



# Exploring the Diabetes and Alzheimer's Link

Researchers hypothesize part of the body's natural defense against infection may underlie both diabetes and Alzheimer's

*Diabetes mellitus is estimated to affect some 23.6 million Americans today with incidence rates increasing every decade. People most at risk from type II (commonly called mature or late-onset) diabetes are in the same elderly population at risk of Alzheimer's disease.*

Cure Alzheimer's researchers Dr. Rudy Tanzi, chairman of CAF's Research Consortium and director of the Mass General Genetics and Aging Research Unit, and Dr. Robert Moir from Massachusetts General Hospital were awarded funding from the Helmsley Trust through Cure Alzheimer's Fund to explore the similarities between the protein amylin in diabetes and its analog in Alzheimer's, both hallmarks of each disease's pathology.

"We are deeply grateful for this generous gift from the Leona M. and Harry B. Helmsley Charitable Trust for a \$600,000 grant to Cure Alzheimer's Fund to be paid over two years," said Tim Armour, president of Cure Alzheimer's Fund. "This is an exceptional opportunity that is going to allow significant progress into better understanding the twin rising epidemics of diabetes and Alzheimer's".

Diabetes mellitus is estimated to affect some 23.6 million Americans today with incidence rates increasing every decade. People most at risk from type II (commonly called mature or late-onset) diabetes are in the same elderly population at risk of Alzheimer's disease.

In addition to both being amyloid diseases, diabetes and Alzheimer's long have been known to share a broad array of clinical features, and a large body of evidence suggests the pathologies of these two disorders are strongly linked. However, as yet no common molecular mechanism has been identified that can explain the long list of epidemiological commonalities between diabetes and Alzheimer's.

The research, supported by the Helmsley Trust and Cure Alzheimer's Fund, will focus on the toxic deposits called amyloid thought to mediate cellular and tissue degeneration in patients with diabetes and patients with AD and, more specifically, will investigate the activities of the proteins that form diabetic and AD amyloids (for Alzheimer's, this is the Aβeta peptide, and for diabetes, it is a peptide called amylin).

Drs. Moir and Tanzi recently discovered that the Amyloid-beta protein, a key contributor and acknowledged by most researchers as the "key bad guy" in Alzheimer's pathology, may have a different role. The prevailing theory was that Aβeta has no function other than as a waste product created by the brain. But research published in the March issue of the journal *PLoS One*, by Drs. Moir and Tanzi show the protein may be part of the body's natural defense against infection.

## BREAKING NEWS

### More on the Diabetes/ Alzheimer's link from Dr. Sam Gandy

Gandy published research in *The Journal of Neuroscience* on September 29th announcing that the gene for a protein called SorCS1, which is associated with Type 2 Diabetes, participates directly in the pathogenesis of Alzheimer's.

This work, supported by Cure Alzheimer's Fund, is critically important because it gives new targets for therapy and provides new understanding of both diseases. It is a direct result of our Alzheimer's Genome Project. Read more on our website [www.curealzfund.org](http://www.curealzfund.org)

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## Exploring the Diabetes and Alzheimer's Link

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This research suggests that Abeta has a very positive function—protecting the brain from invading microbes and defending against bacteria.

“These data change the way we look at Abeta,” says Dr. Tanzi. “For years, we thought that Abeta was just metabolic garbage produced as a byproduct of other processes within the brain, but new data suggest it is a normal component of the brain’s innate immune system.” Rob Moir adds, “Our laboratory has recently shown that Abeta is, in fact, a potent, naturally occurring antibiotic. In preliminary experiments, we have shown that amylin also appears to be a potent natural antibiotic.”

It appears both proteins may be members of an ancient family of biomolecules called antimicrobial peptides (AMPs) that are the first line of defense against invading organisms. AMPs are the foot soldiers of our innate immune system—an older defense system separate from the antibodies and cells of adaptive immunity.

Notably, while AMPs are critically important for killing invading pathogens, many also can cause collateral damage to host tissue. Aggregation is a key mechanism for the function of AMPs and at least three cause amyloid pathologies. Moir and Tanzi’s findings link, for the first time, the pathologies of diabetes and AD at the molecular level by identifying a common and totally unanticipated antimicrobial function for amylin and Abeta.

These findings suggest that the same or similar site-specific overactive innate immune response to a perceived infection (real or incorrectly identified) may underlie both diabetes and AD. In the brain, this response causes Alzheimer’s; when it occurs in the pancreas, the result is diabetes.

