WINTER 2010

NORTHWESTERN UNIVERSITY FEINBERG SCHOOL OF MEDICINE

CNADC NEWS

Produced by the COGNITIVE NEUROLOGY AND ALZHEIMER'S DISEASE CENTER

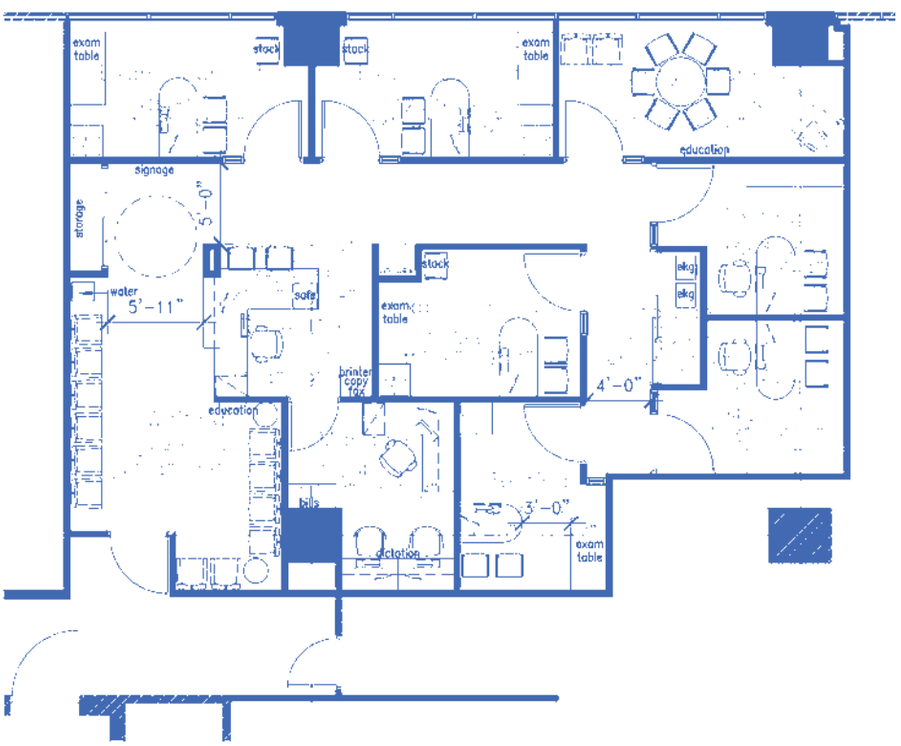
Issue 28

Clinical Service Prepares for a New Home

The Northwestern Neurobehavior and Memory Health Clinic, the clinical arm of the CNADC, will be moving from the Galter Pavilion to new office space on the ninth floor of 676 North St. Clair Street in March.

Being built to CNADC's specifications, the clinical space is intended to facilitate the most comprehensive, dignified, and compassionate care for persons with Alzheimer's disease and related disorders and their families. Among other things, it will provide the center for the first time with a large conference room for families accompanying loved ones to an appointment for education and supportive counseling.

The CNADC Community Advisory Board, chaired by Donna Elrod, has been active in securing funding and contributing to the planning process by meeting with the architects, reviewing plans, and offering consultation.



The CNADC's new home will include a large conference room (upper right) for families accompanying loved ones to an appointment for education and supportive counseling.

The Neurobehavior and Memory Health Clinic will continue to offer these services:

- Evaluation and follow-up care by behavioral neurologists who are doctors especially trained in dementias
- Evaluation of memory and other thinking abilities by specialized tests given by a clinical neuropsychologist
- Management of medication for memory disorders
- Opportunities to participate in clinical research and trials
- Psychiatric evaluation and treatment for mood and behavior disorders associated with neurological disease
- Education and counseling for patients and families
- Information and referral to quality-of-life enrichment programs and other supportive services

Until the move, the clinic will remain open in Suite 20-100 of the Galter Pavilion, 675 North St. Clair Street.

If you are interested in more information or would like to schedule a consultation, contact

NORTHWESTERN NEUROBEHAVIOR AND MEMORY HEALTH CLINIC

Galter Pavilion
675 North St. Clair Street
Suite 20-100
Chicago, Illinois 60611
Phone: 312-695-9627
Fax: 312-695-6072

WWW.BRAIN.NORTHWESTERN.EDU

M.-Marsel Mesulam

Dear Friends and Colleagues:

It has been 15 years since I arrived at Northwestern University to establish the Cognitive Neurology and Alzheimer's Disease Center and its clinical services. Over these past years the CNADC has made great strides in keeping true to our multiple missions: offering state-of-the-art diagnostic evaluation services for persons with cognitive impairment; furthering our understanding of Alzheimer's disease and related disorders through research; transferring the benefits of this research to patients and families; providing training initiatives for promising scientists and clinicians who want to enter this field; and offering education and support for patients, families, and the community at large.

Although all of us who work in the field of Alzheimer's disease were disappointed last year when two drugs considered potentially promising, Alzhemed and Flurizan, failed to prove effective in clinical trials, the search continues. New clinical trials are being conducted at the CNADC and elsewhere. Investigators around the world are collaborating to discover effective drugs for dementias. Please see page 11 of this newsletter and visit our web site, **www.brain.northwestern.edu**, for information about trials that are still recruiting.

The CNADC Advisory Board has had a major reorganization. Donna Elrod, Craig Grannon, and Terry Chapman have graciously agreed to form an executive committee, rotating the chairmanship for two years at a time. Donna Elrod has the first watch. On behalf of the entire CNADC community, I want to thank the three of them and all board members for their devotion and continued trust in the mission of the CNADC.

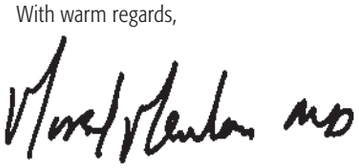
An equally important milestone is the upcoming relocation of our patient services to a new site at 676 North St. Clair Street, across from the Galter Pavilion, where our current clinic is located. Patients will be able to use the same parking areas as before and cross from the Galter outpatient building to the 676 building through a bridge without having to go outside. Our new space will be configured to our specifications for optimal efficiency and comfort. It is fortunate that the advisory board has agreed to take an active role in planning the new space. Our campaign to fund the space is proceeding well, and we have received preliminary commitments to name four rooms. Further information about the campaign can be obtained from Barbara Monroe, senior associate director of major gifts, at 312-503-0761.

I am also happy to announce the establishment of the Jerome and Florane Rosenstone Fund to support the training of students and fellows in the areas of Alzheimer's disease and related dementias. The establishment of the fund is a lasting testament to the Rosenstone family's pivotal role in the life of the CNADC. Peter Gliebus, MD, has been named the first Rosenstone Fellow.

