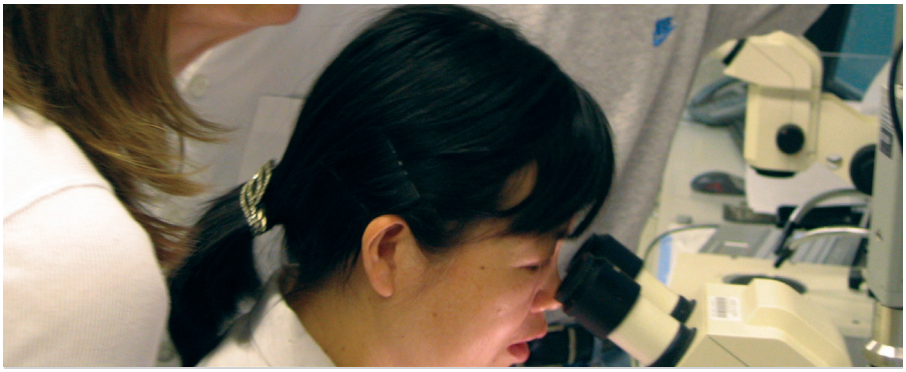
SUMMER 2013

Nerve Growth Factor

The Next Generation In Alzheimer's Disease Therapeutic Research



Dear NGF Participants and Friends:

I am writing to you in my role as the Project Director of the Nerve Growth Factor study, and as the Director of the Alzheimer's Disease Cooperative Study, the organization coordinating this project.

This newsletter is intended to give you an update on the progress of the study and to convey my heartfelt thanks for your role in furthering Alzheimer's research. Of course, without you we could not conduct this important research.

As we explained to you when you enrolled we cannot conduct our final analysis and determine who received the active drug and who received placebo until two years after the final surgery. That final surgery took place in December 2012 when we finished enrollment with 49 patients. We will be able to open the records and find out who received active drug or placebo in January of 2015. I know that is a long time to wait. But I hope you will continue to stay enrolled, coming in for the regular assessments, until release of the final results. These assessments are essential to our analysis of the effects of the treatment.

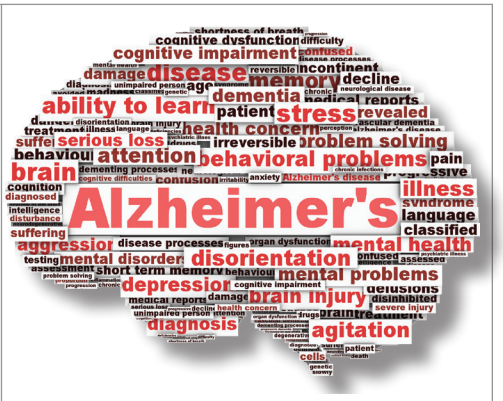
In this newsletter once again we are providing you with information on Alzheimer's disease research in general, and will give you an idea of the grand research effort in which you play a critical role.

If you have any questions, please don't hesitate to ask the study staff at your institution.

Again, thank you for your time and your patience.

Sincerely,

Paul Aisen, MD, Director, Alzheimer's Disease Cooperative Study
Professor, Department of Neurosciences, UC San Diego



Seeing the Brain with CLARITY

By Michael Rafii, MD, PhD
Director, Memory Disorders Clinic
Associate Medical Core Director
Alzheimer's Disease Cooperative Study
UC San Diego

A team of engineers has developed a way to turn organs from mammals, such as lab mice or human bodies donated to science, transparent. Once transparent, scientists can add chemicals to the organs that attach to and highlight specific features, such as different cell types. The result is an intact organ that scientists can see inside and study.

The techniques, called CLARITY, involve a series of chemical treatments that replace the fatty lipid membranes surrounding

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IN THIS ISSUE

Secrets of SuperAger Brains

Elderly SuperAgers have brains that look and act decades younger than their age

Researchers have found super aged brains had fewer fiber-like tangles than the brains of those who had aged normally. Tangles are found in moderate numbers in the brains of the elderly and increase substantially in the brains of Alzheimer's disease patients.

