Spring 2011

JT SOUTHWESTERN MEDICAL CENTER

Alzheiner's

FROM THE DIRECTOR | Roger N. Rosenberg, M.D.



On Jan. 4, 2011, President Obama signed into law the National Alzheimer's Project Act (NAPA). Thousands of Americans from every walk of life sent messages to Congress and the White House to urge its passage. All of us in the Alzheimer's Disease Center at UT Southwestern strongly supported this initiative and worked closely with the Alzheimer's Association to lobby legislators.

NAPA' s objective, the association says, is "to create a coordinated national plan to overcome the Alzheimer crisis in America and to ensure the coordination and evaluation of all national efforts in Alzheimer research, clinical care, institutional, and home-and community based programs and their outcomes."

The first goal is finding new therapies to prevent, delay or even reverse this disease. Without effective therapy the incidence and prevalence of Alzheimer's disease is expected to double in the next 25 years. Bringing a new drug to market is costly, and it might take as much as \$1 billion and 10 years to discover and implement a new concept and idea. The Congress must now do for Alzheimer's disease research and therapy development what it has done for cancer therapy development.

There are now several drugs being provided to cancer patients that are highly effective at delaying and even curing the disease. One such drug, Gleevec, has reduced the mortality rate of children with leukemia from 90 percent to less than 10 percent. The drug was developed through funding basic science, finding new therapeutic targets and focusing drug development directed to these targets. The same must be done for Alzheimer's disease. The next step for us all is to continue the pressure on Congress to secure funding for Alzheimer's disease drug development.

In this regard, it is important to call attention to the research of Dr. Steven McKnight, chairman of the Department of Biochemistry, and his colleague Dr. Andrew Pieper, assistant professor of psychiatry and biochemistry, our featured speakers at the March 23 Spring Forum. Theirs is the type of innovative and creative neuropharmacology that is needed for Alzheimer's disease.

Continued on page 5 »

FORUM SPEAKERS TO DISCUSS KEY NEURON PRESERVER

By Aline McKenzie

In their search for a drug that could keep brain cells from dying, a team of UT Southwestern researchers faced more than a needlein-a-haystack search. They first had to assemble the haystack.

But the resulting three-year investigational journey has led to a compound that preserves the viability of newly created brain cells and boosts learning and memory in an animal study.

Dr. Steven McKnight, chairman of biochemistry, and Dr. Andrew Pieper, assistant professor of psychiatry and biochemistry, will describe their work in a talk at a March 23 Spring Public Forum presented by the Friends of the Alzheimer's Disease Center.

The 7 p.m. forum, titled "Early-Stage Efforts to Discover Drugs That Preserve Brain Cells," will be held in the Simmons/Hamon Biomedical Research Buildings on

Continued on page 5 »

WHAT'S INSIDE

- Research Studies
- Clinical Trials
- Memory Tip



Research Studies



RESEARCHERS CREATE EXPERIMENTAL ALZHEIMER'S VACCINE

By Aline McKenzie

Researchers at UT Southwestern have created an experimental vaccine against beta-amyloid, the small protein that forms plaques in the brain and is believed to contribute to the development of Alzheimer's disease.

Compared with similar socalled DNA vaccines that the UT Southwestern researchers tested in an animal study, the new experimental vaccine stimulated more than 10 times as many antibodies that bind to and eliminate betaamyloid. The results appeared in the journal Vaccine.

Future studies will focus on determining the safety of the vaccine and whether it protects mental function in animals, said Dr. Roger Rosenberg, director of the Alzheimer's Disease Center at UT Southwestern and senior author of the study.

"The antibody is specific; it binds to plaque in the brain. It doesn't bind to brain tissue that does not contain plaque," said Dr. Rosenberg, who holds the Abe (Brunky), Morris and William Zale Distinguished Chair in Neurology. "This approach shows promise in generating enough antibodies to be useful clinically in treating patients."