Special thanks go to all of our research participants and caregiving families for your continued support of the CNADC. We are not able to conduct vital research on Alzheimer's disease, frontotemporal disease, or primary progressive aphasia without your participation, so we are truly grateful for your time and service.

This newsletter covers some of our more newsworthy achievements of the past year. These stories illustrate the broad spectrum of research and patient-care activities conducted by our core and affiliated faculty and staff. Thank you for your interest in our work. Please check our web site over the year for updates on our progress.

With warm regards,



M.-Marsel Mesulam, MD
CNADC Director and Ruth and Evelyn Dunbar Professor of Neurology, Psychiatry, and Psychology

COGNITIVE NEUROLOGY AND ALZHEIMER'S DISEASE CENTER

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Your Gifts

ARE MORE VITAL THAN EVER

The CNADC depends on public *and* private resources to operate.

Competitive grant funding supports the basic infrastructure of the CNADC. But at a time when Alzheimer's disease threatens to become the greatest public health crisis in the history of our nation, federal and other funding for our efforts has been reduced in this precarious economy and may continue to be. This hard reality makes your gifts and bequests ever more vital.

With your financial support we can go beyond basic functioning. We can pursue and sustain new goals in research and strengthen our services for the growing number of patients and families claimed by Alzheimer's disease and other dementias, including frontotemporal dementia and primary progressive aphasia. Over the years the generosity of friends, patients, and alumni has enabled the CNADC to attract new physicians and scientists and to initiate a number of projects, which eventually may lead to major developments in research, treatment, and care.

To pledge a gift to support the Cognitive Neurology and Alzheimer's Disease Center or to learn more about special gift options, please contact

Northwestern University
Feinberg School of Medicine
Office of Medical Development
Rubloff Building, ninth floor
750 North Lake Shore Drive
Chicago, Illinois 60611-2923
312-503-3088

Make your gift instantly and securely online. At our web site, **www.brain.northwestern.edu,** click on **Giving Opportunities**, and you will be directed to the online donation form.

RESEARCH

LEARNING DISABILITIES

ASSOCIATED WITH LATER LANGUAGE PROBLEMS

Emily Rogalski

People with a neurodegenerative condition affecting language appear more likely to have had a history of learning disabilities than those with other types of dementia or no cognitive problems, according to a report in the February 2008 issue of *Archives of Neurology*. The lead author was Emily Rogalski, a research assistant professor at the CNADC.

The condition known as primary progressive aphasia causes individuals to lose language abilities as they age, even though their other brain functions appear unaffected for at least the first two years. "Although risk factors for Alzheimer's disease have been well studied, much less is known about risk factors for primary progressive aphasia," Rogalski and her colleagues wrote.

They studied 699 people — 108 with primary progressive aphasia (PPA), 154 with Alzheimer's disease, 84 with frontotemporal dementia, and 353 controls without dementia. Participants were questioned about the history of learning disabilities in their immediate families. A medical record review was conducted for the 23 people with PPA who reported either a personal or family history of learning disability.

Patients with PPA were more likely to have had learning disabilities or a close family member with learning disabilities than were those with other forms of dementia or without dementia. The review of patients with both aphasia and learning disabilities showed families with unusually high rates of learning problems, especially dyslexia.

For example, "In three cases, 9 of the 10 children of the probands [participants] were reported to have a history of specific learning disability in the area of language," the authors wrote. "In our clinical practice, we encounter many patients with primary progressive aphasia who report that spelling was never their 'strong suit' or that they could not learn new languages, but who would not have identified themselves as having a learning disability."

The findings suggest that some individuals or families may have an underlying susceptibility to difficulties with language. "This relationship may exist in only a small subgroup of persons with dyslexia without necessarily implying that the entire population with dyslexia or their family members are at higher risk of primary progressive aphasia," the authors concluded.

This study was supported by the National Institute on Aging, an Alzheimer's Disease Core Center grant, and a grant from the National Institute on Deafness and Other Communication Disorders.

EDUCATION AND OUTREACH

RAISING ALZHEIMER'S AWARENESS IN LIMITED-ENGLISH COMMUNITIES

CLESE executive director Marta Pereyra (third from left, back row) and the CNADC's Darby Morhardt (second from left, front row) with community partners

The CNADC's work with limited-English-proficiency communities has shown the desirability of increasing health promotion and education on Alzheimer's disease in those communities.

The CNADC collaborated with the Coalition for Limited English Speaking Elderly (CLESE) and the Alzheimer's Association Greater Illinois Chapter beginning in 2001 to raise awareness of Alzheimer's disease and related dementias in Chicago's limited-English-proficiency communities.

Two federal Administration on Aging Alzheimer's Disease Demonstration Grants to States funded the program. The second five-year grant, which ended in June 2008, served Arab, Assyrian, Bosnian, Hindi, and Urdu communities. Educational programs were offered, home-care services provided, and primary-care physicians who speak the languages of the communities were given native-language guidelines and cognitive screening tools for diagnostic evaluations. In addition, educational materials for families were translated.

Although 267 people had been identified as having cognitive impairment through an ethnic agency's cognitive screening, by the end of the second year of the grant, only 13 percent agreed to a diagnostic evaluation. When it became apparent that a large percentage of people were refusing diagnostic screening, the Chicago Community Trust provided funding to CLESE to partner with the CNADC and ethnic agencies to study how each community conceptualizes dementia, how this conceptualization affects willingness to seek a diagnosis, and how the family copes with symptoms of dementia.

Forty-eight interviews were conducted with family members of persons identified as having cognitive impairment. Questions were asked about views of memory loss, Alzheimer's, and seeking a doctor's help for cognitive changes. For those who sought a diagnosis, the experience was discussed.

Analysis of the interviews revealed that families believed memory loss to be explainable and a normal response to factors such as aging or medication. Many believed that the trauma of war, family problems, and immigration can affect cognition. Most families felt they could live with what they saw as normative changes in family members until behaviors become unmanageable.

If other psychosocial stressors were of more concern than the memory loss, evaluation would not be sought. Those who sought an evaluation wanted treatment to slow or cure the disease or to get help for bothersome symptoms. The experience in the doctor's office was affected by a family's understanding of Alzheimer's and expectations of what could be done.

The CNADC will continue to work with CLESE and its member agencies to explore the adequacy of community services for persons with dementia and their families. The ultimate goal is to develop the most appropriate diagnosis, treatment, support, and education for the populations and their families.

