Published Papers Document Achievements in Research

Cure Alzheimer’s Fund is proud to present a collection of 19 papers, either published or in press, that result from Cure Alzheimer’s Fund support.

Most of the papers grow out of the Alzheimer’s Genome Project (AGP)™, which is only right as that is where most of our investment has gone. And it has paid off handsomely!

The AGP has met its first major milestone in identifying most of the remaining genes that affect risk or provide protection from Alzheimer’s disease in three years for about $3 million. Some 70 genes have been identified and now are available for follow-up by Cure Alzheimer’s Fund-supported researchers and others. The papers stemming from AGP come from Dr. Rudy Tanzi’s lab at Massachusetts General Hospital/Harvard Medical School, either alone or in collaboration with others. They represent a significant output of information about this breakthrough basic “foundational” research, all funded by Cure Alzheimer’s Fund.

The other papers represent innovative and in most cases collaborative investigations of more “translational” research—research enabled by the identification of the first four Alzheimer’s genes, of which, three were co-discovered by Dr. Tanzi. These papers point to ways for potentially faster development of therapies that affect the disease mechanism, not just the symptoms.

Pages 2 through 4 of this Quarterly Report contain a listing of “layperson” descriptions of each paper. We are grateful to the researchers for translating the work of their papers into language more accessible to most of us than the more precise technical language useful to them and their peers.

We thank all the researchers and lab personnel for their dedication and commitment to the common mission of ending this disease, and we congratulate all of them for the important work reflected in these papers.

We also are grateful to all of those who literally made this work possible. Without those of you who have supported Cure Alzheimer’s Fund projects through your generosity, these papers and the forward momentum they represent would not exist.

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**Alzheimer’s Genome Project**


This paper represents a functional follow-up of earlier genetic findings obtained by Drs. Bertram and Tanzi that suggest a modest but significant increase in AD risk conferred by genetic variants in the insulin degrading enzyme (IDE) in certain familial AD cases. The paper revealed that the potential biochemical mechanism underlying the genetic association may be a reduced activity of IDE in these families. Since IDE is one of the major A-beta degrading enzymes, this finding could be of immediate relevance as less A-beta degradation could lead to a buildup of beta-amyloid plaques, one of the hallmark lesions in the brains of AD patients.

Kavvoura FK, McQueen MP, Khoury MJ, Tanzi RE, Bertram L, Ioannidis JPA. *Evaluation of the potential excess of statistically significant findings reported genetic association studies: application to Alzheimer’s disease*. Am. J. Epidemiol. 2008; Published Ahead of Print.

This study addressed how best to assess composite statistical data in determining bonafide AD candidate genes using a novel state-of-the-art analysis.


This is a review article highlighting the potential functional implications underlying the most consistent genetic associations observed via systematic meta-analyses performed as part of AlzGene. The paper also provides a background on the statistical approach of AlzGene and other novel methodologies in complex disease genetics.


This review proposes a new approach in detecting errors in genome-wide association (GWA) studies using transmission rates in family-based data. The approach highlights certain technological weaknesses inherent in the GWA approach that cannot be detected in a simple case-control setting, which is the predominant design in the vast majority of current genome-wide studies.


This study confirms the gene known as GAB2 plays a role in genetic susceptibility to AD in analyses of more than 1,300 families with AD.


This study describes a genetic association between risk for Alzheimer’s disease and the gene known as GSK3B. We found this gene to be associated with risk for frontotemporal dementia, which involves tangle-type pathology, but not beta-amyloid. The GSK3B gene produces a protein that is known to regulate both beta-amyloid production and tangle formation.


This study addresses which AD candidate genes identified through case-control studies and analyzed on the Alzgene.org website play a role in genetic susceptibility to AD in family-based studies of more than 1,300 families with AD. Three novel AD genes were confirmed in these analyses.
This paper describes the results of the first family-based genome-wide association study in Alzheimer’s disease. The primary screen was performed using the Affymetrix 500K SNP chip array in ~1,400 hundred individuals from more than 400 multiplex AD families. Overall, four novel putative AD genes were identified in addition to the well-established APOE association. Two of these novel associations were replicated in nearly 3,000 additional and independent family-based samples. The results strongly imply the existence of at least two novel AD risk genes that are independent of APOE.

This paper represents a functional follow-up of earlier genetic findings obtained by Drs. Bertram and Tanzi that suggest a modest but significant increase in AD risk conferred by genetic variants in the ubiquilin-1 (UBQLN1) gene in certain familial AD cases. This paper shows that changes in the expression of UBQLN1 can have substantial effects on the unfolded protein response (UPR), a general cellular defense mechanism against the accumulation of unfolded or misfolded proteins, including accumulated Abeta.

This paper backs up previous work that shows that nerve cell communication is directly linked with levels of the amyloid-beta peptide. In this work, we show in the human brain in critically ill patients with head injury and certain types of stroke that the amyloid-beta peptide levels are dynamically very closely linked with the clinical state of the patient. If the patient is doing better, it increases; if they are going to do worse, it decreases. This may turn out to be a useful method to help physicians decide how to treat critically ill patients with brain damage.

This study shows that stroke, and perhaps head trauma, can trigger a series of biochemical events that increase amyloid-beta production in the brain, and subsequent development of Alzheimer’s disease. Novel therapies could interfere with this process and reduce the risk of Alzheimer’s disease in stroke or head trauma patients.

This study showed that the detrimental effects of the general anesthetic isoflurane on nerve cells could be ameliorated by treatment with the Alzheimer’s drug memantine (Namenda) in mice.
This study shows that the commonly used anesthetic isoflurane, when administered to mice, increases Abeta protein levels and causes nerve cell death.


