imagine
stopping the progression of Alzheimer's disease
ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE

ADNIExclusive

A Special Newsletter for Participants in the Alzheimer's Disease Neuroimaging Initiative

Fall 2012

Dear Friends:

Michael Weiner, M.D.
Fellow Participant & ADNI Principal Investigator

The phrase "may you live in interesting times" can be interpreted as both a blessing and a curse. I say, with confidence, that these are indeed "interesting times" in Alzheimer's disease (AD) clinical research. So far in 2012, AD research news has been a roller-coaster of potential breakthroughs and apparent dead ends.

It doesn't help that the scores of news reports often appear to be contradictory – especially in the mainstream media. You can expect this trend to continue through to the end of the year as a number of high-profile AD clinical trial results are presented in Europe and the US and disseminated throughout the medical and mainstream media.

This attention to AD will not be going away. As everybody involved in ADNI knows, AD is the sixth leading cause of death in the US and it is the only leading cause of death that we haven't been able to prevent, arrest or cure. By 2025, the number of people diagnosed with AD is expected to increase by at least thirty percent.

Moreover, despite the explosive growth in AD clinical research over the last 10 years, there haven't been any new AD drug therapies approved for use to treat AD since 2003. Nor have researchers been able to definitively identify behavior modifications — involving things like exercise and/or diet — to prevent or stop the progression of AD. **continued on page 2**

FALL 2012

For more information email us at **brainlink@ucsd.edu**

ADNI IN MEDIA:

ADNI needs more volunteers with Alzheimer's!

In the Spring and Summer of 2012 — in response to slow/low enrollment of ADNI participants with AD — ADNI PI (and study volunteer) Mike Weiner, reached out to media outlets to highlight the immediate need for ADNI volunteers who have been diagnosed with mild-to-moderate AD. Dr. Weiner spent significant time writing blogs, working with television networks, web sites and print media to draw attention to the need for more people to volunteer for clinical trials generally and ADNI's ongoing need to enroll 100 volunteers with mild AD.

You can view a few examples of the results of Dr. Weiner's ADNI media work in the sidebar. (Note: Mike's fellow ADNI volunteers may find the video on the Inside E Street link, on the right, to be of particular interest.

— **CBS Evening News**
http://tinyurl.com/9xwpgda

— **Huffington Post**
http://tinyurl.com/9kcqrvc

— **InSide E Street**
http://tinyurl.com/6nh3wod

Michael W. Weiner, MD (continued from page 1)

That doesn't mean that AD clinical research isn't working. There is good reason to remain hopeful about progress in finding ways to prevent, treat or ultimately cure AD within the next several years.

Why am I Optimistic?

Perhaps I am too much of an optimist, but my optimism is rooted in the process that enabled several of the major medical advancements over the last few decades. That is — breakthroughs in medical treatments and prevention of major diseases which were identified only after we gained a clear understanding of the biology of the disease.

For instance, during medical school and my subsequent years of training in the 1960s and early 1970s, the diagnosis and treatment of heart disease relied on things like a patient reporting a history of shortness of breath or chest pain. Today, through scans, biomarkers and other tools we are able to look at a patient's heart, examine the blood flow and monitor heart functions. Those tools have enabled us to accurately diagnose and effectively treat and prevent heart disease.

But we figured out how to prevent, treat and cure heart disease only after we had the ability to observe the organ functioning and to establish uniform measurements of the biology and pathology of heart disease. The same can be said for lung and liver disease — today we know what's going on because we came to understand the biology.

ADNI Contribution

As every ADNI participant also knows, ADNI is designed to provide a comprehensive understanding of AD biology and pathology.

To state the obvious, AD is an inherently complex disease because it involves the brain. Ten years ago, we identified AD almost exclusively through behavior (cognitive deterioration for no other apparent reason) in older people. However, the only way we could positively diagnose AD was during autopsy – the same way physician Alois Alzheimer originally identified AD plaques and tangles 100 years earlier.