Partnership with Atlas Senior Center Reaps Rewards

The CNADC continues to enjoy a wonderful partnership with the Francis J. Atlas Regional Senior Center of the Chicago Department of Senior Services. Through its research opportunities and outreach programs the CNADC is able to both learn from and be of service to Atlas seniors.

The CNADC Memory Research Team continues to visit the Atlas Center to enroll participants in its Memory Research Registry. Seniors who volunteer for the program receive free ongoing memory screenings and the latest information on keeping memory healthy. They are also compensated for their time. The CNADC is grateful to them for leaving a legacy of hope for future generations.

Atlas Center seniors interested in participating in memory research at the Atlas Center and/or volunteering for one of the CNADC's many studies should contact Mallory Swift at 312-926-1851 or m-swift@northwestern.edu.

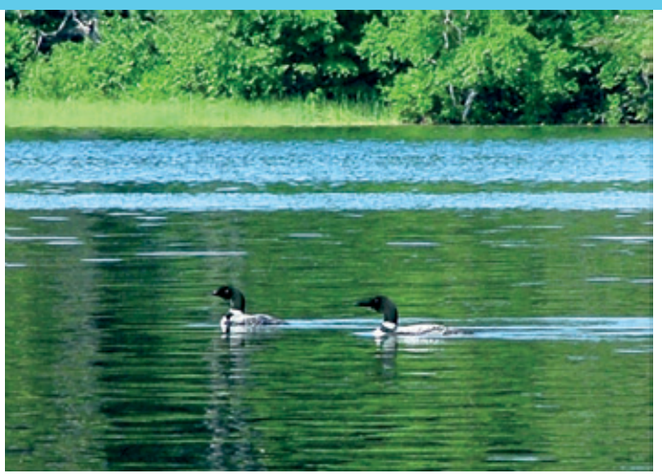
Alzheimer Day Featured UCLA Professor

Jeffrey L. Cummings, professor of neurology and psychiatry and director of the Alzheimer's Disease Center at the University of California, Los Angeles, questioned the focus of current Alzheimer's research in his lecture at the CNADC's 15th annual Alzheimer Day, May 8, 2009.

More than 300 community members, research scientists, and clinicians heard Cummings speak on "Developing New Treatments for Alzheimer's Disease: Promises and Challenges." His lecture challenged the focus on the amyloid oligmer hypothesis, which drives many current therapeutic trials. Cummings described some unresolved issues around diagnosis definition and explained other potential clinical targets and directions. His slides can be seen on the CNADC's web site (www.brain.northwestern.edu/events/pasteventsAD.html), along with the 2009 Alzheimer Day "Abstract Book." The book features the recent research findings of Northwestern scientists, researchers, and clinicians that were showcased in the afternoon poster session.

Concluding the day was a townhall-style meeting where segments of the HBO documentary film *The Alzheimer's Project* were debuted.

The 2010 Alzheimer Day will be held on May 6.



This photograph by Gretchen, a 52-year-old with FTD, was published in *Reflections: Loving and Living with Individuals with FTD and PPA.*

FTD/PPA Conference Well Attended

The 2009 FTD/PPA Caregiver and Professional Education Conference on August 10, 2009, continued the event's excellent attendance record. Over the last two years the FTD/PPA (frontotemporal dementia/primary progressive aphasia) conferences have attracted an average of 170 caregivers and professionals from all over the country.

Tiffany Chow, assistant professor of neurology and psychiatry at the University of Toronto, was the keynote speaker at the 2009 conference, cosponsored by the Association for Frontotemporal Dementias and the Alzheimer's Association Greater Illinois Chapter.

Sandra Weintraub, clinical core director of the CNADC, provided an update on FTD/PPA research.

The afternoon featured facilitated education and support sessions, the trailer of an upcoming film on FTD, and a closing plenary session featuring Dan McAdams, Northwestern professor of education and social policy and of psychology, who specializes in self-identity and personality development.

CNADC's FTD/PPA caregiver support group published a collection of essays, poems, and photos for the last two conferences. A copy of the book, *Reflections: Loving and Living with Individuals with FTD and PPA*, was given to each attendee.

Annual Family Caregiver Conference Held on Chicago's South Side

A member of the South Side Dementia Consortium (SSDC), the CNADC held its annual family caregiver conference at Chicago's Kennedy-King College in September. The center is an active member in the SSDC as part of its outreach and partnership with the African American community.

The event drew more than 150 caregivers and family members. Keynote speaker Jay Gottfried, CNADC behavioral neurologist, explained the importance and process of obtaining a diagnosis for Alzheimer's disease and related disorders and spoke about treatment and recent scientific advances.

Medical students Matt Sondag (second from right) with his buddy, Ken (third from left), and Julie Nam (right) with her buddy, Harriet (second from left), will be seen in the film *I Remember Better When I Paint.*

Buddy Program Receives Foundation Funding

The Glen and Wendy Miller Family Foundation has made a generous donation to the CNADC for the Buddy Program®, which is in its 13th year of matching Feinberg School of Medicine students with persons with Alzheimer's disease and related dementias for mutual enrichment.

Due to interest in replicating this successful program, the Miller Foundation funding ($75,000 over three years) is going toward a training and curriculum manual for organizations. A similar program at Boston University Medical School is in its second year, and a program will be added to the fall curriculum at the New York University School of Social Work.

Eleven medical students joined the program last academic year. A Big Ten Network television crew was on hand when they were matched with their buddies in October 2008. (To view the Big Ten Network news story, visit www.youtube.com/watch?v=6ZhdQz7LTiQ.)

Two pairs of buddies — members of CNADC's Early Stage Memory Loss Support Group and Northwestern medical students — are featured in the documentary film *I Remember Better When I Paint.* They are seen discussing the Georges Seurat painting *A Sunday Afternoon on the Island of La Grande Jatte*. Inspired by the story of an artist who continued to paint into the later stages of Alzheimer's disease, the film shows how the creative arts can help individuals with dementia continue to engage meaningfully in life and art. Produced by the Hilgos Foundation and French Connection films, *I Remember Better When I Paint* will be released in winter 2010. For more information visit http://hilgos.org.

NPR'S StoryCorps Interviews Patients at the CNADC

National Public Radio's StoryCorps came to the CNADC last year to interview people affected by memory loss. Four people in the early stages of dementia shared the story of their lives and their memory loss for the national oral history project that was launched in 2006.

Some of the participants were interviewed by a family member, and others by their medical student buddies in the Buddy Program. *Chicago Tribune* reporter Bonnie Rubin Miller interviewed participants for a story, "With a Microphone, Memories Saved: Oral History Project Collects Stories from Those Who Have Alzheimer's," that appeared on April 6, 2008. To read it, see http://archives.chicagotribune.com/2008/apr/07/health/chi-storycorpsapr07.

