SHILEY-MARCOS ADRC HOSTS “DATA BLITZ”

Updates From the San Diego Neurosciences Community

For more than 20 years the Neuroscience Community in San Diego has been a leader in basic and clinical research into the cause, effects, and treatment of Alzheimer’s disease (AD) and related neurodegenerative disorders. This long and distinguished tradition has been made possible by the expertise and vision of the diverse body of neuroscientists that makes up our community, and by the collaborative spirit that characterizes their scientific endeavors.

In order to continue and enhance this tradition of cutting-edge collaborative research, the Shiley-Marcos ADRC hosted a “Data Blitz” last Fall in which leading research scientists from UCSD, Scripps Research Institute, the Salk Institute, and the Burnham Institute gave brief presentations describing their most recent findings on AD, neurodegeneration, and brain aging.

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Living each day with early-onset Alzheimer’s

By Curran Gaughan

Peggy and Michael Powell know first-hand the unique circumstances of early-onset Alzheimer’s disease. The Escondido couple noticed changes in Peggy’s work as a kindergarten teacher nearly four years ago, when activities such as calculating grades and collecting money for a class pizza party became increasingly challenging. Then, after years of dancing in a performance of The Nutcracker, one day Peggy could not remember the steps to the dance. These and other changes initiated an arduous process of discovery for the Powells, who sought an explanation for why Peggy, in her early 50’s, was having difficulty with her memory.

They quickly realized that common assumptions about a younger person experiencing memory loss can create challenges in obtaining a diagnosis and finding acceptance from friends and relatives. Because of Peggy’s young age, doctors first suspected that the changes were due to something psychological or perhaps hormonal.

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It was our hope that this event would help investigators who are currently working in these areas, or interested in doing so, to become familiar with the breadth and depth of research being carried out by their colleagues and to identify resources and potential collaborations that would enhance their own research efforts. The Data Blitz was organized around several themes of clinical and basic research being conducted in our local scientific community:

### Early diagnosis

Researchers interested in **neuroimaging and other biomarkers of early AD** presented evidence that loss of cortical gray matter volume and changes in white matter connections in the brain occur early in the course of disease and correlate with cognitive decline. Increased brain activity during cognitive tasks was also shown to occur in people in the earliest “preclinical” stages of AD, presumably because extra brain areas have to be recruited to maintain a normal level of cognitive function. People in the “preclinical” stage of AD were also shown to have declines in cognitive processes and brain activity associated with the sense of smell, and it was hypothesized that this olfactory dysfunction could be an early marker of the disease. Another biomarker discussed was the presence of the constituents of the plaques and tangles of AD measured in cerebrospinal fluid. These measurements might provide a way to definitively diagnosis the disease in mildly affected patients.

A number of researchers interested in **clinical aspects of Alzheimer’s disease** presented data on risk factors and on the nature of the cognitive deficits that occur early in the disease. A high level of chronic stress and a decrease in effective sleep in the elderly were both shown to increase the risk of developing memory impairment and to hasten the onset of dementia associated with AD. On the other hand, being bilingual was shown to be potentially protective against the onset of dementia, delaying the age-of-onset in people who eventually developed AD. It was hypothesized that the extra cognitive processing that occurs in managing two languages grants a cognitive “reserve” that protects against the neural decline associated with the disease. Newly identified cognitive features of very early AD included 1) asymmetry between verbal and visuospatial abilities that may precede actual deficits in cognition, 2) an inability to effectively integrate information that is successfully processed in different areas of the brain, and 3) a loss of newer (but not older) past personal memories that were well established before the onset of the disease.

### Cognitive reserve

Researchers interested in the basic **biological mechanisms that cause Alzheimer’s disease**, or that might be targets of new therapies, presented data showing that the transport of important cellular proteins inside neurons (nerve cells in the brain) might be blocked in AD, and that neurons that produce an important neurochemical for cognition known as acetylcholine might be rescued from dying in AD by the application of growth factors. Other researchers discussed the development of acetylcholine producing neurons throughout the life-span, and the development or “birth” of new neurons in the normal adult brain in a region important for memory known as the hippocampus. If this knowledge could be applied to the development of new hippocampal cells or acetylcholine producing
cells in people with AD, it might provide a novel treatment for the disease. Researchers also presented new data about how the biological mechanisms involved in processing certain proteins in the brain (e.g., amyloid) go awry in AD and lead to the development of the plaques and tangles that characterize the disease.