A traditional vaccine – an injection of beta-amyloid protein itself into the arm – has been shown in other research to trigger an immune response, including the production of antibodies and other bodily defenses against beta-amyloid. However, the immune response to this type of vaccine sometimes caused significant brain swelling, so Dr. Rosenberg and his colleagues focused on developing a nontraditional DNA vaccine.



Dr. Roger Rosenberg, director of the Alzheimer's Disease Center, and colleagues including Dr. Doris Lambracht-Washington, assistant instructor of neurology and neurotherapeutics, have developed an experimental vaccine against beta-amyloid, a protein that has been linked to Alzheimer's.

The DNA vaccine does not contain beta-amyloid itself but instead a piece of the beta-amyloid gene that codes for the protein. In the current study, the researchers coated tiny gold beads with the beta-amyloid DNA and injected them into the skin of the animals' ears. Once in the body, the DNA stimulated an immune response, including antibodies to beta-amyloid.

The next step in the research is to test long-term safety in animals, Dr. Rosenberg said. "After seven years developing this vaccine, we are hopeful it will not show any significant toxicity, and that we will be able to develop it for human use," he said.

Other UT Southwestern neurology researchers involved in the study were Dr. Bao-Xi Qu, assistant professor; Dr. Doris Lambracht-Washington, research scientist; Min Fu, research associate; Dr. Todd Eagar, assistant professor; and Dr. Olaf Stüve, associate professor. *

BLOOD TEST COULD DIAGNOSE ALZHEIMER'S DISEASE

By Aline McKenzie

A set of proteins found in blood serum shows promise as a sensitive and accurate way to diagnose Alzheimer's disease, researchers at UT Southwestern have found as part of a statewide study.

An analysis of the proteins, plus a clinical exam, proved 94 percent accurate in detecting suspected Alzheimer's and 84 percent accurate in ruling it out in people without the disease, the researchers said.

"This research uses a novel technology that makes it possible to analyze several biomarkers in a single blood sample in a cost-effective way," said Dr. Ramón Díaz-Arrastia, professor of neurology at UT Southwestern and senior author of the study in Archives of Neurology.

Researchers have been seeking a simple blood test for Alzheimer's for years, Dr. Díaz-Arrastia said, but no single substance, or "biomarker," has been shown to be useful. Such a test, he said, would be comparable in principle to measuring blood cholesterol as a biomarker of cardiovascular disease.

Alzheimer's disease is difficult to diagnose, particularly in its early stages when it resembles other cognitive problems. Currently, a definitive diagnosis is possible only after examining the brain tissue of deceased individuals. Tests for suspected Alzheimer's are often expensive or invasive, and not every patient is able or willing to undergo them, the researchers stated.

A blood test would provide a convenient diagnostic method that could be performed by health care workers nearly anywhere. In addition, a definitive diagnosis is important because treatments specifically targeting Alzheimer's might not be effective against other forms of neurodegenerative disease or cognitive decline, Dr. Díaz-Arrastia said.

Researchers associated with the Texas Alzheimer's Research Consortium, a five-university group funded by the state, carried out the research. In the current study, the scientists analyzed blood samples from 197 Texas patients who had suspected Alzheimer's and 203 people without the disease.

The researchers measured more than 100 blood proteins and created a mathematical analysis that could measure a person's risk of having Alzheimer's. The analysis, combined with information from a clinical exam, accurately detected Alzheimer's 94 percent of the time, and correctly ruled out Alzheimer's 84 percent of the time in people without the disease, Dr. Díaz-Arrastia said.

Neither the blood test nor a clinical exam alone was as accurate on its own as the blood test and clinical exam combined, the researchers found.

"Having a diagnosis is an important step, but it's not the end of the road unless you've got a treatment or a cure," Dr. Díaz-Arrastia said.

The next step in the work is to determine whether the biomarker test can detect accurately Alzheimer's in preserved blood serum from patients who have been diagnosed definitively by an autopsy.

Other UT Southwestern researchers participating in the study were Dr. Guanghua Xiao, assistant professor of clinical sciences; Dr. Joan Reisch, professor of clinical sciences and family and community medicine; and Dr. Perrie Adams, professor of psychiatry. *

"This research

- uses a novel technology that makes it possible to analyze several biomarkers in a single blood sample in a cost-effective way."
 - Ramón Díaz-Arrastia, M.D.