Since 2003 tens of thousands of people have interviewed family and friends through StoryCorps. Each conversation is archived at the Library of Congress, and selected stories are broadcast on NPR.

Early-Stage Memory Loss Support Group Launches Advocacy Work

The members of the CNADC's Early-Stage Memory Loss Education and Support Group have written a letter to 14 members of Congress in Illinois and Indiana to advocate for increased awareness and support for dementia research.

They say they were inspired by a desire to change the public perception of dementia, to enhance resources available to those coping with memory loss, and to increase funding for continued research in the field.

In addition to being sent to local representatives, the letter was published in the newsletter *Perspectives*, an international publication for people with memory loss. See News at www.brain.northwestern.edu to read the letter.

CNADC Receives Awards

The CNADC received two supplemental grants under the American Recovery and Reinvestment Act of 2009. One award will fund an evoked response potential laboratory to measure millisecond response of electrical activity in the brains of persons with primary progressive aphasia. The second award supports the launch of an international registry for persons from around the world with PPA. The CNADC has already received data from Belgium, Argentina, Germany, Italy, and Brazil.

Center Testifies at Social Security Hearing

Three representatives of the CNADC testified at a hearing the Social Security Administration held July 29, 2009, in Chicago about how to identify early-onset Alzheimer's disease and related dementias.

CNADC director M.-Marsel Mesulam, clinical core director Sandra Weintraub, and education core director Darby Morhardt testified on behalf of individuals diagnosed with primary progressive aphasia and their families. PPA, typically a diagnosis of early onset (under the age of 65), is not well known in the health care and social service communities.

Along with obtaining information about possible methods of identifying people, the hearing looked into the advisability of implementing compassionate allowances for people with early-onset diseases. "Compassionate allowances" is a term applied to conditions that obviously meet the definition of disability under the Social Security Act and can be identified with minimal objective medical information.

One of those who testified, Mary Beth Riedner, a caregiver for her husband with PPA, detailed the current cumbersome process of applying for Social Security Disability Insurance.

Frontotemporal dementia was added to the compassionate allowances list of illnesses in October 2008, largely due to the advocacy of the Association for Frontotemporal Dementias. As a result, the disability application process for someone diagnosed with FTD can be expedited, sparing the person not only a delay but also possible denial of benefits.

The testimony of all participants at the Social Security Administration hearing can be viewed at www.socialsecurity.gov/compassionateallowances/hearings0729alt.htm.

RESEARCH

Probing Why Some Aging Brains Stay Sharp

An 85-year-old who still whips through the newspaper crossword puzzle every morning, or a 94-year-old who never forgets a name or a face: Some people don't seem to suffer the ravages of memory that beset most others as they age.

Changiz Geula

Researchers at the Feinberg School of Medicine wondered if the brains of the elderly with still laser-sharp memory – called "super agers" – were somehow different from everyone else's. Instead of the usual approach of exploring what goes wrong when older people lose memory, they investigated what goes right in an aging brain that stays nimble.

Now they have a preliminary answer. The brains of five deceased people who were considered super agers because of high performance on memory tests after age 80 were compared with the brains of elderly, nondemented people. Researchers found the superagers' brains had many fewer fiber-like tangles than the brains of those who had aged normally. Tangles, which consist of a protein called tau that accumulates inside brain cells and is thought to kill the cells eventually, are found in moderate numbers in the brains of the elderly and increase substantially in the brains of Alzheimer's disease patients.

"This new finding in superagers' brains is very exciting," said Changiz Geula, principal investigator of the study and a research professor of neurology at the Cognitive Neurology and Alzheimer's Disease Center at Feinberg. "It was always assumed that the accumulation of these tangles is a progressive phenomenon through the aging process. But we are seeing that some individuals are immune to tangle formation and that the presence of these tangles seems to influence cognitive performance."

Those who have few tangles perform at superior levels, while those who have more tangles appear to be normal for their age, Geula noted. The lower number of tangles in the super aged appears to be the critical difference in their memory skills.

Some of the super agers in the study performed memory tasks at the level of people who are about 50 years old. For example, after being told a story, they were able to remember it immediately after and still accurately recall its details 30 minutes later. They also recalled a list of 15 words after 30 minutes.

Geula said new research will focus on what makes cells in superagers' brains more resistant to tangle formation. "We want to see what protects the brains of these individuals against the ravages that cause memory loss," he said. "Understanding the specific genetic and molecular characteristics of the brains that make them resistant may someday lead to the ability to protect average brains from memory loss."

Geula presented his findings in November 2008 at the Society for Neuroscience annual meeting in Washington, D.C. His research is part of a larger super-aging study at CNADC. The goal is to identify high-functioning individuals over 80 and investigate what factors are important to maintain this ability into old age. Recruitment continues for the study.

Feinberg School collaborators on the study are M.-Marsel Mesulam, CNADC director and the Ruth and Evelyn Dunbar Professor of Neurology, Psychiatry, and Psychology; Sandra Weintraub, professor of psychiatry and behavioral sciences; and Emily Rogalski, research assistant professor at CNADC.

— Marla Paul, health sciences editor, Northwestern University

RESEARCH

BRAIN STARVATION MAY TRIGGER ALZHEIMER'S

Robert Vassar

A slow, chronic starvation of the aging brain appears to be one of the major triggers of a biochemical process that causes some forms of Alzheimer's disease.

A study from the Feinberg School of Medicine has found that when the brain doesn't get enough sugar glucose — as might occur when cardiovascular disease restricts the blood flow in arteries to the brain — a process is launched that ultimately produces the sticky clumps of protein that appear to be a cause of Alzheimer's.

Robert Vassar, lead author of the study published in the December 26, 2008, issue of the journal *Neuron,* discovered a key brain protein is altered when the brain has a deficient supply of energy. The altered protein, called eIF2alpha, increases the production of an enzyme that, in turn, flips a switch to produce the sticky protein clumps. Vassar worked with human and mice brains in his research.

"This finding is significant because it suggests that improving blood flow to the brain might be an effective therapeutic approach to prevent or treat Alzheimer's," said Vassar, a professor of cell and molecular biology at the Feinberg School.

According to the Alzheimer's Association, an estimated 10 million baby boomers will develop Alzheimer's in their lifetimes. The disease usually begins after age 60, with risk rising with age. Exercise, cholesterol reduction, and hypertension management can improve blood flow to the brain, Vassar said.

