Results of IGIV Study Disappointing But Not Discouraging

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The first results from the GAP study of Intravenous Immunoglobulin (IGIV) for Alzheimer’s disease were just announced and are disappointing but not entirely discouraging. The primary results are clear - IGIV did not significantly slow decline of thinking abilities or preserve daily function in a large group of Alzheimer’s patients when compared to an inactive placebo. However, some positive responses were seen in certain subgroups of the participants who received IGIV.

The GAP study was a late-stage clinical trial of IGIV carried out by the ADCS over the past five years with support from Baxter Healthcare and the National Institute on Aging. It enrolled 390 patients with mild to moderate Alzheimer’s disease from 45 ADCS sites in the US and Canada. Participants were given either IGIV or placebo for 18 months. They were tested at regular intervals to see if IGIV was safe and effective in reducing dementia symptoms. The ADAS-Cog, a test of thinking abilities, and the ADCS-ADL, a measure of daily function, were the two primary endpoints measures. A host of other tests, scans and biomarker studies were carried out as secondary or exploratory outcomes to further examine IGIV’s effects. The study was carried out to a very high standard, setting goals that have not yet been reached by any medication for Alzheimer’s that is approved or under investigation.

After 18 months of treatment, the group of patients who received IVIG were not significantly different from those who were given a placebo on either of the two primary endpoints. This means that IGIV was not effective in slowing the progression of Alzheimer’s disease. The news was not all bad, however. IGIV was well-tolerated, and some positive effects were observed in at least two subgroups of participants treated with IGIV. While the subgroup results are encouraging, they do not negate the primary outcomes. A positive result that is limited to a subgroup of patients can be considered a justification for further study, but does not provide the kind of evidence necessary for IGIV to be considered a useful treatment for Alzheimer’s disease. Only positive outcomes on the primary measures could have led to IVIG being accepted as a new treatment for Alzheimer’s and in this case, the primary endpoints were negative.

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What we stand to learn from the GAP study cannot be overstated. IGIV was chosen for study because it contains antibodies the human body produces naturally that react with clumps of beta amyloid protein and other molecules thought to be involved in the development of Alzheimer's disease. In earlier phases of clinical study, IGIV showed considerable promise in slowing dementia-related decline, albeit in small numbers of patients. It was essential to determine whether or not IGIV could help most persons with Alzheimer's and that is exactly what the GAP study has accomplished. While the negative primary results are undeniably a disappointment, the clear answers provided by the GAP study are a major step forward for Alzheimer's research.

IVIG is approved to treat a number of disorders, but not Alzheimer's disease. It is expensive and in limited supply. Over the past several years, some physicians have chosen to administer IVIG to their patients with Alzheimer's disease in what is called “off label” treatment based on the positive findings from earlier studies. The GAP study's primary findings should discourage this kind of off-label use of IGIV for treatment of Alzheimer's for the foreseeable future. However, Alzheimer's patients already receiving off label treatment with IGIV should discuss their options carefully with their physician, taking into account that there were some positive effects observed in subgroups of IVIG-treated participants in the GAP study.

The study results are still under analysis and a full study report will be presented to the medical and scientific community in July at the AAIC meeting in Boston. This will include some of the brain imaging results and biomarkers that were collected from blood and spinal fluid during the study. These additional analyses will help to put the study's findings into better focus and may provide new directions for future studies.

As the GAP study leader, I want to acknowledge and express my gratitude to all of the participants in this study, especially the Alzheimer's patients and their study partners for their invaluable and selfless contribution to Alzheimer's research. I would also like to acknowledge the extraordinary efforts of the investigators and the research teams at the 45 ADCS sites that took part in the study as well as the many highly skilled persons at the ADCS, Baxter and the NIA that helped to bring this important study to fruition.

Norman Relkin MD, PhD
Weill Cornell Medical College
Scientists At Mount Sinai Discover A Key Mechanism For The Most Common Form Of Alzheimer’s Disease

By Mount Sinai Medical Center

Research identifies potential therapeutic targets for Late Onset Alzheimer's Disease (LOAD) by revealing a network of genes involved in the inflammatory response.

Scientists from the Icahn School of Medicine at Mount Sinai, in collaboration with researchers from Icelandic Heart Association, Sage Bionetworks, and other institutions, have discovered that a network of genes involved in the inflammatory response in the brain is a crucial mechanism driving Late Onset Alzheimer's Disease (LOAD). The findings, published online in the journal Cell, provide new understanding of key pathways and genes involved in LOAD and valuable insights to develop potential therapies for the disease.

To date, scientists have been challenged in understanding LOAD, the most common form of AD. Despite decades of intensive research, the causal chain of mechanisms behind LOAD has remained elusive. Currently, no effective disease modifying or preventive therapies exist and the number of Americans suffering from LOAD is expected to double by 2050.

