SPRING—SUMMER '09

Mount Sinai School of Medicine

Alzheimer's Disease Research Center newsletter

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Can Gene Therapy Slow the Progression of Alzheimer's?

The Mount Sinai ADRC is excited to announce the initiation of a new nationwide study examining the effect of gene therapy on the progression of cognitive and functional decline in mild to moderate AD. Previous studies suggest that a protein called Nerve Growth Factor (NGF) can help promote the survival of acetylcholine neurons that degenerate in Alzheimer's Disease (AD). We are conducting the Nerve Growth Factor study to examine an experimental gene therapy treatment, CERE-110, which delivers the genes for Nerve Growth Factor directly into the brain. CERE-110 is surgically injected into the Nucleus Basalis of Meynert (NBM), a region of the brain where brain cell death occurs in AD. Researchers hope that the surgical injection of CERE-110 will positively affect Basal Forebrain Cholinergic Neuron (BFCN) function, keeping these nerves healthy despite the presence of AD. Previous studies have linked BFCN loss to memory and other cognitive problems in AD, as well as the continued worsening of AD symptoms.

In a study conducted at Rush University Medical Center in Chicago and at UC San Diego, the administration of CERE-110 in ten participants with mild-to-moderate AD was generally safe and well tolerated. Increases in brain metabolism were observed in four of the participants, suggesting a potential reversal of patterns typically observed in AD, although there were not enough participants receiving the current dose of NGF to see a clear pattern of clinical response.

Our study team will be led by Dr. Judith Neugroschl who will work closely with research coordinator Jessica Egan and other members of our team. Dr. Neugroschl comments, "We are excited to be doing this at our ADRC because it is an incredible opportunity to try to directly effect the cholinergic system and try to intervene in the neurodegenerative changes that we know happen to that system in Alzheimer's disease."

You may be eligible to participate in the Nerve Growth Factor (NGF) study if you or your loved one:

- Are between 55-80 years old with a diagnosis of mild to moderate AD
- Have been on approved AD treatments for 3 mos.
- Have a study partner who has contact with you or your loved one an average of 10 hours/week or more
- Are fluent in English or Spanish
- Are in good general health
- For more information, call ***Jessica Egan*** at **(718) 584-9000 ext. 1704**

Ask the Expert: Samuel Gandy, M.D., Ph.D.

Q: I've recently heard about vaccinations for Alzheimer's Disease. What is the history behind these treatments, and how promising are they for the treatment of Alzheimer's?

R: A potential "Alzheimer's vaccine" has long been an interest for researchers and a hope for patients and families. The primary target for most vaccines to date has been the amyloid plaque which is found in the brains of patients with AD, and is thought by many to be the cause of the disease. The idea of using the body's own immunity to combat amyloid buildup has great appeal, but the first clinical trial ran into serious problems. That first drug, known as AN-1792, was designed to present the body with a vaccine comprised of amyloid protein in order to induce the patient's own immune system to attack the amyloid in their brains. These trials were attended by great enthusiasm, since studies in mouse models of AD showed that plaque

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Mumbai Corner

A Cup of Coffee with Dr. Girish Nair

Dr. Girish Nair received his medical training at T.D. Medical College in Alleppey, Kerala, India. He completed his residency at the Government Medical College in Miraj, India, and then went on to specialize in neurology at the Bombay Hospital Institute of Medical Sciences in Mumbai. He joined the Memory and Aging Research Center at Nair Hospital in Mumbai in October, 2007 as Research Officer to work in the Memory Clinic and to develop his research on cognitive disorders.

Kathleen: Hi Dr. Nair, thank you for agreeing to share your experiences with the readers of our ADRC newsletter. How did you start working for this project, what attracted you to it?

Dr. Nair: I was introduced to the project by my mentor Dr. A. B. Shah, who is also the Principal Investigator (Mumbai Site) of the project. Cognitive neurology was my area of interest right from the early days of my neurology training. The project offered me an opportunity to be part of a multi-disciplinary team working on the evaluation, diagnosis and management of cognitive disorders. The cross cultural component of the study was another huge attraction. I am looking forward to be introduced to the profile of dementing illnesses in my visit to Mount Sinai ADRC soon, which would provide a chance to observe and learn about it.