"If people start early enough, maybe they can dodge the bullet," he said. For people who already have symptoms, vasodilators, which increase blood flow, may help the delivery of oxygen and glucose to the brain, he added.

Vassar said it also is possible that drugs could be designed to block the eIF2alpha protein that begins the formation of the protein clumps, known as amyloid plaques.

The initial trigger of Alzheimer's has long been a mystery.

Ten years ago it was Vassar who discovered BACE1, the enzyme responsible for making amyloid plaques. The cause of the high levels of the protein in people with Alzheimer's was unknown, however. Vassar's study now shows that energy deprivation in the brain might be the trigger.

Vassar said Alzheimer's disease may result from a less severe type of energy deprivation than that occurring in a stroke.

"A stroke is a blockage that prevents blood flow and produces cell death in an acute, dramatic event," Vassar said. In contrast, in Alzheimer's, rather than dying, the brain cells may react by increasing BACE1, which may be a protective response in the short term but harmful in the long term.

"What we are talking about here is a slow, insidious process over many years where people have a low level of cardiovascular disease or atherosclerosis in the brain," Vassar said. "It's so mild, they don't even notice it, but it has an effect over time because it's producing a chronic reduction in the blood flow."

Vassar's research was funded by the National Institute on Aging, the MetLife Foundation, and Northwestern University.

— *Marla Paul, health sciences editor, Northwestern University*

NEWS

CNADC Welcomes Diana Kerwin

Diana Kerwin

Diana R. Kerwin, MD, a specialist in the identification of risk markers and prevention of cognitive decline and dementia, has joined the CNADC.

Kerwin is an assistant professor in the Department of Medicine, Division of Geriatrics, at the Feinberg School of Medicine. Her clinical practice focuses on the care, evaluation, and management of memory loss and cognitive decline in persons over age 60.

Kerwin's interest in geriatrics developed during her internal medicine residency when she noted that patients with cognitive issues were at risk for medication errors, had difficulty with compliance and safety, and were in need of physicians fully cognizant of their cognitive deficits and dementia and how medical care could help them.

In a national competition, Kerwin was named the 2006 T. Franklin Williams Research Scholar for her research investigating the effects of body weight and vascular risk factors in the development of cognitive decline and dementia. She has lectured extensively on Alzheimer's disease both regionally and nationally and is the academic partner on several community initiatives to improve care of elderly with dementia in underserved areas.

THE CNADC GRATEFULLY ACKNOWLEDGES MAJOR GIFTS FROM

Bernard, Susan, and Terry Chapman

Chicago Community Trust, Robert and Linda Mendelson

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Kemper Educational Charitable Fund

Carl and Gloria LaGrassa Family Foundation

Glen and Wendy Miller Family Foundation

David and Linda Moscow Foundation

Jerome Rosenstone

Tuft Family Foundation

John and Kay Van Cleave

Anonymous

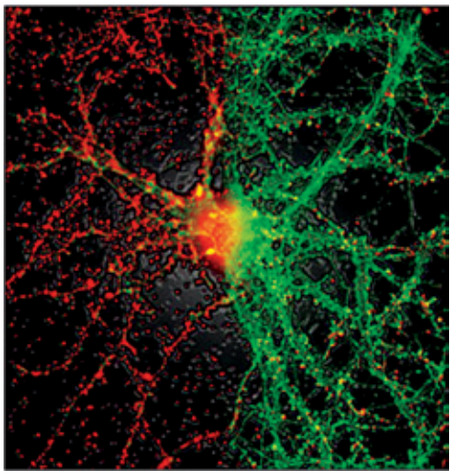
RESEARCH

Insulin a Possible Treatment for Alzheimer's

A Northwestern University–led research team reports that insulin, by shielding memory-forming synapses from harm, may slow or prevent the damage and memory loss caused by toxic proteins in Alzheimer's disease.

The findings, which provide additional new evidence that Alzheimer's could be due to a novel third form of diabetes, were published online in February by the *Proceedings of the National Academy of Sciences (PNAS).*

In a study of neurons taken from the hippocampus, one of the brain's crucial memory centers, the scientists treated cells with insulin and the insulin-sensitizing drug rosiglitazone, which has been used to treat type 2 diabetes. (Isolated hippocampal cells are used by scientists to study memory chemistry; the cells are susceptible to damage caused by ADDLs, toxic proteins that build up in persons with Alzheimer's disease.)



A composite image of two neurons: At left, red shows the attachment of ADDLs to a nerve cell; green indicates synapses, parts of nerve cells where memory formation begins. When ADDLs are attached, synapses are eliminated. At right is a nerve cell treated with insulin before being exposed to ADDLs. The cell is normal, with high levels of synapses (green) and almost no ADDLs (red) bound to it.

The researchers discovered that damage to neurons exposed to ADDLs was blocked by insulin, which kept ADDLs from attaching to the cells. They also found that protection by low levels of insulin was enhanced by rosiglitazone.

ADDLs (short for "amyloid beta-derived diffusible ligands") were discovered at Northwestern and are known to attack memory-forming synapses. After ADDL binding, synapses lose their capacity to respond to incoming information, resulting in memory loss. The protective mechanism of insulin works through a series of steps by ultimately reducing the actual number of ADDL binding sites, which in turn results in a marked reduction of ADDL attachment to synapses, the researchers report.

"Therapeutics designed to increase insulin sensitivity in the brain could provide new avenues for treating Alzheimer's disease," said senior author William L. Klein, a professor of neurobiology and physiology in Northwestern's Judd A. and Marjorie Weinberg College of Arts and Sciences and a researcher in the Cognitive Neurology and Alzheimer's Disease Center. "Sensitivity to insulin can decline with aging, which presents a novel risk factor for Alzheimer's disease. Our results demonstrate that bolstering insulin signaling can protect neurons from harm."

The amyloid beta oligomers, or ADDLs, form when snippets of a protein clump together in the brain. In Alzheimer's disease, when ADDLs bind to nearby neurons, they cause damage from free radicals and a loss of neuronal structures crucial to brain function, including insulin receptors. This damage ultimately results in memory loss and other Alzheimer's disease symptoms. The Alzheimer's drug Namenda® has been shown to partially protect neurons against the effects of ADDLs.

"The discovery that antidiabetic drugs shield synapses against ADDLs offers new hope for fighting memory loss in Alzheimer's disease," said lead author Fernanda G. De Felice, a former visiting scientist in Klein's lab and an associate professor at the Federal University of Rio de Janeiro, Brazil.

"Recognizing that Alzheimer's disease is a type of brain diabetes points the way to novel discoveries that may finally result in disease-modifying treatments for this devastating disease," adds Sergio T. Ferreira, another member of the research team and a professor of biochemistry in Rio de Janeiro.