The scientists performed an integrated analysis of the DNA of 376 deceased patients with LOAD, along with gene expression data (how the genes operate), to reveal the interconnected relationships among a large network of genes that drive the key pathways (the mechanisms) of the disease. The study authors created a biological network model, a complex mathematical representation of large amounts of data. These networks provide a unified map that integrates not only the key genes involved in the disease but also the biological pathways that those genes control. This network model provides a novel, comprehensive understanding of Alzheimer's disease and identifies potential targets for intervention.

The scientists identified a pathway involving an inflammatory gene, TYROBP, that had not been previously implicated in Alzheimer's disease. TYROBP is known to interact with TREM2, another gene recently discovered to be involved in Alzheimer's by Rita Guerreiro, University College London, and Thorlakur Jonsson, deCODE Genetics, et al. Thus, the new paper draws attention to the TREM2-TYROBP pathway playing a central role in driving common forms of Alzheimer's disease.

"Defining the precise steps of the inflammatory response crucial to causing Alzheimer's disease has been elusive. We are pleased to discover these novel insights into that process," said Bin Zhang, PhD, a co-lead author of the study and an Associate Professor of Genetics and Genomic Sciences at Mount Sinai. "As a next step, we will evaluate drugs that impact the TREM2-TYROBP pathway as potential therapies for the disease. This discovery enables us to design more specific compounds that target these key steps precisely, in contrast to existing anti-inflammatory drugs that may be less ideal for hitting this target."

Eric Schadt, PhD, an author of the study and Director of the Icahn Institute for Genomics and Multiscale Biology, and Chair of the Department of Genetics and Genomic Sciences at Mount Sinai, said "Creating a predictive model of Alzheimer's disease is a landmark achievement, yielding valuable insights into the complex mechanism of the disease." Christopher Gaiteri, PhD, a co-lead author of the study and Senior Scientist at Sage Bionetworks, said, "In the same way that sophisticated predictive mathematical models drive decision making in the global financial markets (what stocks to buy, when to sell, etc.), the field of medical research has begun to rely on network models such as this to derive meaning from vast amounts of patient data, enabling better understanding and treatment of human disease."
Jun Zhu, PhD, Professor of Genetics and Genomic Sciences at Mount Sinai and also an author of the new study, stated "This paper in Cell, along with recent discoveries, provides unequivocal proof that inflammation plays a central role in Alzheimer's disease, which is a consistent theme among common complex diseases that also include obesity and type II diabetes." Valur Emilsson, PhD, Head of Systems Medicine at Icelandic Heart Association and also a senior author of the paper, added, "Currently, we see a long lag time between appearance of amyloid on brain scans of patients and the appearance of clinical symptoms. An individual’s inflammatory response could well play a role in the disease progression, and an appropriate anti-inflammatory drug, given after amyloid is detected but before symptoms begin, could be an important part of dementia prevention."

Study authors include scientists from Icelandic Heart Association; Sage Bionetworks; Merck Research Laboratories; University of Bonn; Fred Hutchinson Cancer Research Center; Massachusetts General Hospital; University of Miami; Rush University Medical Center; and GNF Novartis. The human postmortem brain samples were provided by Harvard Brain Tissue Resource Center (HBTRC).

For more information, visit http://www.mountsinai.org
Alzheimer’s Markers Predict Start Of Mental Decline

By Michael C. Purdy
Washington University in St. Louis

Scientists at Washington University School of Medicine in St. Louis have helped identify many of the biomarkers for Alzheimer’s disease that could potentially predict which patients will develop the disorder later in life. Now, studying spinal fluid samples and health data from 201 research participants at the Charles F. and Joanne Knight Alzheimer’s Disease Research Center, the researchers have shown the markers are accurate predictors of Alzheimer’s years before symptoms develop.

“We wanted to see if one marker was better than the other in predicting which of our participants would get cognitive impairment and when they would get it,” said Catherine Roe, PhD, research assistant professor of neurology. “We found no differences in the accuracy of the biomarkers.”

The study, supported in part by the National Institute on Aging, appears in Neurology.

The researchers evaluated markers such as the buildup of amyloid plaques in the brain, newly visible thanks to an imaging agent developed in the last decade; levels of various proteins in the cerebrospinal fluid, such as the amyloid fragments that are the principal ingredient of brain plaques; and the ratios of one protein to another in the cerebrospinal fluid, such as different forms of the brain cell structural protein tau.

The markers were studied in volunteers whose ages ranged from 45 to 88. On average, the data available on study participants spanned four years, with the longest recorded over 7.5 years.

The researchers found that all of the markers were equally good at identifying subjects who were likely to develop cognitive problems and at predicting how soon they would become noticeably impaired.

