Though one might think the brains of people who develop Alzheimer’s disease (AD) possess building blocks of the disease absent in healthy brains, for most people with Alzheimer’s, this is not true. Every human brain contains the ingredients necessary to spark AD, but while an estimated 5 million Americans have AD – a number projected to triple by 2050 – the vast majority of people do not and will not develop the devastating neurological condition.

For researchers like Subhojit Roy, MD, PhD, associate professor in the departments of Pathology and Neuroscience and a cell biologist and neuropathologist with our Shiley-Marcos Alzheimer’s Disease Research Center, these facts produce a singular question: Why don’t we all get Alzheimer’s disease?

In a paper published in the August 7, 2013 issue of the journal Neuron, Roy and colleagues offer an explanation – a trick of nature that, in most people, maintains critical separation between a protein and an enzyme that, when combined, trigger the progressive cell destruction characteristic of AD.

“It’s like physically separating gunpowder from the match so that the inevitable explosion is avoided,” said Roy, “Knowing how the gunpowder and match are separated may give us new insights into possibly stopping the disease.”

The severity of AD is measured in the loss of functioning neurons (brain cells). There are two tell-tale signs of AD: clumps of a protein called beta-amyloid “plaques” that accumulate outside neurons and threads or “tangles” of another protein, called tau, found inside neurons. Most neuroscientists believe AD is caused by the accumulating assemblies of beta-amyloid protein triggering a sequence of events that leads to impaired cell function and death. This so-called “amyloid cascade hypothesis” puts beta-amyloid protein at the center of AD pathology.

Creating beta-amyloid requires the merging of a protein called amyloid precursor protein (APP) and an enzyme that cleaves APP into smaller toxic fragments called beta-secretase or BACE.

“Both of these proteins are highly expressed in the brain,” said Roy, “and if they were allowed to combine continuously, we would all have AD.”

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But that doesn’t happen. Using cultured hippocampal neurons (from a region of the brain involved in memory) and tissue from human and mouse brains, Roy – along with Utpal Das, a postdoctoral fellow in Roy’s lab, and colleagues – discovered that healthy brain cells largely segregate APP and BACE-1 into distinct compartments as soon as they are manufactured, ensuring the two proteins do not have much contact with each other.

“Nature seems to have come up with an interesting trick to separate co-conspirators,” said Roy.

The scientists also found that the conditions promoting greater production of beta-amyloid protein boost the convergence of APP and BACE. Specifically, an increase in neuronal electrical activity – known to increase the production of beta-amyloid – also led to an increase in APP-BACE convergence. Post-mortem examinations of AD patients revealed increased physical proximity of the proteins as well, adding support to the significance of this occurrence in human disease.

Das said the findings are fundamentally important because they clarify some of the earliest molecular events triggering AD and show how a healthy brain naturally avoids them. In clinical terms, they point to a possible new avenue for ultimately treating or even preventing the disease.

“An exciting aspect is that we can perhaps screen for molecules that can physically keep APP and BACE-1 apart,” said Das. “It’s a somewhat unconventional approach.”

Co-authors are David Scott, Archan Ganguly and Yong Tang, UCSD Departments of Pathology and Neurosciences; and Edward H. Koo, UCSD Department of Neurosciences and co-director of our Shiley-Marcos Alzheimer’s Disease Research Center.

To watch an educational and entertaining brief video about this research, see: http://www.roylab.org/app-bace_video.html Funding for this research came from the American Federation for Aging Research, National Institutes of Health grant P50AG005131 and a gift from Darlene Shiley to the ADRC.

This article was originally written by Scott LaFee and published on the UC San Diego Health System’s website. It was revised and reprinted with permission.
SAGE Test Useful to Screen for Memory Disorders in Community Settings, Ohio State Study Shows

By Eileen Seahill
Ohio State University Wexner Medical Center

The Self-Administered Gerocognitive Examination (SAGE test), which takes less than 15 minutes to complete, is a reliable tool for evaluating cognitive abilities. Findings by researchers at The Ohio State University Wexner Medical Center confirming the feasibility and efficiency of the tool for community screening large numbers of people are published in the January issue of The Journal of Neuropsychiatry and Clinical Neurosciences.

Memory disorders researchers visited 45 community events where they asked people to take a simple, self-administered test to screen for early cognitive loss or dementia. Of the 1047 people who took the simple pen-and-paper test, 28 percent were identified with cognitive impairment, said Dr. Douglas Scharre, who developed the test with his team at Ohio State.