In other recent and related work, Klein, De Felice, and their colleagues showed that ADDLs bound to synapses remove insulin receptors from nerve cells, rendering those neurons insulin resistant.

The outcome of the molecular-level battle between ADDLs and insulin, which in the current *PNAS* study was found to remove ADDL receptors, may determine whether a person develops Alzheimer's disease.

In addition to Klein, De Felice, and Ferreira, other authors of the *PNAS* paper, "Protection of Synapses Against Alzheimer's-linked Toxins: Insulin Signaling Prevents the Pathogenic Binding of Aß Oligomers," are Wei-Qin Zhao, a former visiting scientist at Northwestern, now with Merck & Co.; Pauline T. Velasco, Mary P. Lambert, and Kirsten L. Viola from Northwestern; and Marcelo N. N. Vieira, Theresa R. Bomfim, and Helena Decker from the Federal University of Rio de Janeiro.

This work was supported by the Alzheimer's Association, the American Health Assistance Foundation, the National Institute on Aging, the Howard Hughes Medical Institute, Conselho Nacional de Desenvolvimento Cientifico e Tecnologico (Brazil), Fundacao de Amparo à Pesquisa do Estado do Rio de Janeiro (Brazil), and the Human Frontier Science Program.

— Megan Fellman, science and engineering editor, Northwestern University

RESEARCH GRANT

Study May Shed Light on Protein's Role in AD

Linda J. Van Eldik, PhD, professor of cell and molecular biology at the Feinberg School, has received a 2009 Zenith Fellows Award to further her research into p38alpha mitogen-activating protein kinase (p38alpha MAPK), which has been shown to play a key role in brain inflammation. The research could lead to a better understanding of Alzheimer's disease.

Linda J. Van Eldik

Research has found associations between the protein and the increased production of inflammation-related molecules called cytokines. However, little is known about how the association between p38alpha MAPK and cytokines may affect the progression of Alzheimer's disease, which is partly characterized by brain inflammation.

Van Eldik and her colleagues hypothesize that p38alpha MAPK contributes to both the brain inflammation and brain cell damage involved in Alzheimer's. In an earlier study with mice engineered to develop Alzheimer's-like symptoms, the researchers found that a molecule called compound 069A could inhibit the activities of p38alpha MAPK. This treatment also moderated the overproduction of cytokines in animals' brains and reduced the severity of brain damage. Specifically, the animals showed less damage to their synapses, the specialized junctions through which brain cells send and receive chemical messages.

With the Zenith grant, Van Eldik's team hopes to conduct a more thorough study to test how p38alpha MAPK is involved in brain disease. The researchers will use genetically engineered mice to compare the effects of p38alpha MAPK and a related molecule called p38beta MAPK on cytokine overproduction and synaptic damage. They expect to find that the p38alpha form is more closely associated with these pathologies than is the p38beta form. Van Eldik's group also hopes to verify that compound 069A can ameliorate brain inflammation and synaptic loss by inhibiting p38alpha MAPK activities.

The findings of this study could shed new light on how Alzheimer's progresses and lead to novel drug therapies for the disease.

RESEARCH

Researchers Discover Memory Trainer

When you meet your boss's husband at the office holiday party, then bump into him an hour later over the onion dip, you will remember his name if your brain has enough kalirin-7.

Peter Penzes

Researchers at the Feinberg School of Medicine have discovered kalirin, a brain protein, is critical for helping you learn and remember what you learned.

Since previous studies by other researchers found that kalirin levels are reduced in brains of people with diseases like Alzheimer's and schizophrenia, the discovery of kalirin's role in learning offers new insight into the pathophysiology of these disorders.

"Identifying the key role of this protein in learning and memory makes it a new target for future drug therapy to treat or delay the progression of these diseases," said Peter Penzes, assistant professor of physiology at the Feinberg School and lead author of the study that was published November 21, 2008, in the journal *Neuron*.

Penzes studied the brains of laboratory rats, which are similar to human brains. He said that kalirin behaves like a personal trainer for memory. When you learn something new, kalirin bulks up the brain's synaptic spines, which resemble tiny white mushrooms. Synaptic spines are the sites in the brain where neurons (brain cells) talk to each other.

The spines grow bigger and stronger the more you repeat a lesson. It works the same whether you're learning a new cell phone number, skiing a new double black diamond slope, or testing a cheesecake recipe.

"If these sites are bigger, the communication is better," Penzes said. "A synapse is like a volume dial between two cells. If you turn up the volume, communication is better. Kalirin makes the synaptic spines grow."

Kalirin's role in learning and memory helps explain why continued intellectual activity and learning delay cognitive decline as people grow older. "It's important to keep learning so your synapses stay healthy," Penzes said.

His research was funded by the National Institute of Mental Health, the National Alliance for Research on Schizophrenia and Depression, and the National Alliance for Autism Research.

— Marla Paul, health sciences editor, Northwestern University

EDUCATION AND OUTREACH

SUPPORT GROUPS

The CNADC is committed to providing emotional support and life enrichment for people diagnosed with Alzheimer's disease and related disorders and for their families. As we continue to research disease treatment and prevention, it is important to help those affected to cope with the diagnosis and continue to lead rich and meaningful lives.

Families often find it helpful to share their experiences and thoughts in a group setting. Support groups provide an opportunity for family members to discuss concerns, air feelings, share strategies on providing care, find local resources, and have access to disease education and information.

For more information about the quality-of-life enrichment programs, contact **m-ohara@northwestern.edu** or call **312-503-0604**.

Spouses/Partners Caregiver Support Group

Fourth Monday of the month, 10:30 a.m.–noon
645 North Michigan Avenue (entrance on Erie), suite 630,
Department of Medicine conference room

Adult Children Support Group

First Monday of the month, 6:30–8 p.m.
251 East Huron Street, Feinberg Pavilion, third floor, room B

Frontotemporal Dementia (FTD) and Primary Progressive Aphasia (PPA) Caregiver Support Group

Third Monday of the month, 6–7:30 p.m.
251 East Huron Street, Feinberg Pavilion, third floor, room C

Early Stage Support Group for persons with Alzheimer's or a related dementia and their families

Spring and fall sessions (12 weeks each)
This program serves persons experiencing memory loss and related changes in thinking and behavior as well as their family members and care partners. An interview is required to participate. Group members who are in the early stages of their conditions discuss coping strategies, changes in relationships, changes in daily living skills, planning for the future, research, and available treatments. Care partners can attend a concurrent group at the same time. Every other week professionals in the field are invited to address both groups.