Next, the scientists paired the biomarkers data with demographic information, testing to see if sex, age, race, education and other factors could improve their predictions.

“Sex, age and race all helped to predict who would develop cognitive impairment,” Roe said. “Older participants, men and African Americans were more likely to become cognitively impaired than those who were younger, female and Caucasian.”

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Roe described the findings as providing more evidence that scientists can detect Alzheimer’s disease years before memory loss and cognitive decline become apparent.

“We can better predict future cognitive impairment when we combine biomarkers with patient characteristics,” she said. “Knowing how accurate biomarkers are is important if we are going to some day be able to treat Alzheimer’s before symptoms and slow or prevent the disease.”

Clinical trials are already underway at Washington University and elsewhere to determine if treatments prior to symptoms can prevent or delay inherited forms of Alzheimer’s disease. Reliable biomarkers for Alzheimer’s should one day make it possible to test the most successful treatments in the much more common sporadic forms of Alzheimer’s.

Funding for this study was provided by the Longer Life Foundation; the National Institute of Neurological Disorders and Stroke (P30 NS057105); the National Institute on Aging ( P50 AG005681, P01 AG003991, and P01 AG026276); Fred Simmons and Olga Mohan, and the Charles and Joanne Knight Alzheimer’s Research Initiative of the Washington University Knight Alzheimer’s Disease Research Center.

Roe CM, Fagan AM, Grant EA, et. al. Amyloid imaging and CSF biomarkers in predicting cognitive impairment up to 7.5 years later. *Neurology*, DOI 10.1212/WNL.0b013e3182918ca6
Alzheimer’s Risk Gene Presents Potential Treatment Target

Mass. General study finds protective gene variant promotes clearance of toxic amyloid beta protein from the brain

Massachusetts General Hospital (MGH) investigators have determined that one of the recently identified genes contributing to the risk of late-onset Alzheimer's disease regulates the clearance of the toxic amyloid beta (A-beta) protein that accumulates in the brains of patients with the disease. In their report receiving advance online publication in *Neuron*, the researchers describe a protective variant of the CD33 gene that promotes clearance of A-beta from the brain. They also show that reducing expression of CD33 in immune cells called microglia enhances their ability to clear away A-beta protein, raising the possibility that blocking CD33 activity could help the brain’s immune system remove A-beta.

"Our findings show, for the first time, a "switch" that controls how fast microglial cells can clear A-beta protein from the brain as we age – CD33 is the key," says Rudolph Tanzi, PhD, director of the Genetics and Aging Research Unit in the MGH Department of Neurology and senior author of the *Neuron* paper. "If we can find a way of safely inactivating CD33 on microglia, we should be able to slow the accumulation of A-beta in aging brains and hopefully reduce risk for Alzheimer's disease."

In 2008, as part of the Alzheimer’s Genome Project, Tanzi's team identified four novel genes containing variants that increased the risk of late-onset Alzheimer's, the most common form of the devastating neurological disorder. One of these was CD33. The protein was known to play a role in regulation of the innate immune system – the body's first line of defense against infection – but how it might function in the brain and possibly contribute to Alzheimer's risk was not known.

In the current study, the researchers first found that CD33 activity was significantly higher in microglia cells in brain samples from Alzheimer's patients than in cells from non-demented controls. Moreover, they showed that the presence of a version of the gene that protected against Alzheimer's disease reduced CD33 protein levels in the brain. Importantly, the same protective version of CD33 was found to reduce levels of A-beta 42 – the primary constituent of the amyloid plaques that characterize the disease. Greater numbers of CD33-containing microglia also were associated with higher levels of A-beta 42 and more plaques overall.

In an Alzheimer's mouse model, knocking out the CD33 gene improved the ability of microglia in the brain to clear away A-beta 42 and reduced the presence of amyloid plaques. Experiments with cultured microglia showed that increasing CD33 expression on the cells' surface inhibited their ability to take up A-beta 42, while reducing CD33 activity led to greater clearance of A-beta 42.

"Collectively these experiments indicate that CD33 directly modulates the ability of microglial cells to clear A-beta 42 from the brain." says Tanzi. "Our findings raise the possibility that inhibiting CD33 activity in the brain could represent a potentially powerful new approach to treating and possibly preventing Alzheimer's disease."

Primary support for the study includes grants from the Cure Alzheimer's Fund and National Institutes of Health grants R37MH060009, P01AG15379, R01AG08487 and P50AG05134. In addition to Tanzi, the Kennedy Professor of Neurology at Harvard Medical School, co-authors of the *Neuron* paper are lead author Ana Griciuc, PhD, of the MGH Genetics and Aging Research Unit; Antonio Parrado, Andrea Lesinski, Caroline Asselin, Kristina Mullin, Basavaraj Hooli, PhD, and Se Hoon Choi, PhD, MGH Genetics and Aging Unit; and Alberto Serrano-Pozo, MD, and Bradley Hyman, MD, PhD, MGH Alzheimer's Disease Research Laboratory.