Kathleen: How would you describe a typical day at the center?

Dr. Nair: A typical day starts with the clinical team (including other clinicians, psychologists, and clinical staff) assembling by 9:30am. Over coffee, the team reviews appointments for the day. Referral note information for new patients (screens) and background data for follow-up patients scheduled for the day are discussed. Up to four patients are scheduled for clinical evaluation every day; each session lasting two to three hours. At the end of the day, the team would discuss and iron out any conundrums and to schedule cases for the weekly diagnostic meeting.

Kathleen: That's a busy day. Can you tell us: what have been some of your most memorable experiences working on this project?

Dr. Nair: Well, that's a tough one, for there have been several of them! The treatable dementias have been a source of immense professional satisfaction. We had, recently, a charming elderly couple come in. The gentleman had long standing Parkinson's disease and Mild Cognitive Impairment. He was failing fairly frequently. As we went about assessing his difficulties walking, his wife remarked that during courtship, he would never let go of her hand - if only now he would continue doing the same, he might not fall so frequently!

Kathleen: That's a great anecdote. Tell us a little about your research interests, has your work on the project influenced them?

Dr. Nair: My work at the project with patients of cognitive impairment has whetted my interest in cognitive neurology. In India reversible nutritional/ metabolic factors contribute to the severity in degenerative dementias. This reversible/treatable aspect of dementing illnesses greatly interests me. The infectious dementias are another area of interest.

Kathleen: What are you looking to accomplish in the future?

Dr. Nair: My aim is to work at a center of excellence in dementia and develop my research interest on cognitive disorders. I would also like to work towards a greater understanding of the clinical expressions of degenerative, vascular, and nutritional deficiency, and metabolic and toxic dementias in the Indian context.

Kathleen: This has been a pleasure, Dr. Nair. Thank you so much for sharing your thoughts with us.

Pictured to the left:

The Memory Clinic of the Nair Hospital / Mount Sinai Dementia Research Development Project Team: (from left to right):

Dr. Urvashi Shah,
Shanti Shanker,
Dr. Sumedh Kakade,
Vaishali Ganwir,
Dr. Rashmi Parmar,
Dr. Hemant Mittal,
Dr. Girish Nair

Alzheimer's Disease Research Center News

Congratulations to ADRC researcher **Dr. Effie Mitsis** and colleagues whose abstract, "FDG-PET imaging of patients with amnestic mild cognitive impairment with and without depression" was recently accepted by the World Congress of Biological Psychiatry for presentation at the annual meeting to be held in Paris, France this June.

Dr. Mitsis and colleagues recruited people with mild cognitive impairment (MCI) for a brain imaging study. MCI allows for the early identification of people who may eventually develop Alzheimer's disease (AD). Not all individuals with MCI progress to AD or dementia. However, depresssion is often found in patients with MCI, which suggests that depression may be a risk for subsequent dementia in individuals with MCI. In a pilot study of individuals 55 years of age and older, differences in brain activity were investigated in individuals with amnestic MCI both with and without depression as compared to a group of patients with probable AD and healthy, normal aging controls using fluorodeoxyglucose (FDG) positron emission tomography (PET). PET imaging is used to take pictures of the brain's glucose activity (sugar consumption) in both clinical and research settings.

(Continued on page 6)

Congratulations to **George Marzloff,** one of our ADRC research coordinators, who was recently published in the January 2009 issue of *Developmental Neuroscience.*

While pursuing his undergraduate degree, George and other researchers from the Massachusetts Institute of Technology investigated the effects of supplementing rat mothers with uridine and docosahexaenoic acid (DHA) on the brains of rat pups. Uridine monophosphate is found in breast milk, and DHA is an omega-3 fatty acid found in fish oils. George and his team found that when rat mothers were given UMP and DHA in their daily diet during pregnancy and while nursing, physical changes occurred in the brains of their pups. Levels of proteins and phospholipids found in *synapses* (the junctions through which signals travel between neurons) increased, and neurons began to sprout new branches called *dendritic spines* in the *hippocampus* (an area of the brain involved in memory formation). The authors suggest that administration of these compounds to lactating mothers or infants may promote neuronal connections and thus be useful for treating some development disorders.