The Data Blitz also served to celebrate the recent appointment of Douglas Galasko, M.D. as Director of the UCSD Shiley-Marcos Alzheimer’s Disease Research Center (Edward Koo, M.D., Co-Director) and the recruitment and appointment of Paul Aisen, M.D. as Director of the UCSD Alzheimer’s Disease Cooperative Study. Over the years our Alzheimer’s disease research community has been fortunate to have had exceptionally strong leadership that guided us to national and international prominence. We anticipate that this level of excellence will continue under Dr. Galasko and Dr. Aisen, and we look forward to San Diego remaining a leading center for the study of Alzheimer’s disease and related disorders.

I am excited to be a part of the great staff at the Shiley-Marcos ADRC and to continue my work at the University of California conducting neuropsychological testing. I transferred from the Department of Psychiatry at UCSD in October 2007, where I worked for the Vietnam Era Twin Study of Aging (VETSA). Through VETSA, I conducted a full day of neuropsychological testing on Vietnam era twins and oversaw the cortisol research aspect of the study.

Before working at UCSD, I attended school at the Pacific Graduate School of Psychology in the San Francisco Bay Area where I obtained my Ph.D. in Clinical Psychology. I moved to San Diego to complete my pre-doctoral internship at the University of San Diego, Counseling Center and received my Ph.D. last June. While in graduate school, I worked in many clinical settings primarily with children and adolescents. I am looking forward to gaining a more diverse experience working with Alzheimer’s and aging.

I grew up in Phoenix, Arizona then moved to Seattle, Washington to attend undergraduate school at the University of Washington. After graduation, I moved to San Mateo, California to attend graduate school and lived there for 5 years. I am happy to be in San Diego and out of the rain of Seattle and heat of Phoenix. I enjoy all types of dance, classic cars, and driving my 1957 Chevy. I also enjoy taking weekend road trips and playing with my cat and dog.
After ruling out those possibilities, doctors informed the couple in May 2006 that this was Alzheimer’s disease. Many people close to the Powells were in disbelief; they denied the news and told the couple that the doctors must not have known what they were talking about. Peggy and Michael had trouble accepting the diagnosis themselves, and they sought a second opinion by enrolling in the Shiley-Marcos Alzheimer’s Disease Research Center’s (ADRC) longitudinal study. A thorough evaluation confirmed the initial findings: at age 53, Peggy had early-onset Alzheimer’s.

The term early-onset refers to Alzheimer’s disease that affects individuals younger than 65. In the United States, up to 10 percent (about 400,000 people) of those with Alzheimer’s have early-onset. While most public attention goes toward later onset Alzheimer’s, developing the illness at a relatively young age creates distinct challenges for the diagnosed person and their loved ones. In Peggy and Michael’s case, actions that would typically take place in later stages of life – retirement, long-term care planning – have arrived in advance. Moreover, with two daughters currently in their 20’s, they have faced the added financial burden of helping put kids through college while addressing complex medical and social needs. And while there are many support services available to people impacted by Alzheimer’s disease, many of these services are not tailored to a younger population.

Michael, age 58, works full-time as an elementary school teacher, leaving the house at 5:30 each morning and returning around 4:30 p.m. Seeking to understand Alzheimer’s as well as possible, he takes interest in educational programs offered in the community. However, when these programs take place in the daytime, he and other working caregivers cannot attend. The Powells have also had to search for meaningful activities for Peggy, who stopped teaching two years ago but still wishes to maintain a dynamic lifestyle. Adult day centers did not provide her with a peer group of younger, more physically active individuals. These types of concerns are very common among those with early-onset Alzheimer’s.

Fortunately, Peggy has found two programs—Out & About, based at the ADRC, and Friday Club, at Silverado in Encinitas—that are more to her liking. These programs combine friends, good food, enjoyable volunteer projects, light physical exercise, and culturally enriching outings. Having always been a friendly, active person, Peggy says, “I like being around the people” on Out & About and at Friday Club. On other days, Peggy and a neighbor go on walks or swimming at the gym, where she recently set a personal record for number of laps in a row. These activities appear to have eased Peggy’s struggle to adapt to Alzheimer’s: “There’s help,” she says. “It’s a terrible thing, but after a while you get used to it.” Although some close friends have drifted away over the past two years, the Powells have made new ones participating in a support group at the Alzheimer’s Association for early-onset couples; Michael also uses several online support networks.