Researchers have long chronicled what goes wrong in the brains of older people with dementia. But Northwestern University researcher Emily Rogalski wondered what goes right in the brains of the elderly who still have terrific memories. And, do those people – called cognitive SuperAgers – even exist?

Rogalski's new study has for the first time identified a group of elderly people age 80 and older whose memories are as sharp as people 20 to 30 years younger than them. On 3-D MRI scans, the SuperAger participants' brains appear as young – and one brain region was even bigger – than the brains of the middle-aged participants.

She was astounded by their outer layer of the brain, important for memory, attention and other thinking abilities. Theirs was thicker than the cortex of the normal group of elderly (whose showed significant thinning) and closely resembled the cortex size of participants ages 50 to 65, considered the middle-aged group of the study.

"These findings are remarkable given the fact that grey matter or brain cell loss is a common part of normal aging," said Rogalski, the principal investigator of the study and an assistant research professor at the Cognitive Neurology and Alzheimer's Disease Center at Northwestern University Feinberg School of Medicine.

Rogalski is senior author of the paper published in the Journal of the International Neuropsychological Society.

By identifying older people who seem to be uniquely protected from the deterioration of memory and atrophy of brain cells that accompanies aging, Rogalski hopes to unlock the secrets of their youthful brains. Those discoveries may be applied to protect others from dementia.

"By looking at a healthy older brain, we can start to deduce how SuperAgers are able to maintain their good memory," Rogalski said. "Many scientists study what's wrong with the brain, but maybe we can ultimately help Alzheimer's patients by figuring out what goes right in the brain of SuperAgers. What we learn from these healthy brains may inform our strategies for improving quality of life for the elderly and for combating Alzheimer's disease."

By measuring the thickness of the cortex – the outer layer of the brain where neurons (brain cells) reside – Rogalski has a sense of how many brain cells are left.

"The thickness of the outer cortex of the brain provides an indirect measure of the health of the brain," she said. "A thicker cortex, suggests a greater number of neurons."

In another region deep in the brain, the anterior cingulate of SuperAger participants' was actually thicker than in the 50 to 65 year olds.

"This region is important for attention. Attention supports memory. Perhaps the SuperAgers have really keen attention and that supports their exceptional memories," Rogalski said.

Ten percent of the people who "thought they had outstanding memories" met the criteria for the study. To be defined as a SuperAger, participants needed to score at or above the norm of the 50 to 65 year olds on memory screenings.

For the study, Rogalski viewed the MRI scans of 12 Chicago-area Superager participants' brains and screened their memory and other cognitive abilities. The study included 10 normally aging elderly participants who were an average age of 83.1 and 14 middle-aged participants who were an average age of 57.9. There were no significant differences in education among the groups.

Northwestern co-authors on the study include Marsel Mesulam, M.D., Sandra Weintraub and Theresa Harrison, formerly with Northwestern and now a graduate student at UCLA.

This project was supported by a grant from The Davee Foundation and grants AG13854, P30 299 AG010129 and K01 AG030514 from the National Institute on Aging of the National Institutes of Health.

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Alzheimer's Disease Cooperative Study
University of California San Diego
9500 Gilman Drive # 0949
La Jolla, CA 92093-0949

(858) 246-1317
www.adcs.org

ADCS Director: Paul Aisen, MD
Editor: Jeffree Itrich

Mount Sinai Leads Global Program Using Stem Cells to Accelerate Cures for Alzheimer's Disease

Researchers collaborate with the New York Stem Cell Foundation using skin samples and brain imaging to identify causes and cures.

Sam Gandy, MD, PhD, of the Icahn School of Medicine at Mount Sinai is leading an international team of researchers working to reprogram skin cells into brain cells to gain a better understanding of Alzheimer's disease (AD). As part of the Consortium, Dr. Gandy is collaborating with Scott Noggle, PhD, the NYSCF – Charles Evans Senior Research Fellow for Alzheimer's Disease and Director of the New York Stem Cell Foundation (NYSCF)'s laboratory in Manhattan.

Dr. Gandy heads the Stem Cell Research Consortium funded by the Cure Alzheimer's Fund (CAF). The Consortium consists of six institutions that plan to directly investigate, for the first time, brain cells in petri dishes from individual patients who have the common form of AD.