Today, as a direct result of ADNI, we are honing in on distinct AD biomarkers earlier and earlier in the disease process. In clinical research settings, we are able to definitively diagnose AD using a combination of biomarkers, scans and cognitive testing.

Specifically, ADNI data combined with earlier AD research data resulted in the general acceptance of the concept that AD pathology begins several years before any external symptoms appear. The presence of biomarkers like amyloid is the first known indication of the relatively slow descent leading to mild cognitive impairment and finally to dementia. Without question, the results from ADNI had a huge influence in accelerating general acceptance of this concept. Second, virtually all of the clinical AD trials recently completed, underway or in planning are designed using ADNI data and performed using ADNI methods.

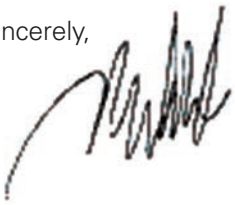
Finally, there is, of course, the World Wide ADNI (WW ADNI) — a collaborative effort of scientists from around the world and the umbrella organization for neuroimaging initiatives including our ADNI (known internationally as North American ADNI) and European ADNI (E-ADNI), Japanese ADNI, Australian ADNI (AIBL), Taiwan ADNI and Korea ADNI.

As both an ADNI volunteer and Principal Investigator, I am well aware that we are constantly measuring, scanning and testing ADNI participants. I hope I have made the case that we do so for good reason: The more we know about the nuances of normal aging and the nuances of AD-related changes — the faster we will be able to find the treatments, preventions and, perhaps, a cure for AD.

As ADNI continues to shed light on the earliest indications of AD pathology, we continue to move the clinical research forward and closer to the knowledge needed to finish the job. So, in my opinion - these are interesting times in AD clinical research and that is a good thing.

I will write to you later this year to update you on the ADNI whole genome sequencing project as well as on the outcome of several AD treatment trials expected to be reported this fall.

Sincerely,



Michael W. Weiner, MD
Director, Center for Imaging of Neurodegenerative Diseases
ADNI Principal Investigator & ADNI Participant
University of California, San Francisco
San Francisco, CA

Another ADNI Milestone:
First AD–related "Big Data" Project in US

Jeffree Itrich, MSW, MJ
ADCS
ADNI Coordinating Center,
University of California, San Diego

"The current ADNI database already includes detailed, long-term assessments of neuropsychological measures, standardized structural and functional imaging, and precise biomarker measures from blood and spinal fluid. Adding whole genome sequences to this rich repository will allow investigators all over the world to discover new associations between these disease features and rare genetic variants, offering new clues to diagnosis and treatment."

ADNI Data and Publications co-chair Robert C. Green, M.D., M.P.H., of Brigham and Women's Hospital and Harvard Medical School, who is leading coordination of sequencing efforts within ADNI.

In July 2012, we reached another big milestone in AD research when ADNI became the first, pioneering "Big Data" project for Alzheimer's disease. A new partnership between the Alzheimer's Association and the Brin Wojciki Foundation will enable scientists to obtain whole genome sequences on the largest cohort of individuals related to a single disease (the ADNI GO and ADNI 2 clinical trial cohorts) in the US.

Currently, 800 individuals from ADNI GO and ADNI 2 will be sequenced. The new ADNI whole genome sequencing work is expected to generate at least 165 terabytes of new genetic data. The project is a significant extension of ADNI.

Whole genome sequencing determines all six billion letters in an individual's DNA in one comprehensive analysis. Once the sequences are completed — which will take several months — the raw data will rapidly be made available to qualified scientists around the globe to mine for novel targets for risk assessment, new therapies, and additional insight into the causes of AD.

Sequencing the ADNI participants and making the genetic data immediately available to researchers around the world will significantly improve our understanding and approach to Alzheimer's disease. *"The ADNI team and the Alzheimer's Association are impressive in their ability to quickly make decisions that are truly in the best interest of people with Alzheimer's,"* said Anne Wojcicki from the Brin Wojcicki Foundation.