(Continued on page 6)

ADRC Winter Retreat

Pictured to the far left:
(from left to right):
Dara Mitchell, Erica Mirigliani, Shelly Rivas, Stephanie Leung, Lauren Brickman

Pictured to the right:
(from left to right):
Jessica Egan, Scott Buell, Tessa Lundquist, George Marzloff, Corbett Schimming, M.D.

The ADRC winter retreat took place in February at Mountain Creek Ski Resort in Vernon, NJ. Staff from both Mount Sinai and the Bronx VA Hospital were in attendance. It was a wonderful day for skiing, with clear skies and moderate temperatures. Clinical trials coordinator Jessica Egan thought it was a nice warm up day for her later ski trip to Vail, Colorado. Dara Mitchell, a Family Studies coordinator, remarked, "The trip was a great opportunity to learn how to ski. Skiing was easier than I expected, but I had helpful coworkers to show me what to do. Despite the awesome bruises, I look forward to next year!" During the day, we also spent time off the slopes for round table discussions about patient recruitment, retention and means of communicating new research findings to our patients. Some of our new ideas will be implemented during April's Participants' Appreciation event.

Ask The Expert (continued from page 1) . . .

buildup could be markedly reduced, or, under certain circumstances, completely prevented. The first 200 elderly subjects with AD tolerated AN-1792 well under a "Phase I" design, but unfortunately, when 300 more subjects were treated in a "Phase II" design, approximately 6% of those 300 (i.e., 18 affected out of 300 treated) developed an allergic inflammation of the brain, necessitating the termination of the study.

A vaccination can be "active" like AN-1792 (vaccination with amyloid plaque material so the body produces its own anti-amyloid antibodies) or it can be "passive" (where anti-amyloid antibodies are created in a lab and infused into patients). Because some patients developed that allergic inflammation of the brain during the AN-1792 study, many researchers have turned to immunotherapies that rely on passive immunity against amyloid plaques. Recent estimates indicate that there are 10-15 amyloid immunotherapy trials ongoing worldwide at this time, and most of those focus on passive immunity because of the problems with AN-1792. One such synthetic antibody, "Bapineuzumab", is currently in Phase III trials, and the Mount Sinai ADRC is one of its sites.

In July, 2008, the results of a Phase II study of Bapineuzumab was reported to the public, and the benefit was marginal. Further, some subjects had a significantly increased risk of mild brain swelling (usually only detectable on brain scan), known as "vasogenic edema" (V.E.). . Since the V.E. was often unnoticed clinically and since the overall results were interpreted as encouraging, a larger "Phase III" trial, of Bapineuzumab is now in progress nationwide. Other studies using infusion of synthetic antibodies are being conducted by Lilly (under the drug name "LY2062430") and Pfizer (under the drug name "RN1219"). The Lilly antibody has completed Phase II trials, while the Pfizer antibody is in Phase I.

In addition to the infusion of synthetic antibodies, there are Phase III trials ongoing using the antibody-rich drug, Intra-Venous Immuno-globulin "IV-Ig". In contrast to synthetic antibodies IV-Ig is prepared from donor human blood. Studies of IV-Ig have shown that there are, in normal human donor blood, naturally occuring circulating antibodies against amyloid clumps. Though theoretically promising there have not yet been sufficiently large, randomized clinical trials of IV-Ig that permit us to draw any conclusions about efficacy. However, small single-site studies have been sufficiently encouraging to warrant a larger controlled study. As of this writing (mid-January, 2009), this study has begun and will be recruiting subjects at 38 centers around the US, including the Mount Sinai ADRC.

Memory Enhancement Program

Dr. Margaret Sewell of the ADRC is offering a free series of seminars on memory improvement for healthy seniors over 65 years of age. At these seminars, you can learn: how memory changes as we age, how you can improve your day-to-day memory skills with simple techniques, how lifestyle factors—diet, medication, exercise—impact memory skills, and how to boost your brain power and attention.

For information about upcoming classes, call Dr. Margaret Sewell at 212-241-0188 or email her at margaret.sewell@mssm.edu.