\$2 MILLION CHALLENGE GRANT CREATES NEW CENTER

By Rachel Skei Donihoo

A new Center for Alzheimer's and Neurodegenerative Diseases has been created with a \$2 million challenge grant. The center will be directed by Dr. Joachim Herz.

"I am enormously grateful for this highly motivating gift, which was instrumental in founding our new center," said Dr. Herz, professor of molecular genetics and neuroscience. "This gift - and others made by donors who continue to make this center a reality - will enable UT Southwestern to recruit and retain outstanding faculty to join our targeted efforts to prevent and treat Alzheimer's disease. Without this kind of major support, it would be impossible to proceed at the pace necessary to meet the challenge posed by this debilitating and increasingly common disease."

Dr. Herz, who holds the Thomas O. and Cinda Hicks Family Distinguished Chair in Alzheimer's Disease Research, is noted for his groundbreaking research into how a mutation in a single protein trig-

gers the devastation of Alzheimer's disease, which affects 5.3 million Americans and is the country's seventh leading cause of death. Dr. Herz's most recent work focuses on the study of molecules called APOE receptors, which are embedded in the membranes of nerve cells. APOE receptors serve as "signal modulators," making the cells more responsive to incoming signals from other nerve cells, or neurons. The receptors can greatly change the sensitivity of neurons, over the course of a single day, affecting how strongly nerve cells interact with each other.

"Joachim Herz has played an extraordinary role in the progress UT Southwestern has made as a pre-eminent medical center," said Dr. Daniel K. Podolsky, president of UT Southwestern and holder of the Philip O'Bryan Montgomery Jr., M.D., Distinguished Presidential Chair in Academic Administration and the Doris and Bryan Wildenthal Distinguished Chair in Medical Science. "We are enormously grateful

for this investment in our work. In 2007 Dr. Herz was awarded Germany's highly respected Heinrich Wieland Prize for his research related to lipid and cholesterol regulation.



He was cited for his discovery of novel and essential functions of lipoprotein receptors in the transmission of signals between cells. His research team identified important signaling pathways that control not only critical steps during embryonic organ development, but also in the brain.

In the course of their work, funded in part by the Berry Cox Family Foundation, Dr. Herz and his lab members further identified a specific protein that plays a key role in determining whether fatty substances and cholesterol build up inside arteries. Accumulation of cholesterol in the walls of blood vessels is a leading cause of heart attacks and stroke. *

FRIENDS GRANT HELPS SUPPORT SEARCH FOR NEW THERAPIES

By Rachel Skei Donihoo

The Friends of the Alzheimer's Disease Center awarded \$65,000 to Dr. Andrew Pieper, assistant professor of psychiatry and biochemistry.

Dr. Pieper and his team have discovered a new class of small, druglike molecules that protect brain cells from dying. Together with biochemistry department colleagues Drs. Steven McKnight, chairman, Joseph Ready, associate professor, and Jef De Brabander, professor, Dr. Pieper is working to learn how these molecules work and also to synthesize new, more highly active variants with improved properties for drug development. The team also is conducting rigorous testing to determine which patients would most likely benefit from a drug that might emerge from the research program.

One result of administering this class of molecules to mice is a substantial increase in the net production of new brain cells, or neurons, in the region of the brain known as the hippocampus. Normally, new neurons are born every day of our lives in the hippocampus. In some conditions, however - such as Alzheimer's disease - not enough of these newborn neurons survive, and the hippocampus can no longer function properly to mediate learning and memory. Dr. Pieper's hypothesis is that some learning and memory problems could be addressed by a drug that blocks the degradation of the hippocampus.