Confirmation of this hypothesis would prompt a major re-think of the origins of these diseases. In addition, it would identify the pathways of innate immunity as new drug targets for treating, and possibly even preventing, diabetes and AD. ■

## Scientific Advisory Board Member Given Lifetime Achievement Award

Marsel Mesulam, M.D., was recognized for his extraordinary achievements in advancing Alzheimer’s research at the Alzheimer’s Association International Conference on Alzheimer’s Disease 2010 in Honolulu.

He is the recipient of the 2010 Bengt Winblad Lifetime Achievement Award. Dr. Mesulam’s research addresses the connectivity of the monkey brain, the organization of human cholinergic pathways, the representation of cognitive functions by large-scale neurocognitive networks, and the neurobiology of dementias. Dr. Mesulam’s work on cholinergic pathways has been groundbreaking in understanding Alzheimer’s.



Dr. Marsel Mesulam

Dr. Mesulam was born in Istanbul in 1945. He received the degrees of bachelor of arts in 1968 and medical doctor in 1972, both from Harvard University. Dr. Mesulam was appointed professor of neurology at Harvard Medical School, where he founded and led the Behavioral Neurology Unit of Boston’s Beth Israel Hospital. In 1994 he was appointed the Dunbar Professor of Neurology and Psychiatry and the director of the multidisciplinary Cognitive Neurology and Alzheimer’s Disease Center at Northwestern University’s Feinberg School of Medicine in Chicago. He currently serves on the Cure Alzheimer’s Fund Scientific Advisory Board. ■

## Robert Malenka and Thomas Südhof Join Research Consortium

Cure Alzheimer’s Fund is pleased to welcome two new members of the Research Consortium, Dr. Robert C. Malenka and Dr. Thomas C. Südhof. Researchers are invited to serve on the Research Consortium to guide Cure Alzheimer’s Fund-supported work and determine the “roadmap for research” for the most effective and efficient route to slowing, stopping and/or reversing Alzheimer’s disease.

Dr. Robert C. Malenka is the Pritzker Professor of Psychiatry and Behavioral Sciences, director of the Pritzker Laboratory, and co-director of the Stanford Institute for Neuro-Innovation and Translational Neurosciences at the Stanford University School of Medicine. He is a world leader in elucidating the molecular mechanisms by which neural circuits are reorganized by experience. His many contributions over the last 25 years have laid the groundwork for a much more sophisticated understanding of the mechanisms by which neurons communicate and the adaptations in synaptic communication which underlie all forms of normal and pathological behavior. He has been at the forefront of helping to apply the knowledge gained from basic neuroscience research to the treatment and prevention of major neuropsychiatric disorders.

Dr. Südhof is the Avram Goldstein Professor in the School of Medicine at Stanford University. He is also an investigator of the Howard Hughes Medical Institute, a member of the National Academy of Sciences, the Institute of Medicine, and the American Academy of Arts and Sciences. Dr. Südhof’s research interests focus on the physiological and pathological mechanisms operating on the synapse, in particular on how synapses form, how they transmit signals, and how they become abnormal during diseases such as Alzheimer’s disease and autism. His studies have identified key molecules in synapses, such as synaptotagmins as the calcium sensors for neurotransmitter release, Munc18 as a major fusion protein at the synapse, and neuroligins and neuroligins as central trans-synaptic cell adhesion molecules. One of the major current interests in his laboratory is to elucidate the relation of synaptic activity to synapse loss and neurodegeneration in Alzheimer’s disease. ■

# *University of Pittsburgh and Massachusetts General Hospital (MGH)/Harvard Share \$400,000 Grant to Fund an Innovative Joint Research Project*

In a collaborative grant, University of Pittsburgh and MGH researchers will identify and characterize novel curcumin-like derivatives for the treatment and early prevention of Alzheimer's disease.

Several recent studies have suggested promise for the treatment of Alzheimer's with the major component of curry spice or turmeric called curcumin. However, the major drawback in this treatment is that the rapid breakdown of the curcumin by the stomach and liver leads to poor bioavailability or absorption by the brain. The purpose of the research study is to develop means of overcoming obstacles to rapid breakdown and creating methodologies for precisely delivering curcumin derivatives to appropriate locations within the brain.

Jeffrey Morby, Cure Alzheimer's Fund chairman and co-founder and a Pittsburgh resident, praised the project and its novel approach to treatment and prevention of Alzheimer's disease.

"As chairman and co-founder with my wife Jacqui of Cure Alzheimer's Fund, we have looked forward to the opportunity to help bring these two prestigious institutions together for this great cause," said Morby, who announced the grant at a University of Pittsburgh World Alzheimer's Day forum. "This pioneering collaborative research on Alzheimer's disease will help to better understand this devastating disease and could lead to better treatment, ways to reverse its effects and even find a cure." ■



Researchers from University of Pittsburgh and Mass General Hospital gather along with Cure Alzheimer's founders Jeff and Jacqui Morby and University of Pittsburgh Chancellor Mark A. Nordenberg in Pittsburgh at a World Alzheimer's Day forum.