He describes their approach as “living each day.” This suggests both pragmatism—being able to adapt to ever-changing circumstances—and a focus on quality of life. When reflecting on Alzheimer’s disease, Michael says, “It doesn’t seem to help to think about it as either positive or negative. It comes back to living: what are we doing in this moment? Thinking about it is something else. Thinking about the way it should have been, or what it could have been, or what it was like – it’s like okay, it’s time to be here. We want to live.”
StoryCorps is a national oral history project that invites people across the country to share their life stories. Since 2003, thousands of people around the country have interviewed family and friends about their life experiences, memories, relationships, and beliefs at StoryCorps booths that travel around the country. These stories are recorded on an audio CD that can be shared with others. With permission, a second copy of the interview is archived at the American Folklife Center at the Library of Congress so that future generations can learn of the everyday lives of Americans. Excerpts of selected StoryCorps interviews are broadcast on National Public Radio’s Morning Edition.

In 2006, StoryCorps launched an initiative to reach out to people with memory loss. The aim of the Memory Loss Initiative is to support and encourage people with memory loss to share their stories so that they can be preserved. Hearing the voices and experiences of people with memory loss nationwide helps to ease the stigma of Alzheimer’s and related disorders and honors their rich story-filled legacies. Last Fall, StoryCorps staff came to our Shiley-Marcos ADRC and set up a recording studio for interviews. Eleven ADRC families participated in the project. Each person with memory loss was accompanied by a spouse or adult child who served as interviewer for a 40-minute session. Donna LaBonte accompanied her husband, Joe and recalls, “The StoryCorps session was fun. I felt like a reporter conducting an interview. We both are especially appreciative to have a CD recording of the interview to share with our family.”

Story Corps staff, Naomi Greene, Jenna Weiss-Berman, and Mike Rauch, were especially attentive and respectful as they worked to make the experience meaningful for those involved. They consider themselves “shepherds” for those who come in to tell their stories and note that they are often deeply moved by the stories they hear. Jay Villarini accompanied and interviewed her husband, David, so they could make a recording for their young daughter. “StoryCorps came into our life at the right time”, she says. “David was able to say everything he wanted to say and he expressed his feelings knowing someone was there recording him. This will be such a great gift for our daughter.”

If you would like to participate in or learn more about StoryCorps, visit their web site at www.storycorps.net.
Contact: (858) 622-5800

Clinical Trials

Are you interested in clinical trials but don’t find one that suits you? You can now join our Shiley-Marcos ADRC registry to be placed on a list for future studies.

PARTICIPANTS CAN BE:
- Normal Controls
- Have a mild memory problem
- Be diagnosed with early-to-moderate Alzheimer’s

Call the Shiley-Marcos ADRC at (858) 622-5800

Clinical Trials Registry

THERE ARE MANY NEW CLINICAL TRIALS AND RESEARCH PROTOCOLS ENROLLING AT THE SHILEY-MARCOS ADRC

If you are interested in participating or would like more information, please contact the Study Coordinator listed with each trial.

- They can all be reached at the Shiley-Marcos ADRC - (858) 622-5800
- There is no cost to participate in any of these research protocols
- The Shiley-Marcos ADRC is under the direction of Douglas Galasko, M.D.

UPDATE

Nerve Growth Factor Gene Therapy for Alzheimer’s Disease

“Neurotrophic factors” are natural proteins that are present in the nervous system, which enhance cell survival and stimulate cell function. In animal models, a neurotrophic factor called “Nerve Growth Factor” has been shown to prevent the death of one class of cells that dies over time in people affected by Alzheimer’s disease.

In 2004, a potentially more potent form of Nerve Growth Factor gene therapy for Alzheimer’s disease was tested in a second clinical trial. This time, “AAV vectors” were used for the gene therapy procedure, which produce higher levels of growth factors in the brain over several years than the version of gene therapy tested in the first UCSD trial. Two doses of AAV-Nerve Growth Factor were tested in 6 patients at Rush Medical Center in Chicago, and were found to be safe. Brain hemorrhages did not occur.