> **Having all the cell types together in the same dish enables us to mimic as closely as possible the normal and the diseased adult human brain…**

Dr. Gandy is working with Dr. Noggle's team to reprogram skin cells from AD patients into brain cells using stem-cell technology. The research team will obtain and monitor adult AD brain cells, providing not only a way to study the causes of the disease but also a system for discovering potentially effective drugs. The strategy has been nicknamed "the patient-specific disease in a dish" and enables studies on a time scale of minutes or hours, compared with mouse model testing, which routinely requires nine months to one year.

"This approach is one of our best shots at understanding common forms of Alzheimer's. Once defects are identified, we can use these same brain cells to screen for new drugs," said Dr. Gandy, Professor of Neurology and Psychiatry and Director of the Center for Cognitive Health at Mount Sinai. "This breakthrough technology will enable us to identify genetic and biochemical differences underlying the most common form of Alzheimer's disease."

In collaboration with Mary Sano, PhD, Professor of Psychiatry and Director of the Mount Sinai Alzheimer's Disease Research Center (ADRC), Dr. Gandy plans to select carefully characterized patients and healthy participants from the ADRC who will have skin biopsies and will also undergo brain scans to detect the amount of amyloid plaque, the hallmark of AD, present in the brain. Samples will also be collected from a skin cell bank at

Seeing the Brain with Clarity... (continued from page 1)

cells with a chemical mesh that keeps microscopic details intact without scattering light like lipid does. Neurotransmitters and other important molecules remain in place and can be visualized with a rainbow palette of fluorescent dyes.

Until now, neuroscientists typically had to cut a brain into ultra-thin slices to visualize such features. But that destroys one of the things they're most interested in studying: the cable-like axons that carry signals from one part of the brain to another. The new method makes it possible to visualize these long-range connections as well as the fine-scale anatomy and molecular make-up of neurons, the scientists reported recently in the journal Nature. This is probably one of the most important advances for understanding the structure of the brain in decades.

Although they developed the method in mouse brains, the team shows that it works on human postmortem brain tissue too. In the Nature paper, they describe abnormal neural connections in an autistic boy whose brain had been stored in formalin for more than six years.

With this breakthrough, researchers plan to compare circuitry in banked tissue from people with other neurological diseases, including Alzheimer's disease, and from controls whose brains were healthy. Such studies in living people are impossible, because most neuron-tracing methods require genetic engineering or injection of dye in living animals. Scientists might also revisit the many specimens in repositories that have been difficult to analyze because human brains are so large.

Chung et al, Structural and molecular interrogation of intact biological systems, Nature 2013.

Stem Cells (continued from page 3)

the National Institutes of Health. The scans will be used to confirm AD, the risk for developing AD, and whether a brain is amyloid-free.

Dr. Noggle will reprogram these skin cells into the various cell types that make up the brain, employing the NYSCF Global Stem Cell Array, a breakthrough automated robotic technology that produces standardized stem cell lines. Results are specific to the patient's genetic makeup, allowing researchers to uncover Alzheimer's-related changes at an individual level and to track changes that might otherwise go undiscovered.

"Having all the cell types together in the same dish enables us to mimic as closely as possible the normal and the diseased adult human brain," said Dr. Gandy. "In these mixed cultures, we will study the roughly three-dozen genes that have been linked to AD to see if any are dysfunctional in such a way as to cause one or more known features of the disease."

To encourage international collaboration in Alzheimer's treatment, consortium researchers will create a stem cell bank that can be accessed globally to accelerate drug screening worldwide. This collaboration is an example of NYSCF's commitment to work with global collaborators to advance research.

We can, for the first time, test drugs across a large, diverse population of Alzheimer's patients, using only their cells. This stem cell resource will embolden scientific investigations and accelerate bench to beside delivery of new treatments," said Dr. Noggle. "We're incredibly excited to be working with Dr. Gandy and fellow collaborators to find a cure for Alzheimer's disease."

Other organizations involved in the Consortium are Hadassah University Medical Center, Harvard Medical School and Massachusetts General Hospital, Harvard University Stem Cell Institute, and The Rockefeller University, who is pursuing related research separately funded by CAF.

For more information, visit http://www.mountsinai.org.