## **Tanzi and Armour Present at White House**

The status of research in the United States to find a cure for Alzheimer's disease was the focus of discussion at a White House-sponsored event on Sept. 21, World Alzheimer's Day.

Cure Alzheimer's Fund Research Consortium Chair Dr. Rudolph Tanzi and Tim Armour, president of Cure Alzheimer's Fund, participated on a scientific panel at the White House event before a select audience of White House senior staff, policymakers, leading scientists, advocates and others including Jeff Morby, chairman and co-founder of Cure Alzheimer's Fund, and Melody Barnes, director of the White House Domestic Policy Council. The topics covered included the current status of biomarker identification for the disease, current thinking about prevention, the strength of the drug pipeline for Alzheimer's and possible policy initiatives to accelerate progress toward a cure.

Panelists agreed more funding from both the public and private sectors needs to be invested in finding a cure and better treatments; and more aggressive efforts at creating public-private partnerships to provide focus for research efforts is crucial.

All agreed the nation cannot afford to wait, and the development of effective therapies to prevent or stop Alzheimer's has to be a national priority, backed by a clear strategy and resources to implement it. ■

**Help us fund research with the highest probability of slowing, stopping or reversing Alzheimer's disease. Donations can be made through our website [www.curealzfund.org](http://www.curealzfund.org) or sent directly to our office.**

**For gifts of securities or direct wire transfers, please contact Tim Armour at [877-CURE-ALZ \(287-3259\)](tel:877-CURE-ALZ) for further information.**

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## Mission

Fund research with the highest probability of slowing, stopping or reversing Alzheimer's disease.

## Research Consortium

**Rudolph E. Tanzi**, Ph.D., Chairman, Research Consortium,  
 Harvard Medical School/ Massachusetts General Hospital

**Sam Gandy**, M.D., Ph.D., Mount Sinai School of Medicine

**Charles Glabe**, Ph.D., University of California at Irvine

**David Michael Holtzman**, M.D., Washington University, St. Louis

**M. Ilyas Kamboh**, Ph.D., University of Pittsburgh

**Virginia M.-Y. Lee**, Ph.D., MBA, University of Pennsylvania

**Robert C. Malenka**, M.D., Ph.D., Stanford University

**Roberto Malinow**, Ph.D., University of California, San Diego

**Sangram S. Sisodia**, Ph.D., University of Chicago

**Thomas C. Südhof**, M.D., Stanford University

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## CHARITY DESIGNATION

Cure Alzheimer's Fund® is a "doing business as" name for the Alzheimer's Disease Research Foundation, a 501(c)(3) public charity with federal tax ID # 52-2396428.

## Financial Update

	This Quarter	This Year	Inception to date
<b>Fundraising</b>	\$465,000	\$1,381,000	\$16,419,000
<b>Expenses paid for by the founders</b>	\$129,000	\$448,000	\$3,017,000
<b>Funded Research</b>	\$950,000	\$1,890,000	\$11,464,000

## Research Update

Research funded during the third quarter of 2010.

Project	Researcher	Distribution Amount
<p><b>Novel Soluble Gamma-Secretase Modulators</b></p> <p>Building on in vitro characterization of a novel series of soluble gamma-secretase modulators (SGSMs) funded by Cure Alzheimer's Fund, the current project is a thorough pharmacological or in vivo examination of these molecules to identify the best or "lead" drug candidate.</p>	<p>Dr. Steve Wagner,                      University of California at San Diego, and                      Dr. Rudy Tanzi,                      Massachusetts General Hospital</p>	\$250,000
<p><b>Abeta as an Anti-Microbial Agent</b></p> <p>This is a continuation of a project exploring the concept that Abeta has a positive function—protecting the brain from invading microbes and defending against bacteria.</p>	<p>Dr. Rob Moir and                      Dr. Rudy Tanzi,                      Massachusetts General Hospital</p>	\$300,000
<p><b>Curcumin Collaborative Project</b></p> <p>This collaborative project will identify and characterize novel curcumin-like derivatives for the treatment and prevention of Alzheimer's disease. The purpose of the study is to develop means of overcoming obstacles to rapid breakdown and creating methodologies for precisely delivering curcumin derivatives to appropriate locations within the brain.</p>	<p>Dr. William Klunk,                      University of Pittsburgh</p> <p>Dr. Rudy Tanzi,                      Massachusetts General Hospital</p>	<p>\$300,000</p> <p>\$100,000</p>
<b>Total Distributed to Research</b>		<b>\$950,000</b>

**Thanks!** Thank you to Will Pollock, our summer intern, for his dedicated work. Will helped us further develop our social media outreach (follow us on Twitter and Facebook!), produced content for our blog and worked on expanding our marketing reach through new opportunities and strategies. Will graduated in May from Trinity College in Hartford with a major in political science and after a summer in Boston has headed to New York City to find fame and fortune.