"We've already shown that blocking neuron cell death and increasing the net production of new brain cells in the hippocampus is associated with protecting aged rats from their expected decline in learning and memory," said Dr. Pieper. "We now intend to evaluate



Andrew Pieper, M.D., Ph.D.

the efficacy of our neuroprotective molecules in an animal model of Alzheimer's disease. We're hopeful that we'll see similar benefit and thus help develop a new approach to treating patients. These are expensive experiments and, because our work represents an early-stage and nontraditional approach to Alzheimer's, we have not yet obtained traditional funding. With this wonderful support from the Friends, however, we are now able to push our research forward immediately." *

FROM THE DIRECTOR

Continued from page 1

The ADC is working closely with them and the synergism, we believe, will produce positive results.

The center also participates in several national research networks funded by the National Institutes of Health's National Institute on Aging. The Alzheimer's Disease Neuroimaging Initiative studies structural and functional changes in the brains of thousands of Alzheimer's patients. Regions of the brain most vulnerable to the disease process have been identified and studied for their rates of glucose metabolism, storage of the amyloid protein and loss of neurons. These vital studies have yielded much new data that will expedite drug development.

We are optimistic and enthused about the rate and quality of Alzheimer's disease research in the past several years, including significant accomplishments by our own UT Southwestern faculty, including Drs. Joachim Herz, Ilya Bezprozvanny, Janine Prange-Kiel, Gang Yu, Dwight German, Ramon Diaz-Arrastia, Kyle Womack, Myron Weiner, Charles White III and Craig Powell.

I thank all of the Friends of the ADC and the patients and caregivers who are involved in our research. Your participation is vital to our continued progress and there is no substitute for your support. Together we will make a difference. *****

FORUM SPEAKERS TO DISCUSS KEY NEURON PRESERVER

Continued from page 1

the North Campus, 6000 Harry Hines Blvd. Complimentary valet parking is available.

The forum is free to the public, but because seating is limited, attendance should be confirmed by calling the medical center's Office of Development at 214-648-2344.

The research team led by Drs. McKnight and Pieper screened 1,000 individual molecules to see which ones might enhance the production of neurons in the adult mouse hippocampus, a region of the brain critical to learning and memory. The scientists found that one of the compounds, called P7C3, achieved this by protecting newborn neurons from dying.

"We don't know yet whether P7C3 can block the death of mature nerve cells, which is what occurs in humans suffering from Alzheimer's disease and other neurodegenerative diseases," said Dr. McKnight, who holds the Sam G. Winstead and F. Andrew Bell Distinguished Chair in Biochemistry and the Distinguished Chair in Basic Biomedical Research.

A test using elderly rats, which characteristically show a decline in the birth and formation of hippocampal neurons, showed that P7C3 increased both the birth and survival of new neurons, and the memory and learning capability of the aged rats.

The researchers currently are studying the mechanism by which P7C3 protects cells from dying, and whether it might have any protective effect in other models of neurodegenerative disease.

The researchers, in collaboration with Dr. Joseph Ready, associate professor of biochemistry and a synthetic chemist, are continuing to work on P7C3, modifying it in an attempt to improve its actions. They also plan to test the substance in animal models of other neurodegenerative diseases, including

Huntington's disease and amyotrophic lateral sclerosis (Lou Gehrig's disease).

The Friends of the Alzheimer's Disease Center was established in 1996 to provide financial support for Alzheimer's research at UT Southwestern. All the group's contributions go directly to support Alzheimer's research at the medical center.



Steven McKnight, Ph.D.

Since its founding, the group has raised more than \$1 million for grants to researchers. For information on joining the group, call the Office of Development at 214-648-2344. *****

IN SICKNESS AND IN HEALTH SPOUSES TAKE PART IN ALZHEIMER'S STUDY, THOUGH NEITHER HAS THE DISEASE

By Aline McKenzie



Lowell and Betty Moon, participants in the ADNI 2 study, visit clinical research coordinator Kristin Martin-Cook (center) at the Alzheimer's Disease Center a few times a year to undergo testing. People such as the Moons, who do not have Alzheimer's, are an important part of the international study.

When Betty Moon, 77, a retired middle school teacher from Rockwall, noticed disturbing lapses of memory, such as remembering the color of a book but not its title, she decided to enroll in a study of Alzheimer's disease.