FTD/PPA Family Support List

The family contact list that CNADC maintains gives the names and contact information of family members of persons with FTD or PPA who are willing to be contacted by others in the same circumstances. Contact **m-ohara@northwestern.edu** for more information.

ONGOING STUDIES

RESEARCH AND CLINICAL TRIALS AT THE CNADC

Volunteer for a Study

Unless another contact number is given, contact the Memory Research team at **312-926-1851** or e-mail **memoryresearch@northwestern.edu** if you are interested in finding out more information about or volunteering for any of the following studies.

Gammaglobulin Alzheimer's Partnership (GAP) Study

• Sponsored by Baxter Pharmaceuticals and the National Institutes of Health (Alzheimer's Disease Cooperative Study)

Since the late 1990s there has been increasing evidence that immunotherapy targeting the amyloid beta (Aβ) peptide can be used to treat Alzheimer's disease. The purpose of this study is to determine whether IGIV (immune globulin intravenous) treatment slows the rate or prevents the decline of dementia symptoms in persons with mild-to-moderate Alzheimer's disease. Participants with be randomized in a double-blind controlled study.

Effects of Stress on Dementia • *Sponsored by the National Institute of Mental Health*

Participants with a diagnosis of Alzheimer's disease, primary progressive aphasia, and frontotemporal dementia are needed. Participation will include completion of two questionnaires about stress and coping ability and collection of saliva samples for analysis of stress chemicals. The study can be completed in a single visit or at home, and time will be compensated. Call 312-695-8173 for more information.

Language in Primary Progressive Aphasia • *Sponsored by the National Institute on Deafness and Other Communication Disorders*

Volunteers with PPA, a gradual and progressive impairment of word finding and usage, will come to Northwestern for three days to undergo an MRI scan and other testing. Participants and their companions will be compensated for meals, travel, lodging, and time. This research program is the largest longitudinal study on PPA to date. Contact Christina Wieneke at 312-908-9681 if interested.

Super Aging • *Sponsored by Northwestern's Cognitive Neurology and Alzheimer's Disease Center*

This longitudinal research study is aiming to determine what factors help keep aging individuals highly functional and free of cognitive decline. Three visits over the course of three years are required. Participants must be over age 80. If you are interested, please contact researcher Emily Rogalski at 312-503-1660.

The Utility of Namenda® in the Treatment of Frontotemporal Dementia • *Sponsored by Forest Pharmaceuticals*

Researchers are evaluating the use of memantine (Namenda) in those with a diagnosis of frontotemporal dementia (FTD). Memantine is an FDA-approved treatment for Alzheimer's disease. Evidence suggests memantine may reduce damage to brain cells and therefore may also be effective in people with FTD. This study is designed to evaluate not only whether memantine will slow the rate of decline in thinking and problem behaviors in FTD but also the drug's safety and tolerability in FTD.

Hello!

MEET THE CNADC STAFF

Joseph Boyle, BA, joined the CNADC in July 2009 as a research coordinator for PPA and superaging studies. Originally from Minnesota, he is a philosophy graduate of the University of Notre Dame.

Shantel Mitchell Cooley, BA, a graduate student in social work from the University of Chicago, joined the CNADC in October 2009. Her BA from Oklahoma Baptist University is in public relations and religion. She sees patients and families in the Neurobehavior and Memory Health Clinic, cofacilitates support groups, and is involved in education and outreach.

Katherine Gasho, BA, joined the CNADC in August 2008 as a research technician in the labs of Changiz Geula, research professor of neurology, and Eileen Bigio, professor of pathology. She graduated in biology from the University of Chicago with a specialization in neuroscience.

Girgis Emil Girgis, BS, is a Geula research assistant. He did his undergraduate work in biology, biotechnology, and analytical chemistry at DePaul University and Schiller International University in London.

G. Peter Gliebus, MD, is a behavioral neurology fellow. In addition to seeing patients, he is involved in basic and clinical research related to Alzheimer's disease, frontotemporal dementia, and other neurodegenerative disorders. He received his MD from Vilnius University in Lithuania and completed a neurology residency at Drexel University/ Hahnemann University Hospital in Philadelphia.

Ramez Hoveydai, BS, studied premed biology at the University of Illinois at Chicago and graduated in 2008. He researches Alzheimer's disease.

Emily Langendorf, BA, joined the CNADC in September 2009 as a social work intern. She sees patients and families in the Neurobehavior and Memory Health Clinic, cofacilitates support groups, and is involved in education and outreach. She is from Urbana, Illinois, and earned her bachelor's degree in psychology at Miami University of Ohio.

Kristine Lipowski, BA, joined the CNADC in December 2008 as the research study programs coordinator and is the primary coordinator for the Eli Lilly, Elan, FTD/memantine, and Exelon patch trials. She graduated from North Central College with degrees in sociology and psychology and plans to attend graduate school.

Julia Rao, BS, joined the CNADC in September 2008 as a graduate student in clinical neuropsychology and works in the lab of Sandra Weintraub, professor of psychiatry and behavioral science. Rao previously worked at the University of Chicago studying language development and early nonverbal gestures. A graduate of the University of Wisconsin–Madison in psychology, she is working on the primary progressive aphasia research project.

David A. Riascos, MD, MSc, joined the CNADC in November 2008 and works in the Laboratory for Cognitive and Molecular Morphometry. He studies the expression of certain calcium-sensitive proteins and tangle development from Alzheimer's disease, looking for a therapeutic option. He is from Colombia.

Elizabeth Smith, BS, RHIA, joined the CNADC in October 2009 as a research study programs coordinator. She graduated in health information management from Illinois State University and plans to attend graduate school.

Mallory Swift, BA, joined the CNADC in October 2008 as a research study programs coordinator and is the primary coordinator for the RAGE (Receptor for Advanced Glycation Endpoints) trial. She graduated from the University of Illinois at Chicago with a degree in research psychology.

Jill Verhagen joined CNADC's Neurobehavior and Memory Health Clinic in December 2008 as its manager. She previously worked as the anesthesia coordinator at Children's Memorial Hospital. She attended DePaul University.

Nicole Wright, BA, joined the CNADC in May 2009 and is a neuropsychology technician for the Neurobehavior and Memory Health Clinic. She studied psychology at the University of Wisconsin–Madison, where she began psychometric training and was a research specialist.

NEW FACULTY

Emily Rogalski, PhD, joined the CNADC in August 2008 as a research assistant professor. She earned a doctorate in cognitive neuroscience from the interdepartmental neuroscience program in 2007 and completed postdoctoral work at Rush University Medical Center in Chicago in 2008. Her research focuses on the structural and behavioral consequences of aging and dementia. She uses both structural magnetic resonance imaging and cognitive tests to identify factors associated with successful aging. She is also interested in characterizing the neuroanatomical correlates of language disruption in primary progressive aphasia.