The ADNI leaders directing the project emphasize the potentially groundbreaking importance of the ability to match existing data from ADNI about Alzheimer's disease markers, indicators, and changes with newly-generated gene sequence data. The new data may enable scientists to better understand how our genes cause and are affected by bodily changes associated with Alzheimer's disease.

As many ADNI volunteers know, a distinguishing feature of ADNI is that the research data — including brain scans, blood and cerebrospinal fluid samples, and cognitive profiles — are made freely available without delay to scientists around the globe, resulting in more than 500 scientific manuscripts so far.

ADNI Data and Publications co-chair Robert C. Green, M.D., M.P.H., is collaborating on the sequencing efforts with ADNI Informatics Core leader Arthur Toga, Ph.D., of UCLA and ADNI Genetics Core head Andrew J. Saykin, Psy.D., of Indiana University. The actual genome sequencing will be performed at Illumina, Inc.

Retired Physician/ADNI Volunteer

Produces a Compelling Video

"We could not conduct research without the support of volunteers like Dr. Nash.

His most recent contribution will prove to be a powerful tool for use in outreach to potential participants through the media."

The University of Texas Southwestern (UTSW ADC) ADNI site shared a video with the ADNI Coordinating Center and we would like to pass the video on to the larger ADNI community. The video features DeWayne Nash, MD, a UTSW ADNI participant volunteer enrolled in the study's MCI cohort.

Dr. Nash discusses his interest in clinical trials for AD and the unanticipated results of his ADNI screening. The video contains a poignant and straight forward discussion about finding a purpose and continuing to make important contributions while living with MCI.

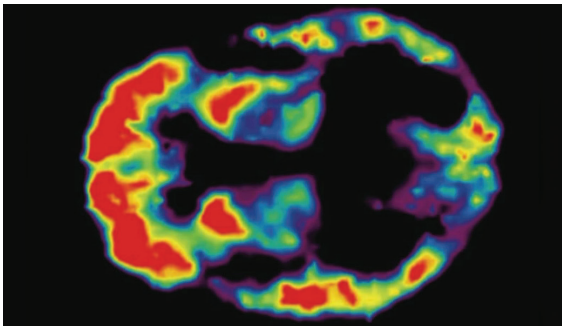
http://tinyurl.com/9p7bom7

The video immediately came to the attention of HHS/NIH/NIA for possible use in the federal clinical trial public awareness campaign which began in August 2012.

UTSW ADNI Study Coordinator Kristin-Martin Cook said, "We could not conduct research without the support of volunteers like Dr. Nash and his most recent contribution will prove to be a powerful tool for use in outreach to potential participants the media. Dr. Nash has a strong family history of Alzheimer's and he graciously shared his story in this video."