Participants' Appreciation Day

On April 22, 2009, the ADRC held its Second Annual Participant's Appreciation Day. The day's festivities included talks from Dr. Mary Sano, the Director of the ADRC, on recent research outcomes, and Dr. Sam Gandy, the Associate Director of the ADRC, on new research coming down the pike. The Museum of Modern Art (MoMA) also gave a presentation on "Meet me at MoMA", offering a unique opportunity to explore art therapy. Overall, over fifty participants attended. We would like to thank all our participants for their ongoing participation!

Pictured to the left:
(from left to right):
Greg Elder, M.D.,
Hillel Grossman, M.D.,
Sam Gandy, M.D., Ph.D.,
Mary Sano, Ph.D.,
Laurel Humble (of MoMA),
Amir Parsa (of MoMA),
Jane Martin, Ph.D.,
Margaret Sewell, Ph.D.

ADRC Studies Currently Enrolling

EPIX PRX-03140 202

There is a new phase 2 study being conducted in the United States to evaluate the efficacy and safety of an experimental drug, PRX-03140, in combination of donepezil-treated (Aricept®) patients with Alzheimer's disease (AD). Findings suggest that PRX-03140 could provide both cognition enhancing and disease modifying activities in AD and other dementias by stimulating Ach/serotonin systems and inhibiting amyloid plaque formation pathways. Volunteers will receive either active study drug or placebo for 8 months, the duration of the study, while continuing to take the prescribed donepezil. All participants will be carefully monitored at the research clinic throughout the study. Participants are eligible to participate if they meet the following criteria: are between 50-90 years of age; have a diagnosis of probable AD; have a Mini-Mental State Exam (MMSE) score of 12-22, inclusive; have a brain computed tomography (CT) or magnetic resonance imaging (MRI) scan consistent with a primary diagnosis of AD within 24 months prior; received at least 4 months of a stable dose of donepezil 10mg for AD prior; and have a caregiver who is able to attend all study visits. For more information, please contact **Danielle Charney** at **(212) 659-8883,** or via email at **Danielle.Charney@mssm.edu.** *MSSM #08-0962; Principal Investigator: Mary Sano, Ph.D. MSSM approved through 10/6/09.*

EPIX PRX-03140 203

There is a new phase 2 study being conducted in the United States to evaluate the efficacy and safety of an experimental drug, PRX-03140, for potential treatment of Alzheimer's disease (AD). Findings suggest that PRX-03140 could provide both cognition enhancing and disease modifying activities in AD and other dementias by stimulating Ach/serotonin systems and inhibiting amyloid plaque formation pathways. Volunteers will receive either active study medication, donepezil (Aricept®), or placebo for 9 months, the duration of the study. All participants will be carefully monitored at the research clinic throughout the study. Participants are eligible to participate if they meet the following criteria: are between 50-90 years of age; have a diagnosis of probable AD; have a Mini-Mental State Exam (MMSE) score of 16-24, inclusive; have a brain computed tomography (CT) or magnetic resonance imaging (MRI) scan consistent with a primary diagnosis of AD within 12 months prior; and have a caregiver who is able to attend all study visits. For more information, please contact **Danielle Charney** at **(212) 659-8883,** or via email at **Danielle.Charney@mssm.edu.** *MSSM #08-0962; Principal Investigator: Mary Sano, Ph.D. MSSM approved through 10/6/09.*