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*Members of the Alzheimer's Disease Center Executive Committee

A Thank You for Brain Donations

As researchers strive to better understand central nervous system disorders, they rely on brain donations from a variety of generous people. The CNADC is privileged to obtain support for our brain donation program from many of our patients and research participants.

Neurodegenerative disorders such as Alzheimer's disease currently can be diagnosed with certainty only through a brain autopsy. But brain donation is useful only if we have all the clinical information from studying a person during his or her lifetime, so participation in our annual testing research program is essential. We must obtain donations from not only individuals who have cognitive and memory impairments but also those who have no problems with mental functioning.

Through generous gifts of brain tissue, our center has provided tissue samples to researchers who have contributed to major advances in the past few years. Our researchers have made important breakthroughs in learning about detrimental alterations in specific proteins localized to the central nervous system. In addition, they have discovered important changes in the levels of highly selective enzymes that are likely to be related to the development of Alzheimer's disease. They have also studied the tissue of people who had frontotemporal lobar degeneration, and our center contributed to the most recent findings about progranulin mutations as a major factor in this disease.

The CNADC is grateful to the donors who made it possible for us to contribute to important past findings. The support we continue to receive from new donations makes possible additional steps toward treatment and prevention of memory problems. Studying the anatomy, chemistry, and pathology of the brain is critical for earlier diagnosis of neurodegenerative disorders such as Alzheimer's. Much work still needs to be done.

The process of brain donation can be difficult to discuss and prepare for, and we are committed to helping participants in our brain donation program and their families understand the important contribution being made. We thank you for the generous donation that will provide hope to others who struggle with memory diseases.

Sandra Weintraub, PhD
Director, Clinical Core

RESEARCH

Another Reason to Love Olive Oil

A new study has found that oleocanthal, a naturally occurring compound found in extra-virgin olive oil, beneficially alters the structure of neurotoxic proteins believed to contribute to the debilitating effects of Alzheimer's disease.

The structural change impedes the ability of highly toxic proteins known as ADDLs to damage brain nerve cells. This effect of oleocanthal could be used to advantage in new therapeutics and diagnostics.

Researchers from Northwestern and the Monell Chemical Senses Center led the study, which was published in the October 15, 2009, issue of the journal *Toxicology and Applied Pharmacology*.

"Binding of ADDLs to nerve cell synapses is thought to be a crucial first step in the initiation of Alzheimer's disease," said study coleader William L. Klein, professor of neurobiology and physiology in Northwestern's Weinberg College of Arts and Sciences and a CNADC member. "Oleocanthal alters ADDL structure in a way that deters the protein from binding to synapses. Translational studies now are needed to link these laboratory findings to clinical interventions."

"Our findings may help identify effective preventative measures and lead to improved therapeutics in the fight against Alzheimer's disease," added Paul A. S. Breslin, a sensory psychobiologist at the Monell Center, who codirected the research with Klein.

ADDLs bind within the neural synapses of the brains of Alzheimer's patients and are believed to directly disrupt nerve cell function, eventually leading to memory loss, cell death, and global disruption of brain function. Synapses are specialized junctions that allow one nerve cell to send information to another.

Klein and his colleagues identified ADDLs in 1998, leading to a major shift in thinking about the causes, progression, and treatment of Alzheimer's disease. Also known as beta-amyloid oligomers, ADDLs are structurally different from the amyloid plaques that accumulate in the brains of Alzheimer's patients.

Reporting on a series of in vitro studies, the team of Northwestern and Monell researchers found that incubation with oleocanthal changed the structure of ADDLs by increasing the protein's size.

Knowing that oleocanthal changed ADDL size, the researchers next examined whether oleocanthal affected the ability of ADDLs to bind to synapses of cultured hippocampal neurons. The hippocampus, a part of the brain intimately involved in learning and memory, is one of the first areas affected by Alzheimer's disease.

Measuring ADDL binding with and without oleocanthal, they discovered that small amounts of oleocanthal effectively reduced short-term binding of ADDLs to hippocampal synapses. Additional studies revealed that oleocanthal can protect synapses from damage caused by ADDLs.

An unexpected finding was that oleocanthal makes ADDLs into stronger targets for antibodies. This action establishes an opportunity for creating more effective immunotherapy treatments, which use antibodies to bind to and attack ADDLs.

"In addition to aiding therapeutics, enhancing ADDL immunoreactivity also could increase the sensitivity of antibody-based Alzheimer's diagnostics," said first author Jason Pitt, a graduate student in Klein's lab, who conducted the studies.

Future studies to identify more precisely how oleocanthal changes ADDL composition may increase our understanding of the structural component responsible for ADDL toxicity. Such insights could provide discovery pathways related to disease prevention and treatment.

The National Institute on Aging funded the research.

The title of the paper is "Alzheimer's-associated Aβ Oligomers Show Altered Structure, Immunoreactivity, and Synaptotoxicity with Low Doses of Oleocanthal." In addition to Klein, Breslin, and Pitt, other authors of the paper are William Roth, Pascale Lacor, and Pauline Velasco from Northwestern; Matthew Blankenship from Western Illinois University; and Fernanda De Felice from the Federal University of Rio de Janeiro.

— Megan Fellman, science and engineering editor, Northwestern University

Klein Gets Alzheimer's Association Grant

CNADC member William L. Klein received a 2009 Zenith Fellows Award from the Alzheimer's Association to set up a program to screen for compounds that shield synapses from highly toxic ADDL molecules.

His award continues Northwestern's track record in this field. Changiz Geula, CNADC research professor, received a 2008 Zenith Fellows Award, and Robert Vassar, Feinberg School associate professor of cell and molecular biology, received the 2009 Potamkin Prize for Research in Alzheimer's Disease and Related Dementias.

COGNITIVE NEUROLOGY AND ALZHEIMER'S DISEASE CENTER

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Feinberg School of Medicine
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UPCOMING EVENTS

Alzheimer's Disease Seminar Series
Thursdays, noon–1 p.m.
See schedule at www.brain.northwestern.edu.

Alzheimer Day
Thursday, May 6, 11:30 a.m.–4 p.m.

For information about all events, contact Darby Morhardt at 312-908-9432 or d-morhardt@northwestern.edu.

Please also see page 11 for the list of support groups for patients and caregivers.

The CNADC is one of 29 Alzheimer's Disease Centers funded by the National Institute on Aging, National Institutes of Health.

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