The SAGE test can also be taken at home by patients, who can then share the results with their physicians to help spot early symptoms of cognitive issues such as early dementia or Alzheimer’s disease, said Scharre, who is director of the Division of Cognitive Neurology and heads the Memory Disorders Research Center at Ohio State’s Wexner Medical Center. Often physicians may not recognize subtle cognitive deficits during routine office visits, he said.

“What we found was that this SAGE self-administered test correlated very well with detailed cognitive testing,” Scharre said. “If we catch this cognitive change really early then we can start potential treatments much earlier than we did without having this test.”

While the test does not diagnose problems like Alzheimer’s, it does allow doctors to get a baseline of cognitive function in their patients, so they can follow them for these problems over time. “We can give them the test periodically and, the moment we notice any changes in their cognitive abilities, we can intervene much more rapidly,” Scharre said.

The SAGE test could also provide health care providers and caregivers an earlier indication of life-changing events that could lie ahead. Earlier research by Scharre found that four out of five people (80 percent) with mild thinking and memory (cognitive) issues will be detected by this test, and 95 percent of people without issues will have normal SAGE scores.

In this study, researchers found that SAGE’s self-administered feature, pen and paper format, and four equivalent interchangeable forms allows it to be given in almost any setting, doesn’t require any staff time to administer or to set up a computer, and makes it practical to rapidly screen large numbers of individuals in the community at the same time.

Study participants were ages 50 or older who had been recruited from a wide variety of community locations and events, including senior centers, health fairs, educational talks to lay public, independent and assisted living facilities, and free memory screens through newspaper advertisement. The study excluded individuals who indicated that they had taken SAGE previously.

Participants are tested on orientation (month + date + year); language (verbal fluency + picture naming); reasoning/computation (abstraction + calculation); visuospatial (three-dimensional construction + clock drawing); executive (problem solving) and memory abilities.

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Participants were provided their score and written information about SAGE, and were advised to show it to their physician for interpretation and potential further screening or evaluation based on their health history. All were told that this test represented their baseline to be compared to future re-screening by their physician. Missing six or more points on the 22-point SAGE test usually warrants additional follow-up by the physician.

Scharre, who specializes in treating Alzheimer’s disease, said treatments for Alzheimer’s and dementia are more effective when started in the earliest stage of the disease. Unfortunately, patients with Alzheimer’s disease often wait three to four years after their symptoms first appear to seek treatment.

Some 5 million Americans have Alzheimer’s disease, and those numbers are expected to almost triple by 2050. An additional 3 percent to 22 percent of those over 60 years of age are thought to currently meet criteria for Mild Cognitive Impairment as well, Scharre said.

“Hopefully, this test will help change those situations,” Scharre said. “We are finding better treatments, and we know that patients do much better than if they start the treatments sooner than later.”

To download the free test please visit [www.sagetest.osu.edu](http://www.sagetest.osu.edu)
Accelerating the Cure for Alzheimer’s Disease Through Regenerative Medicine

Date: November 6, 2014

Duke University Medical Center, Searle Center, Durham, NC
November 6, 2014
Co-Chairs:
P. Murali Doraiswamy, MBBS, FRCP
Professor and Director, Neurocognitive Disorders Program, Department of Psychiatry, Duke Medicine

Joanne Kurtzberg, MD
Professor and Chief Scientific Officer, Robertson Clinical & Translational Cell Therapy Program, Duke Medicine

Conference Organizer:
Joshua Hunsberger, PhD

Worldwide, over 40 million people have dementia due to Alzheimer’s disease and some 100 million older adults are estimated to be at increased risk (preclinical disease) for future dementia. Stem cells hold great promise for regenerating neural tissue, disease modeling and drug discovery but also raise new questions for regulators, ethicists, scientists, physicians and industry. Join us for this exciting workshop, featuring some of the nation’s leading experts, to discuss these exciting new developments.

Distinguished Duke Alumnae Leader and Philanthropist: Marjorie Bekaert Thomas
Keynote address: Mahendra Rao, MD, PhD
Distinguished Speakers: Anthony Atala, MD · Jeff Bulte, PhD · Alexandra Capela, PhD · Stephen Chang, PhD · Eva Chmielnicki, PhD · P. Murali Doraiswamy, MBBS, FRCP · Ellen Fiegal, MD · Thomas Finn, PhD · Hank Greely, JD · Larry Goldstein, PhD · Chris Henderson, PhD · Joanne Kurtzberg, MD · Frank LaFerla, PhD · Akira Sawa, MD, PhD · Lon Schneider, MD · Ajay Verma, MD, PhD

The conference is supported by The Karen L. Wrenn Family Trust; Duke Department of Psychiatry and Behavioral Sciences; Robertson Clinical and Translational Cell Therapy Program at Duke; and the NIH Center for Regenerative Medicine.