CONCERT: A Phase 3 Study Evaluating Dimebon in Alzheimer's Patients on Donepezil

Mount Sinai researchers will be participating in a phase 3 study being conducted nationwide to evaluate how well and how safe a study medication, Dimebon, is in combination with donepezil (Aricept®) in patients diagnosed with mild-to-moderate Alzheimer's disease (AD). This research study will work to evaluate whether Dimebon may improve both the function and outgrowth of brain cells, which is often compromised in a number of neurodegenerative diseases such as AD. Further, the study will evaluate whether Dimebon could provide improvements in cognition and activities of daily living when given in combination with donepezil. Study participants will receive active study drug or placebo (inactive pill) for 12 months for the duration of the study, while continuing to take the prescribed donepezil. All participants will be carefully monitored at the research clinic throughout the study, and will be compensated for transportation to and from the clinic. Participants are eligible to participate if they meet the following criteria: are 50 years of age or older and have mild-to-moderate AD; have a Mini-Mental State Examination (MMSE) score of 12-24, inclusive; have a brain computed tomography (CT) or magnetic resonance imaging (MRI) scan consistent with a diagnosis of probable AD within 12 months prior; have been taking donepezil for at least six months, with stable dosing at 10mg/day for at least the last four months; have a caregiver who is able to attend all study visits. For more information, please contact **Andrew Vigario** at **(212) 241-5692,** or via email at **Andrew.Vigario@mssm.edu.** *MSSM #09-0279; Principal Investigator: Hillel Grossman, M.D. MSSM approved through 3/23/10.*

Investigational Clinical Amyloid Research in Alzheimer's

We're looking for volunteers to participate in a clinical study to evaluate the safety and effectiveness of an investigational drug to help control the progression of Alzheimer's disease. Study participants will be randomized to the investigational product or placebo (a treatment with no active ingredient). There is a 60% chance of receiving the investigational drug and a 40% chance of receiving a placebo. Study participants will be asked to attend 15 study visits during an 83-week period, receive six infusions of the investigational drug every 13 weeks for 65 weeks, and have blood tests and study-related physical and clinical exams. Study participants may be eligible if they are between 50-85 years of age, have a diagnosis of probably AD, and have a caregiver who is willing to be involved in the study. For more information, please call **George Marzloff** at **(212) 241-1514**, or email at **George.Marzloff@mssm.edu.** *MSSM #08-0241, 08-0242; Principal Investigator: Hillel Grossman, M.D. MSSM approved through 3/23/10.*

Trial of a Nutritional Supplement in Alzheimer's Disease

We are seeking patients with Alzheimer's disease to participate in a research study on an antioxidant formula containing **resveratrol**. Some study participants will receive the formula and some will receive a placebo (sugar pill). Participation in the study includes memory testing, neurological exams and blood tests. Resveratrol may reduce brain cell damage caused by harmful chemical byproducts. This study is investigating if resveratrol can help the cognition of Alzheimer's disease patients. The study will be conducted over 12 months and is funded by the Alzheimer's Association. For more information, please call **Danielle Charney** at **(212) 241-8883**, or email at **Danielle.Charney@mssm.edu.** *MSSM #05-1394(0001); Principal Investigator: Mary Sano, Ph.D. MSSM approved through 4/30/10.*

Home-Based Assessments (HBA) study for Memory Protection Research

We are seeking healthy volunteers, 75 or older, to participate in a nationwide research study to examine methods to evaluate memory and thinking skills from the home. Currently, in order to participate in Alzheimer's Disease research studies, volunteers must visit a clinic to meet with researchers. The Home-Based Assessment study will look at three types of home evaluation methods - a telephone, electronic kiosk or mail-in forms - to determine if there may be a better way to gather study information and track memory and thinking-related changes over time. Participants will be assigned by chance to one of the three methods and their memory and thinking skills will be evaluated using their particular method monthly, quarterly or annually. Participants will also have an in-person screening evaluation visit that will include a physical and neurological exam, a medical history, and some cognitive testing. Participants will also be given a multi-vitamin to be taken twice daily, as the study will examine how well the different methods report pill-taking behavior. At the end of the 4-year study, participants will undergo a final in-person evaluation. For more information, please contact **Jessica Egan at (212) 241-8329**. *GCO#91-208 (13); Jane Martin PhD, Principal Investigator, MSSM IRB approved through 08/31/09.*

Functional Deficits of ACC in MCI

A new study is being conducted to examine the effects of aging on memory and attention. Volunteers will be trained for a simple computer task and will perform this task in an MRI scanner. All participants will be compensated for time and travel. Participants are eligible to participate if they meet the following criteria: 1. are between 55 - 90 years of age, 2. are either free of memory problems or are experiencing some memory problems, 3. have a Mini-Mental Status Exam (MMSE) score higher than 24 (if not known, this can be determined through evaluation), 4. have no metal in their body, 5. do not have any current psychiatric disorders, 6. are not claustrophobic. For more information, please contact **Yunsoo Par**k, Clinical Research Coordinator at the Mount Sinai Lab of Neuroimaging by phone at **(212) 241-1613**, or via email at **yunsoo.park@mssm.edu**. *MSSM GCO #08-00443 IRB approved through 6/19/09.*