Her husband, Lowell, 80, had no such "senior moments" but decided to join as well and was placed in a control group.

"At first, I was going with her to be a partner," said Mr. Moon, a real estate appraiser. "But I know people who have had relatives with Alzheimer's, and I see the lives they have to live. I do it for one person – the caregiver." The Moons are participating in a study called the Alzheimer's Disease Neuroimaging Initiative 2, or ADNI 2. ADNI began in 2004 as an international study designed to define biomarkers for use in clinical trials to determine the best way to measure treatment effects on Alzheimer's, but the goal has been expanded to using biomarkers to identify Alzheimer's at a pre-dementia stage.

"For example, a doctor might know that a patient is at risk of heart disease because his or her cholesterol is high," said Dr. Roger Rosenberg, director of the Alzheimer's Disease Center at UT Southwestern. "The cholesterol is what we call a biomarker – a biological feature that can measure the progress of a disease. Biomarkers are invaluable in diagnosing and treating diseases, but there are none available for Alzheimer's disease.

"We especially want to focus on those people who are having consistent but mild senior moments to better understand the relationship between symptoms and the development of more serious memory problems."

Mrs. Moon has been told she has mild cognitive decline.

"I'm curious to see if the senior moments get worse, and if they should, UT Southwestern has said they'd give me medication," she said. "I also want to know as much ahead of time if I'm going to get worse so we can prepare.

"And we know this is a national and international study, so I know I'll be helping someone else."

The Moons come to UT Southwestern a few times a year for testing, including brain imaging and measurements of cognitive function. The Alzheimer's Disease Center at UT Southwestern is seeking more participants – with and without memory loss – for the ADNI 2 study.

"Recruiting study volunteers with early mild cognitive impairment can be difficult, because they might not realize they have it, or feel a stigma," said Dr. Rosenberg, holder of the Abe (Brunky), Morris and William Zale Distinguished Chair in Neurology.

And while the Moons are happy to be helping with the research that can help people in the future, they also want to remind others to help people affected by Alzheimer's now.

"If you want to do something, then once a week get a room in your church or your community center and say to the caregivers, 'Bring us your people and we'll take care of them, and you can go have a break, go out to eat or go see a movie,'" Mr. Moon said. *

CLINICAL TRIALS

To learn more about studies under way, call the UT Southwestern Memory Research Unit at 214-648-9376.

DAVUNETIDE

Participants with progressive supranuclear palsy will receive placebo or davunetide nasal spray twice a day for 52 weeks. Participants must be 41 to 85 years old; be able to tolerate magnetic resonance imaging and lumbar punctures; be able to ambulate independently or with limited assistance; have a caregiver willing to attend all study visits and monitor study medication dosing; and have a 12-month history of postural instability or falls. No memory medications are allowed. Call Jackie Rabb, 214-648-9376.

IMMUNE GLOBULIN

Participants with mild to moderate Alzheimer's will receive infusions of immune globulin, a drug already approved to treat several other conditions. During the 82-week trial, participants will receive 36 intravenous infusions – the first three will be at the clinic and the remainder will be administered by a home health care professional. Call Tamera Lake, 214-648-9310.

EXERCISE STUDY

People with mild cognitive impairment who do not currently adhere to a regular fitness program are sought for a one-year study that will compare individually tailored, supervised aerobic exercise training with flexibility and stretching training. The study will investigate the effects of exercise on cognitive and cardiovascular heath as well as changes in proteins known to damage and/or protect the brain. Call Kristin Martin-Cook, 214-648-9368, or Estee Brunk, 214-345-4665.

OBSERVATIONAL AND BIOMARKER DEVELOPMENT STUDIES

While these studies do not require or offer a new treatment, they are the foundation for future research and therapeutic trials.

ADNI 2 (ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE – PHASE 2)

This study builds on the first ADNI studies and will enroll people ages 55 -90 with no memory problems, mild cognitive impairment and early Alzheimer's disease. Participants will undergo magnetic resonance imaging (MRI), traditional glucosebased positron emission tomography (PET), new amyloid PET scanning to investigate the formation of beta-amyloid plaque formation, and standard neuropsychological and neurological exams. Participants will be compensated for their time and participation. Call Kristin Martin-Cook, 214-648-9368.