Dr. Dewayne and Jo Ann Nash

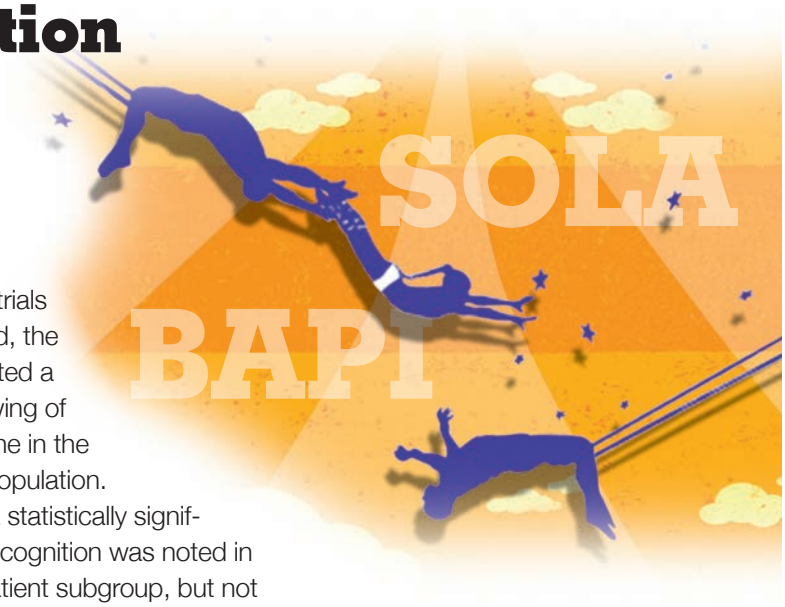
Illustration of neurons



PET scan

Timing is Everything:
Immunotherapy Results Illustrate Need for Earlier Intervention

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



As many of you have undoubtedly read or heard, results from multiple clinical trials were reported this past summer involving both Bapinineuzimab and Solanezumab, two of the leading drug candidates under development for slowing down the progression of AD. Solanezumab and Bapineuzemab are both classified as immunotherapies. These drugs are monoclonal antibodies against beta amyloid, the protein that accumulates in the brain of patients with AD and is thought to be causative of the disease. The studies were all large, Phase 3, double-blind, placebo-controlled trials in patients with mild-to-moderate AD.

Although the trials were negative, a possible efficacy signal was discovered in pre-specified secondary analyses of Solanezumab trials, offering a glimmer of hope. When data from the two Solanezumab trials were combined, the results suggested a significant slowing of cognitive decline in the overall study population. Furthermore, a statistically significant effect on cognition was noted in the mild AD patient subgroup, but not moderate AD subgroup, as compared to placebo. In its release of the trial results, Lilly emphasized that these are the first Phase III data with an anti-beta amyloid agent that appear to show a slowing of cognitive decline, and that the pooled data support the amyloid hypothesis.

The results indicate that drugs against beta-amyloid will need to be tested even earlier in the course of the disease, perhaps in the prodromal stage where symptoms are even milder. This concept of earlier treatment is akin to the need to start cholesterol medication years before a heart attack occurs in order to derive benefit from its use.

Despite the negative results for Bapineuzemab, Pfizer and Johnson & Johnson remain committed to its development as a potential therapy, and in fact, will continue with another trial of Bapineuzemab that is being delivered as a subcutaneous injection, rather than intravenous treatment. This method of drug delivery may actually overcome some of the barriers faced by intravenous Bapineuzemab, in that the drug may linger in the system for longer by virtue of the subcutaneous route, and have longer access times to beta-amyloid in the brain.

The Alzheimer's disease community now awaits the upcoming American Neurological Association (ANA) annual meeting and the Clinical Trials on Alzheimer's disease (CTAD) conference in October, as the full analysis on the pooled and subgroup data are released.

"Although the trials were negative, a possible efficacy signal was discovered in pre-specified secondary analyses of Solanezumab trials, offering a glimmer of hope. When data from the two Solanezumab trials were combined, the results suggested a significant slowing of cognitive decline in the overall study population. Furthermore, a statistically significant effect on cognition was noted in the mild AD patient subgroup, but not moderate AD subgroup, as compared to placebo."

Michael Rafii, MD, PhD
University of California, San Diego
ADCS

BRAIN TEASERS

Word Jumble

RETWEAH 

ROSTM 

NIRA 

DANTOOR 

HIAL 

MDU 

Word jumble answers: weather, storm, rain, tornado, hail, mud

Final Answer: summer

Mad Gabs (Hint: sound out the sentence)

1. Abe An An Appeal
2. Abe Autumn Lisp Hit
3. Abe Ax tree Tally
4. Abe Hair Heat Rash You're
5. Abe Hum Pen Thin Height

Mad Gab Answers

1. A Banana Peel
2. A Bottomless Pit
3. A Back Street Alley
4. A Buried Treasure
5. A Bump in the Night