were more likely to have progressive heart failure and subsequent hospital visits due to heart failure.

SIX MONTHS OF EXERCISE REVERSES DECLINE IN FITNESS DUE TO AGING

Six months of exercise can reverse the decline in physical conditioning associated with aging, researchers at UT Southwestern reported in a 30-year follow-up to the 1966

landmark Dallas Bed Rest and Training Study. They also found that three weeks of bed-rest deconditioning has a more profound impact on physical work capacity than 30 years of aging.

The 1966 study, considered one of the most pivotal studies in exercise science, evaluated the response to endurance exercise training after a 20-day period of bed rest. The two-part, follow-up study, led by Dr. Darren Maguire, professor of internal medicine, was reported in *Circulation*.

CARDIAC HORMONE LEVEL INDICATES INCREASED RISK OF DEATH

Researchers at UT Southwestern have found that elevated levels of a cardiac hormone are predictive of an increased risk of death or heart failure in patients with complications of coronary artery disease.

The findings, published in *The New England Journal of Medicine*, provide physicians with a new method of assessing adverse outcomes in patients with acute coronary syndromes, said Dr. James de Lemos, lead author of the study and assistant professor of internal medicine.

RESEARCHERS DISCOVER HOW NEURONS COMMUNICATE

Researchers at UT Southwestern have discovered a biochemical pathway that helps describe how neurons in the brain and spinal cord form their connections.

Further study into the new data, published in the journal *Nature*, could lead to discoveries in nerve regrowth and regeneration, according to Dr. Mark Henkemeyer, assistant professor in the Center for Developmental Biology.

RESEARCH LINKS GENE TO GLUCOSE SYNTHESIS IN LIVER

Researchers have discovered that a known gene activates the enzymes that generate glucose in the liver - a surprising new finding that could lead to a breakthrough in diabetes research.

The biochemical and genetic study, conducted by Dr. Christopher B. Newgard and others at UT Southwestern and Harvard Medical School, established that the PGC-1 gene turns on several other genes involved in gluconeogenesis, or glucose synthesis from scratch, in the liver. The study was published in *Nature*.

RESEARCHERS UNCOVER NEW STEP IN HOW BRAIN WORKS

Led by Dr. Steven G. Kernie, assistant professor of pediatrics, researchers at UT Southwestern have begun to reveal the cellular mechanisms critical for restoring brain functions after traumatic injuries - a step that could lead to effective treatments of paralysis and other brain and spinal-cord damage.

Published in the *Journal of Neuroscience Research*, the study showed that following traumatic brain injury, the brain's stem-cell proliferation continues at a rapid pace and persists over a much longer time than expected, both at the injury site and even in the most-distant areas affected by the injury.

ALPHA INTERFERON ERROR MAY CAUSE LUPUS

Researchers at UT Southwestern and the Baylor Institute for Immunology Research in Dallas have linked abnormal secretion of alpha interferon to the malfunctioning immune systems of young patients with lupus.

The study, published in *Science*, is a major step toward explaining how systemic lupus erythematosus deceives the body's immune system into destroying healthy cells and could lead to enhanced therapies, says Dr. Virginia Pascual, assistant professor of pediatrics.

DEVICE PROLONGS LIVES OF ADVANCED HEART-FAILURE PATIENTS

In a two-year, multicenter trial evaluating the left ventricular assist device (LVAD), Drs. Clyde Yancy and Dan Meyer at UT Southwestern and others across the country concluded that the mechanical heart-assist device prolongs life and improves quality of life.

Results of the study, published in *The New England Journal of Medicine*, indicated that the LVAD is an acceptable alternative therapy in select patients who are not candidates for cardiac transplantation.

STATIN DRUGS REDUCE MARKER OF CORONARY-ARTERY DISEASE

Two out of three statins, powerful drugs lauded for dramatically lowering low-density lipoproteins (LDL) – the bad cholesterol - have been found to significantly decrease another risk factor for coronary-artery disease, researchers at UT Southwestern report.

In the first head-to-head comparison of the effect of three commonly prescribed statins on remnant lipoprotein (RLP) cholesterol levels, the researchers reported in *Arteriosclerosis, Thrombosis and Vascular Biology* that atorvastatin (Lipitor) and simvastatin (Zocor) significantly reduced RLP levels. Pravastatin (Pravachol), the third drug used in the study, had no significant effect on RLP levels, reported Dr. Ishwarlal Jialal, professor of pathology and internal medicine.

RESEARCHERS DEVELOP NEW METHOD OF DELIVERING VACCINES

Researchers at UT Southwestern have developed a quicker, more cost-efficient method of delivering dendritic cell-based vaccines – a discovery that moves anti-tumor vaccines closer to a practical reality.

Dr. Akira Takashima, professor of dermatology, reported in *Nature Biotechnology* that the current process, which is more expensive and time-consuming, has prevented broader clinical applications for dendritic cell-based vaccines.

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