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MOUNT SINAI SCHOOL OF MEDICINE

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Email: Margaret.Sewell@mssm.edu

Is it time for your annual memory check-up?
CALL (212) 241-8329 TODAY TO SCHEDULE YOUR APPOINTMENT!

Effie Mitsis, Ph.D. (continued from page 4) . . .

The results of Dr. Mitsis's study indicate that patients with AD and MCI with and without depression share a common decrease in relative glucose activity in the temporal and parietal lobes. These are the regions of the brain that are typically affected in AD. In contrast, in the frontal lobe of the brain, a disassociation was seen with increased activity in the AD group in regions of the frontal lobe that possibly represents compensatory activation. However, patients with MCI and depression did not show this compensatory activity but instead showed a decrease, such as that often reported in mood disorders. This suggests that depression may modulate or prevent frontal compensation for temporal lobe deficits (where memory problems arise). Depression is associated with cognitive (memory and thinking) difficulties, with some studies indicating improvement in cognitive abilities following treatment. The findings from Dr. Mitsis's study suggest that antidepressant treatment in MCI with depression may be important for cognitive improvement and that some patients with MCI and depression may represent a subgroup of individuals who will not progress to AD.

Need a Memory Evaluation?

The ADRC's **Memory & Aging Center (MAC)** provides comprehensive evaluation, treatment, and management for those who have memory complaints.

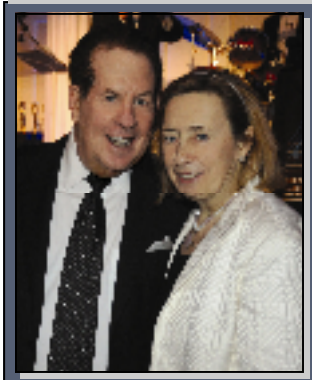
Experts: Our team includes experts in geriatrics, geriatric psychiatry and neuropsychology, neurology, and radiology.

Quick: The evaluation can be completed in one visit, including evaluation by a geriatric memory specialist, neuropsychological testing, and neuroimaging.

Consistent: Patients see the same clinicians each time, and may choose to be followed on a yearly basis or have their report sent to their primary physician.

To make an appointment, please call us at (212) 241-1844.

Thank You Jeff Mann!



On April 27, 2009, Jeff Mann and the Mann Foundation held its fourth annual *Mann of the Year Awards*. Honoring the "stars" of real estate, apparel and the financial industries, the event raises proceeds that directly benefit the Mount Sinai Alzheimer's Disease Research Center.
Thank you, Jeff Mann!

Pictured above: Mr. Jeffrey Mann & Dr. Mary Sano

George Marzloff (continued from page 4) . . .

In an earlier study published in *Brain Research* in 2006, George and other researchers showed that supplementing the daily diet of adult gerbils with the same UMP plus DHA cocktail yielded results similar to those of the rat pup study. In a later study, the researchers showed that rats who received UMP plus DHA performed better at learning tasks than a control group. Because the breakdown of synapses is associated with Alzheimer's disease, the authors suggested that treatment with UMP plus DHA could serve as a novel therapy for Alzheimer's disease. A multinational clinical trial in Europe is underway for patients with Alzheimer's disease based on this translational research. At the Mount Sinai ADRC, we are currently studying the effects of DHA in an eighteen-month clinical trial that will be completed in 2009. George graduated in 2007 from the Massachusetts Institute of Technology with a B.S. in Brain & Cognitive Sciences.

ADRC Upcoming Events

StoryCorps
May 26, 2009

StoryCorps, a national oral history project, records and collects interviews done by everyday people. Starting in 2006, StoryCorps launched their "Memory Loss Initiative" to support and encourage people with memory loss to share their stories. For more information, please call Andrew at 212-241-5692.