For further information please visit http://adstemcellconference.com
Encouraging Older Adults to Participate in Research

By Nina Silverberg, Assistant Director, Alzheimer’s Disease Centers Program, Division of Neuroscience, National Institute on Aging

A survey by Research!America indicates that many older adults would be willing to participate in medical research if they were aware of studies or invited to participate, particularly by a trusted primary care provider. We recently had the chance to address the opportunities and obstacles investigators face in recruitment in a piece in the *Health Affairs* special issue on Alzheimer’s disease. Some strategies for increasing participation we discussed include:

- Bridging the gap between research and clinical care
- Connecting participant registries
- Accommodating participant/caregiver needs
- Raising awareness and building trust with communities

The key to all these strategies of course is connecting participants, health care providers, and researchers at the local level.

So, here’s what we are doing at the federal level to support local efforts: Three federal agencies—NIA, the Administration for Community Living (ACL) and the Centers for Disease Control and Prevention (CDC)—have teamed up to encourage older adults to participate in clinical research. The project, dubbed “ROAR—Recruiting Older Adults into Research,” aims to work through local aging services and public health networks to increase awareness among diverse older adults of the value of participating in research and to include older participants in all types of research. We are starting with a focus on Alzheimer’s disease research, but hope to broaden the message to include all kinds of research over time.

So far, with input on successful messages and strategies from a variety of stakeholders, we are developing materials, focusing on healthy aging and research participation, with the message that “You CAN make a difference for yourself and future generations.”

The materials will be encouraging older adults to start with an easy action step: signing up with a research matching service or registry. The ROAR project is working with ResearchMatch, an NIH-funded service that matches interested people with studies they may qualify for, and offering links to two large-scale, Alzheimer’s-specific registries, the Alzheimer’s Prevention Registry and the Alzheimer’s Association’s TrialMatch, in this first phase.

Right now, the team is reaching out to ACL’s aging network staff, CDC’s public health staff, and NIA-funded Alzheimer’s Disease Centers staff in select locations to work with us trying out the materials. Once we receive and incorporate feedback, we will begin to finalize the materials for wider use. When they become available, we hope you will try them out, give us your feedback, and let us know what else would be helpful, particularly to reach underrepresented communities.
Alzheimer’s research has reached a potentially significant milestone: the launch of the first clinical trials to test whether new drug treatments given before dementia can prevent the disease. Washington University researchers have characterized disease markers in cerebrospinal fluid and have tested neuroimaging techniques for detecting Alzheimer’s, making it possible to diagnose the disease much earlier.

With the help of DIAN family members, researchers created a detailed timeline of the brain’s long, slow descent into Alzheimer’s dementia, showing, for example, that brain plaques can be detected 15 years prior to symptoms (NEJM, 2012). These plaques are made mostly of amyloid beta. This protein, which abnormally accumulates in the brain of people with Alzheimer’s, is thought to play a role in brain cell damage and death.

The DIAN-TU trial (DIAN-TU.org) is testing two drug treatments designed to eliminate amyloid beta from the brain at different points in the plaque production process. The two drugs that have been selected for the trial are gantenerumab and solanezumab, antibodies that bind to forms of the aggregated amyloid beta and help remove them from the brain. Researchers plan to test additional treatments with different mechanisms of action in this and future trials. The treatments were nominated by the DIAN Pharma Consortium (DIANXR.org/pharma), composed of 12 pharmaceutical companies that have been advising researchers on the planning of the trial. From those nominations, the Alzheimer’s researchers chose the first trial drugs.

“We believe that the diverse portfolio of drugs and approaches of the DIAN-TU trial will accelerate the discovery of an effective treatment for Alzheimer’s,” Dr. Randy Bateman said. “This trial is possible because of the outstanding support of multiple stakeholders, including patients and family members, pharmaceutical partners, the Alzheimer’s Association, the National Institutes of Health, academic researchers and highly dedicated trial operations groups.”

This initial study involves 210 participants. Three of every four will receive active forms of trial drugs; the fourth will receive a placebo. Researchers will track biological markers of Alzheimer’s in participants’ cerebrospinal fluid and on brain scans, looking for any indicators that the disease process is slowing or stopping.

If successful, scientists plan to move directly into Phase III clinical trials to prove that Alzheimer’s can be slowed or stopped. Knowledge gained in the DIAN-TU trial may be applied to the more common late-onset Alzheimer’s.

The trial is funded by a unique mix of private and public resources, including: major grants from the National Institutes of Health (NIH) and the Alzheimer’s Association; treatment donations and funding from the drugs’ manufacturers Roche and Eli Lilly & Co.; donation of a new agent for imaging brain plaques, Amyvid, by Avid Radiopharmaceuticals Inc., a wholly owned subsidiary of Lilly; and donation by CogState of computerized cognitive skills tests to help assess function in participants.