BAYER IMAGING STUDY

Participants who are in the later stages of Alzheimer's, are eligible for hospice or have a life-limiting disease process are being sought for a Phase 3 clinical trial of Florbetaben (BAY 94-9172), a novel compound used in the imaging of beta-amyloid proteins in the brain. Through the use of PET imaging and Florbetaben, researchers hope to develop a diagnostic tool that will improve earlier detection, diagnosis and the effectiveness of treatments for Alzheimer's disease. Participants must be willing to undergo magnetic resonance imaging (MRI) and positron emission tomography (PET) scan and agree to brain autopsy after death. They will be compensated for their time. Call Barb Davis, 214-648-9367.

ERK AD-INDEX STUDY

People 50 and older with memory loss or depression, or who have experienced other cognitive decline or impairment, are being sought for a study of the ERK AD-Index, a test that could aid in the diagnosis of Alzheimer's disease in the future. Participants must be available for a one-hour visit that involves consent, medical history, sampling of blood and a skin biopsy, and must agree to a brain autopsy with results contributing to the study. Participants will be compensated for their time. Call Kathy Koch, 214-648-9343.

CORE AND TARC RESEARCH STUDIES

People with mild cognitive impairment, early Alzheimer's disease or frontotemporal dementia are always needed for observational studies, as are healthy people 65 or older to serve as controls. The studies usually involve one visit a year for neuropsychological testing, neurological exams, brain imaging and blood sampling. The data collected from these visits is used by many investigators studying the aging brain and disorders of cognitive function. These visits often involve financial compensation. Call Mac Miles, 214-648-9338, Jackie Rabb, 214-648-9376, or Kristin Martin-Cook, 214-648-9368.-*

Join Us



JOIN THE FRIENDS OF THE ALZHEIMER'S DISEASE CENTER

The Friends of the Alzheimer's Disease Center raises funds to establish yearly grants for promising researchers who are working to unlock the mysteries of Alzheimer's disease. In addition, the Friends sponsor public forums each spring and fall to present the latest scientific information on the disease to the general public. We welcome the community to these sessions.

Fully tax-deductible memberships in the Friends begin at \$500 per year per individual or couple. To join the Friends, call 214-648-2344 or visit our website at www.utsouthwestern.edu/donatenow. Honorary or memorial gifts are another meaningful way to make contributions toward research that is under way at UT Southwestern.

The Alzheimer's Disease Center News is published by The University of Texas Southwestern Medical Center. We welcome your comments or suggestions at 214-648-3404 or robin.loveman@utsouthwestern.edu

Director – Dr. Roger N. Rosenberg Editor – Robin P. Loveman Writers – Aline McKenzie, Rachel Skei Donihoo

MINIMIZING RISKS

Many seniors – especially those with cognitive issues – experience changes in their balance, coordination, gait and spatial perception that put them at risk for falling. Kristin Martin-Cook, clinical research coordinator at the Alzheimer's Disease Center, offered these tips:

- Remove any unanchored rugs
- Add rails and colored traction tape to stairs when possible
- Add grab bars, a nonskid bath mat and a seat in the shower
- Consider toilet accessories such as grab bars, raised seats or a bedside toilet
- Keep areas well lit, especially at night
- Consider a monitored emergency system or a schedule of check-in calls from/to family for people living alone.

Dr. Mary Quiceno, assistant professor of neurology and neurotherapeutics and Education Core Director, said patients and families should discuss with their physician any dizziness or lightheadedness. Because some forms of dementia affect balance and gait, ask whether your diagnosis or medications might increase fall risks. Finally, Dr. Quiceno said, consider whether the patient might benefit from a homesafety evaluation or consultation with a physical therapist.

> Арркезя бериса керисате 0323 Наггу Ніпея Віча. 5323 Катгу Ніпея Віча.

Alzheimer's Disease Center

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