# Research Roundup

News you can use NOW from our researchers

## Get Your Sneakers On, Exercise is Good

There have been an abundance of preventative measures highlighted in the news about ways to ward off Alzheimer's disease, everything from curry to crosswords. And a recent piece in *The New York Times* suggested many preventative measures are not valid. However, while the media can get carried away with some that are farfetched, there is accumulating and substantial evidence that suggests physical exercise lowers risk of Alzheimer's.

Cure Alzheimer's Fund-affiliated researcher Sam Sisodia and colleagues have conducted mouse studies that support the anti-Alzheimer's benefits of exercise.

They have found:

- The positive benefits of exercise on cognition and prevention of age-associated neurodegenerative conditions, including vascular dementia and Alzheimer's disease are well established.

- Exercise largely forestalls onset of amyloid deposits in mice (amyloid deposits are the signature lesions of Alzheimer's).
- A number of genes are known to be "upregulated" (or turned on) in brains of exercised mice. This information reveals that the protein products of these genes have a positive influence on decreasing amyloid deposition.
- Exercise is known to increase the production of neural stem cells and their neuronal differentiation in the hippocampus, a region critical for memory formation.

For more in research showing that exercise has a positive benefit, please visit our website, [www.curealzfund.org](http://www.curealzfund.org). ■



*Sangram S. Sisodia, Ph.D.*  
Thomas A. Reynolds Sr. Family Professor  
of Neurosciences, University of Chicago

## New Guidelines for Diagnosing AD

The diagnostic criteria for Alzheimer's disease (AD) has not been updated in 25 years. The current criteria for the diagnosis of AD were established by a National Institute of Neurological Disorders and Stroke (NINDS)/Alzheimer's Disease and Related Disorders Association (ADRDA) workgroup in 1984. These criteria were almost universally adopted and have been useful. However, experts note, the field has evolved to a great extent since then.

New research criteria, which are still a work in progress, were announced at the International Conference on Alzheimer's Disease meeting in July and identify three "stages" of AD. The guidelines recommend combining the traditional diagnostic methods (such as observable, behavioral criteria) with the use of biomarkers. Biomarkers are accurately quantifiable measures that indicate the presence of a disease process. The biomarkers suggested for use include 1) cerebrospinal fluid measures of amyloid beta42, tau, and phospho-tau; 2) structural MRI scans; and 3) amyloid imaging.

The rationale for the added use of biomarkers is that behavioral diagnosis is not perfect and clinicians can be wrong in regard to diagnosis as often as 15 percent to 40 percent of the time depending on their expertise.

At present, there are no therapies that are known to have a significant effect on the progression of AD. Therefore, it is not yet recommended to obtain these biomarker tests for clinical use except in rare circumstances.

Alzheimer's is thought to begin years, perhaps even decades, before symptoms are noticeable. But the preclinical stage of the disease is not diagnosable without biomarkers. Thus, the new research criteria should be very useful for the purpose of clinical trials as well as in research studies. Earlier detection of people at highest risk and those who have the earliest forms of the disease will facilitate finding the right individuals to participate in risk reduction and prevention research studies.

The new criteria of AD are a work in progress and it is likely they will change as more and more data become available regarding the accuracy of biomarkers combined with clinical criteria in the diagnosis and prognosis of AD. ■

**A great step for clinical trials and research,  
but don't expect to see these tests in your  
doctor's office any time soon.**



*David Michael Holtzman, M.D.*  
The Andrew B. and Gretchen P. Jones Professor of Neurology and  
head of the Department of Neurology, Washington University, St. Louis  
Charlotte and Paul Hagemann Professor of Neurology  
and Molecular Biology and Pharmacology  
Associate Director of the Alzheimer's Disease Research Center  
Member of the Hope Center for Neurological Disorders



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# Memories are Everything: The Seven Summits

Alan Arnette is headed back to the mountains. In 2006 he completed *Memories are Everything: The Road Back to Everest* and raised funds for Alzheimer's research and awareness about the disease. *Memories are Everything: The Seven Summits* will continue this good work as he attempts to climb the highest mountain on each continent. More news on this ambitious adventure coming soon, including his kick-off climb of Mount Vinson in late November.

*Alan atop Sunlight Peak,  
his last of the Colorado 14ers.  
Alan's mother, Ida Arnette,  
passed away in August 2009  
from Alzheimer's.*