Massachusetts General Hospital Office of Public Affairs
Responding to President Barack Obama’s “grand challenge” to chart the function of the human brain in unprecedented detail, the University of California, San Diego has established the Center for Brain Activity Mapping (CBAM). The new center, under the aegis of the interdisciplinary Kavli Institute for Brain and Mind at UC San Diego, will tackle the technological and biological challenge of developing a new generation of tools to enable recording of neuronal activity throughout the brain. It will also conduct brain-mapping experiments and analyze the collected data.

From left, Nick Spitzer, Ralph Greenspan, and Terry Sejnowski. Photos by Erik Jepsen/UC San Diego Publications

Ralph Greenspan—one of the original architects of a visionary proposal that eventually led to the national BRAIN Initiative launched by President Obama in April—has been named CBAM’s founding director.

UC San Diego Chancellor Pradeep K. Khosla, who attended Obama’s unveiling of the BRAIN Initiative, said: “I am pleased to announce the launch of the Center for Brain Activity Mapping. This new center will require the type of in-depth and impactful research that we are so good at producing at UC San Diego. We have strengths here on our campus and the Torrey Pines Mesa, both in breadth of talent and in the scientific openness to collaborate across disciplines, that few others can offer the project.”

Greenspan, who also serves as associate director of the Kavli Institute for Brain and Mind at UC San Diego, said CBAM will focus on developing new technologies necessary for global brain-mapping at the resolution level of single cells and the timescale of a millisecond, participate in brain mapping experiments, and develop the necessary support mechanisms for handling and analyzing the enormous datasets that such efforts will produce.

Brain-mapping discoveries made by CBAM may shed light on such brain disorders as autism, traumatic brain injury and Alzheimer’s—and could potentially point the way to new treatments, Greenspan said. The technologies developed and advances in understanding brain networks will also likely have industrial applications outside of medicine, he said.

The new center will bring together researchers from neuroscience (including cognitive science, psychology, neurology and psychiatry), engineering, nanoscience, radiology, chemistry, physics, computer science and mathematics.

An essential component of the center will be its close relationships with other San Diego research institutions and with industrial partners in the region’s hi-tech and biotech clusters,” said Nick Spitzer, distinguished professor of neurobiology and director of the Kavli Institute for Brain and Mind at UC San Diego.

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Beyond bringing researchers together, the center will seek the resources to support specific projects. Some of these projects will likely build on existing research at UC San Diego while others will be brand new, growing out of the novel collaborations that CBAM will encourage and nurture.

The center aims to compete for national grant funds but will also seek to pursue projects with the help of philanthropists and industry partners.

Administratively, CBAM will be part of the interdisciplinary Kavli Institute for Brain and Mind. Calitz's Qualcomm Institute at UC San Diego will support CBAM with some initial space for collaborative projects.

Greenspan will soon assemble a director’s council, to help guide the center’s scientific program, and an advisory board, to assist on general strategy and fundraising.

Greenspan authored the proposal for CBAM with Spitzer and Terry Sejnowski, director of UC San Diego’s Institute for Neural Computation, who holds joint appointments with UC San Diego and The Salk Institute.

The trio identified the center’s immediate goal as preparing CBAM to compete effectively for federal BRAIN initiative funding. Activities will include, for example, topic-oriented meetings and workshops to identify potential project areas.

Medium-term goals include providing seed-grant support for specific projects, building strong ties among scientists from the different relevant disciplines, and creating an outreach program. The center will also seek dedicated space on campus.

In the long term, CBAM hopes to create an endowment for stable support of the most promising projects and to facilitate the formation of new start-up companies.

“We have the capability and the atmosphere here to make some major advances on the BRAIN Initiative,” Greenspan said. “We are among the best-positioned places anywhere to make a significant contribution to the president’s challenge.

“We invite members of the scientific and philanthropic communities – here in San Diego and further afield,” he said, “to join with us on this vital quest.”
ADNI II Study

The goal of the Alzheimer's Disease Neuroimaging Initiative Study is to learn how to stop the progression of mild cognitive impairment (MCI) and Alzheimer's disease in future generations. Information from the study might, in the future, lead to new treatments.  [http://adcs.org/Studies/ImagineADNI.aspx](http://adcs.org/Studies/ImagineADNI.aspx).

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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](http://adcs.org/Studies/ImagineADNI.aspx)).

To register for DIAN drug trials or DIAN, visit [www.DIANExpandedRegistry.org](http://www.DIANExpandedRegistry.org).

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