For further information on this study see the last page of this e-newsletter.
Can a simple finger prick predict Alzheimer's twenty years before it develops? Two research developments are now bringing us closer to this possibility. The first is the refinement of a new laboratory technology called metabolomics which allows for the analyses of thousands of metabolic changes simultaneously. The second is research showing that memory loss in Alzheimer's disease (AD) may be preceded by changes in multiple metabolic networks, both in the brain and periphery - indeed a dynamic interplay between central and peripheral metabolic pathways may be critical for cognitive health.

The Metabolomics Consortium for Alzheimer's Disease, headed by Duke University Medical Center and working with companies and centers such as University of Pennsylvania and Indiana University, has now begun to examine ADNI blood samples using Metabolomics (and a related technology called Lipidomics) to identify and quantify thousands of small molecules to provide the first detailed map of the human Alzheimer Metabolome. This is the first large scale national effort to map changes in major metabolic and lipid networks in AD, MCI and Preclinical AD using metabolomics.

"Think about your annual checkup where we measure 20 things like glucose and cholesterol. In a few years we will measure 500 chemicals that will tell us much more about your health including 100s of lipid fractions. Imagine all the things that need to happen before plaques and tangles form. Metabolism needs to support these changes. If we have scope we can look and see these earlier changes and they can tell us a lot about disease and ways to try to stop it," said Rima Kaddurah-Daouk, lead investigator from Duke Medicine.

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Figure 1. Metabolomics: A Global Biochemical Approach to the study of Alzheimer’s Disease.

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The metabolome defines a metabolic state as regulated by interactions between gene, gut microbiome and environment influences, and provides information that can possibly bridge the gap between genotype and phenotype. Metabolic signatures for Alzheimer's could identify new diagnostic or predictive tests, and hold a lot of promise for identifying new targets for drug discovery.

In a series of publications, the team pioneered the use of metabolomics and lipidomics to report specific metabolic changes in the blood of Alzheimer's patients. Investigating lipidomics they have identified changes in several classes of lipids suggesting defects in membrane structure and function in AD. Deficient levels of PIsEtn containing docosahexaenoic acid (DHA) at the sn-2 position were identified in both blood and the brain. Their low levels correlate with AD pathology and cognitive decline. Using targeted and non-targeted models they have identified major defects in interconnected neurotransmission systems and in a pathway that regulates fundamental cellular processes including steps in phospholipid and neurotransmitter biosynthesis. They have built the first metabolic network for AD revealing that several of these metabolic changes are interrelated, some linked to tau or amyloid-beta.

That data combined with recent findings from another group at Georgetown University on blood phospholipid defects prior to AD symptoms has highlighted the importance of studying metabolic failures in AD.

The researchers, led by Drs Rima Kaddurah-Daouk, Murali Doraiswamy, John Trojanowski, Steven Arnold, Mitch King, Andrew Saykin, Xianlin Han and Dayan Goodenowe hope to replicate and validate the metabolomics findings using ADNI samples. The work was initiated in early April and is expected to lead to initial reporting of findings in 2015. The research has been funded by NIH, Alzheimer's Drug discovery Foundation and private entities.
ADCS Clinical Trials Enrolling...

For information on the following studies please visit:

http://www.adcs.org/Studies/cclinicalResearchStudy.aspx

A4 – Anti Amyloid in Asymptomatic Alzheimer’s Disease

SNIFF – the Study of Nasal Insulin to Fight Forgetfulness

Enrolling soon:

NOBLE
A New Study for People with Mild to Moderate Alzheimer’s Disease
The Dominantly Inherited Alzheimer Network (DIAN). DIAN is an international research partnership of leading scientists determined to understand a rare form of Alzheimer’s disease that is caused by a gene mutation. Understanding of this form of Alzheimer's disease may provide clues to decoding other dementias and developing dementia treatments.

Funded by a multiple-year research grant from the National Institute on Aging, DIAN currently involves thirteen outstanding research institutions in the United States, United Kingdom, Germany and Australia. John C. Morris, M.D., Friedman Distinguished Professor of Neurology at Washington University School of Medicine in St. Louis, is the project’s principal investigator.

DIAN is currently enrolling study participants who are biological adult children of a parent with a mutated gene known to cause dominantly inherited Alzheimer’s disease. Such individuals may or may not carry the gene themselves and may or may not have disease symptoms (click here for information about genetic testing).

To register for DIAN drug trials or DIAN, visit www.DIANExpandedRegistry.org.