UCSD is performing an extension of this AAV-Nerve Growth Factor clinical trial using a third, higher dose of the drug. The gene therapy procedure requires a two-day hospital stay for surgical introduction of the Nerve Growth Factor gene into the brain. Unlike existing approved therapies for Alzheimer’s, Nerve Growth Factor offers the potential to prevent cell loss in the brain and to slow the course of the disease. A total of four participants in early to mid stages of Alzheimer’s have been enrolled, and the study is currently closed. We will report findings from this small clinical trial in upcoming issues of Currents.
Last November, our UCSD Shiley-Marcos Alzheimer’s Disease Research Center (ADRC) and the Neurotoxicity Society co-sponsored a special one-day event to honor the life achievements of Dr. Robert Terry. Dr. Terry is co-founder of our ADRC, our first neuropathologist, and a pioneer in the field of Alzheimer disease pathogenesis (the cause, development, and effects of Alzheimer’s). The San Diego symposium included the leading experts in the field of neurodegenerative diseases each of whom discussed their own work and the impact Dr. Terry has had on research.

Robert Terry, M.D., has been studying Alzheimer disease (AD) and normal aging of the brain for more than thirty-five years, and is credited with many pivotal scientific advancements in the field. Some of Dr. Terry’s significant contributions include being the first to study plaques and tangles using electron microscopy, and then with colleagues to study the plaques in aged dogs and monkeys. In addition, he was the first to describe the effects of aluminum on neurons and his work includes the first cortical neuron counts in AD and in normal aging with modern techniques.

In the late 1980’s and early 90’s, in association with Dr. Eliezer Masliah, they developed techniques to quantify synapses in autopsied brain tissue, and found that synaptic loss correlated very strongly with cognitive deficiency in AD. In 1988, Dr. Terry was the first winner of the Potamkin prize for Alzheimer research; he also received the Distinguished Service Award from the American Association of Neuropathologists in 1989, the Metropolitan Life Foundation Award in 1991, and he is a Fellow of the American Academy of Arts and Sciences.

From 1990 to 1996, Dr. Terry served on the Advisory Board of the Max Planck Institute in Martinsried, Germany. Over fifty graduate fellows have trained in experimental and diagnostic neuropathology under his supervision. Dr. Terry received his medical degree in 1950 from Albany Medical College, Union University in Albany NY, after serving in WW II in the U.S. Army, 82nd Airborne Division in Europe. He spent 25 years working at the Albert Einstein College of Medicine, 15 years of which he was Chairman of the Department of Pathology, and over 20 years in the Departments of Neurosciences and Pathology at the University of California San Diego where he is now Professor Emeritus. Dr. Terry continues to publish and to lecture at national and international conferences. Notably, he recently gave the opening address on the 100th Anniversary of Alois Alzheimer’s first presentation during the Alzheimer: 100 Years and Beyond conference in Tübingen, Germany. Today he remains a highly respected colleague, mentor, and leader in Alzheimer disease research.
The Shiley Marcos ADRC has just launched its new website at [http://adrc.ucsd.edu](http://adrc.ucsd.edu). The new site has updated graphics, content, resource links, and interactive features. The new webpage was designed by Department of Neurosciences web designer, John Widjaja. We hope you will find our new web site to be informative and user-friendly. Do feel free to contact us with any feedback as you explore the site.

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<td>CALENDAR</td>
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<td>NEWSLETTERS</td>
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Last December, the Shiley-Marcos ADRC held its annual open house and year-end research review. The event was attended by over 100 of our ADRC participants who enjoyed a continental breakfast while listening to our scientists discuss their latest projects and findings.

Larry Goldstein, PhD, began the morning with a summary of stem cells and his research project “Generating Human Models of Sporadic Alzheimer’s Disease” (featured in the last issue of Currents). To inquire about this study, contact Christina Gigliotti at (858) 622-5800 or cgigliotti@ucsd.edu.

Edward Koo, MD, provided an informative overview of the “amyloid cascade hypothesis” that supports the role of a type of beta amyloid protein, Aβ42, as a culprit in the pathology of Alzheimer’s disease (AD). In persons with AD, after Aβ42 is cleaved from a parent protein (amyloid precursor protein), it aggregates and is deposited in plaques that form in the brain. Dr. Koo discussed the hypothesis that new drug compounds under investigation could target this cleaving process and decrease production of Aβ42 to reduce its deposition in the brain.

Mike Rafii, MD, PhD, discussed the use of Positron Emission Tomography (PET) scans to diagnose AD. The technique uses a molecule called Pittsburgh Compound B (PIB), which allows researchers to see the actual amyloid protein deposits in the brain. Dr. Rafii reported on his research findings that the more amyloid there is in the brain, the more the research subjects with AD had difficulties with memory testing. PET scans with PIB may be a useful technique to help evaluate efficacy in experimental drug compounds aimed at lowering levels of amyloid protein in persons with AD.

Shiley-Marcos ADRC director, Doug Galasko, MD, completed the morning talks with a review of current clinical trials and hopeful treatments for AD. Exelon, a drug currently on the market to treat AD, is now available in patch form and is better tolerated than capsules. Findings from experimental clinical trials aimed at slowing AD progression, however, have been mixed. Lowering homocysteine levels (through increased folic acid intake) did not prove to be a useful treatment for persons with AD.

A study of a gamma-secretase inhibitor (LY450139) aimed at lowering levels of beta amyloid protein did show promising preliminary findings, however, and will move into larger clinical trials this year. The Shiley-Marcos ADRC will be participating in the new antibody study (AAB-001 or Bapineuzumab) that aims to infuse antibodies against beta-amyloid in persons with AD to help remove amyloid from the brain. Other clinical trials are up and running and can be found on the centerfold.

We are deeply grateful to all of our Shiley-Marcos ADRC participants for your ongoing volunteerism and partnership with us as we work to better understand, treat, and ultimately cure Alzheimer’s disease. Each year marks new progress, and we certainly could not make these promising strides without you.
The Shiley-Marcos ADRC depends on both public and private resources to operate. Our funding comes primarily from competitive grants from the National Institutes of Health (NIH), from foundation-sponsored programs, and from individual gifts and bequests from patients, families, friends, and other beneficiaries.

NIH funding supports our basic infrastructure, but your donations and bequests are equally critical. In the current funding climate of NIH, less than 10% of grant applications receive federal support, down from 30% a few years ago, accompanied by an increase in the cost of doing research. Grant applications that are funded require significant data collection to be considered and highly innovative research is often excluded. Your gifts allow us to pursue and sustain new avenues of research from our well-established scientists and support the efforts of promising young scientists who have difficulty competing for limited federal funds. Your donation can be designated for clinical research (studies involving living persons), basic science (which delves into the mechanisms of the disease or drug discovery), or programs for persons and their caregivers affected by the disease (our support groups, outings program, and other quality of life programs).

If you have questions regarding the intent of your donation, please contact me, Mary Sundsmo, at (858) 622-5800 or msundsmo@ucsd.edu, and I can help crystallize your ideas.

The University of California, San Diego is a 501(c)3 non-profit organization and all contributions are tax-deductible to the extent allowable by law. You can donate through various means:

- Using the envelope in the centerfold of this newsletter. Both credit card and checks can be used. Checks should be made payable to “UC Regents” with the memo line stating “Shiley-Marcos ADRC”.
- Online with a credit card on our website http://adrc.ucsd.edu where you can set up a one time or a recurring donation
- Contacting Heather Nist, Director of Development, Neurosciences at (858) 622-1030 or hnist@ucsd.edu. Heather can guide you through the process in the case of more complex large gifts or bequests.

Thank you for considering the Shiley-Marcos ADRC as a recipient of your charitable gift. You can be assured that we will put all gifts to meaningful use as we work to treat and prevent AD as well as care for families affected by the disease.
Memories at the Museum

A collaboration between The San Diego Museum of Art and The UCSD Shiley-Marcos Alzheimer’s Disease Research Center

Join us on Friday, April 25th from 2:00-3:00pm at the San Diego Museum of Art, Balboa Park

San Diego Museum of Art docents guide visitors with memory loss through the painting and sculpture exhibits. They facilitate discussions to engage their visual, verbal, and mental abilities, and provide a fun interactive experience. A separate simultaneous tour is provided for an accompanying friend or family member. This program is entirely free of charge to both participants with memory loss and their companions, and is offered quarterly.

Pre-registration is required.
If you would like to participate please contact Lisa Snyder at (858) 622-5800.