This study shows that the commonly used anesthetic sevoflurane, when administered to nerve cells in petri dishes, increases levels of Abeta protein and causes cell death.

ACAT Investigations


This study suggests potential therapeutic applications of BACE1 inhibitors in treating sodium channel dysfunction in AD patients. BACE1 is one of the two enzymes responsible for generation of the amyloid beta peptide (Abeta), a pathogenic molecule that accumulates in the brains of patients affected by Alzheimer’s disease (AD). We now know that BACE1 is not only important for generation of Abeta but also for regulating neuronal sodium channel (Na(v)1) activity. Previous work suggests that elevated BACE1 activity in AD patients would not only increase Abeta levels in the brains of patients, but also contribute to psychiatric symptoms and epileptic seizures by modifying sodium channel activity.

Oligomer Investigations


In the brains of Alzheimer’s disease patients, the levels of a small protein piece, called amyloid β-peptide (Aβ), are highly elevated. Researchers have found that Aβ directly attacks and interferes with the normal function of brain nerve cells, resulting in the impairment of memory, which is a common feature of Alzheimer’s disease. This study reveals that increasing the level of a specific membrane lipid, called PIP2, protects the nerve cells against the harmful Aβ effects. Accordingly, this study helps to devise a novel route of discovery for effective Alzheimer’s disease drugs, which protect neurons by modulating the PIP2 membrane lipid.


Genetic, early-onset familial forms of AD (termed FAD) are caused by inheritance of mutant genes that code for presenilin 1 (PS1). We discovered that these mutant genes impair the self-renewal and neuronal differentiation of stem cells (termed NPCs) in the adult hippocampus, a region of the brain that is critical for making and consolidating memory. In patients with AD, the hippocampus is the region most profoundly affected by the presence of pathological lesions and neuronal cell loss, leading to memory impairments. Thus, perturbations in those processes that are critical for the generation and survival of stem cells that differentiate into neurons in the hippocampus will ultimately compromise memory function. More importantly, we have shown that these impairments in NPC proliferation and neuronal differentiation are modulated by other cells, including microglia, that are resident in the hippocampus. We have identified a number of proteins that are secreted by microglia that are essential for these processes. This may be of therapeutic value in attenuating neuronal deficits and associated dysfunction leading to memory and cognitive impairments in patients with AD.

Microdialysis Drug Discovery Platform


The level of the amyloid-beta peptide in the brain throughout life is important in determining whether the beginnings of Alzheimer’s disease, the buildup in the brain of the amyloid-beta protein, actually start to occur. In this work, we found that nerve cell communication is directly linked to the formation of the amyloid-beta peptide and the details of how this happened. In the future, this work suggests new methods and treatments to develop that might be used to decrease the buildup of amyloid in the brain.
Presentation at the Brae Burn Country Club

Dr. Rudy Tanzi presented his research progress at the Brae Burn Country Club in Newton, MA, with a presentation titled: The Alzheimer’s Genome Project™: A Major Milestone Achieved in the Search for an Alzheimer’s Cure. A special thank you to our hosts Carl Novotny and Rev. Judith Swahnberg.

If you’d like to see or discuss the slides from the event, please contact:

**Tim Armour,**
tarmour@curealzfund.org, or 781-237-3800.

The Longwood Symphony Orchestra Plays for ARTZ

While Cure Alzheimer’s Fund is working to find a cure for Alzheimer’s, we also support other organizations that are doing important work to give people living with Alzheimer’s a life worth living. The ARTZ: Artists for Alzheimer’s™ program is developing community programs for the 5 million Americans and the 50 million people world-wide living with Alzheimer’s. The Longwood Symphony Orchestra, an orchestra made up of medical professionals, has selected ARTZ as its main fundraising beneficiary for its Dec. 6, 2008, concert. For tickets for the performance of Edward Elgar’s Pomp and Circumstance No. 1 and Ralph Vaughan Williams’ A Sea Symphony on Dec. 6, call Sean Caulfield at 781-844-4671.
The Board of Directors of Cure Alzheimer’s Fund is pleased to announce a new member of the Scientific Advisory Board, Prof. John Mazziotta of UCLA. John’s titles are:

- Chair, Department of Neurology
- Frances Stark Chair of Neurology
- Pio Person-Lovelace Investigator
- Director, UCLA Brain Mapping Center
- Associate Director, Neuropsychiatric Institute
- Professor of Neurology, Radiological Sciences and Pharmacology
- Ahmanson-Lovelace Brain Mapping Center
- UCLA School of Medicine

John has previously served on Cure Alzheimer’s Fund’s Research Consortium and has graciously agreed to bring his in-depth knowledge of the Alzheimer’s disease research field to the SAB. Members of the Scientific Advisory Board are invited independently of the Research Consortium to provide advice and counsel to Cure Alzheimer’s Fund regarding the overall scientific soundness of the roadmap and to review grant proposals for consistency with the roadmap, the objectives of Cure Alzheimer’s Fund and with the highest standards of scientific inquiry.

John Mazziotta has had a distinguished career of leadership, scientific achievement and service to the neuroscientific community. Scientifically, he has helped transform our understanding of diseases of the nervous system through the use of neuroimaging. These strategies and insights have greatly advanced our basic understanding of disease mechanisms, diagnostic criteria and the manner by which one can track conventional and experimental therapies.

Of note is the fact that Dr. Mazziotta was the first to develop strategies for using both genetic risk profiles (Huntington’s disease) and later specific genotypes to demonstrate the pattern of abnormal brain function that preceded clinical disease onset. This has now set the stage and provided the means by which to track and monitor presymptomatic individuals with disorders such as Huntington’s and Alzheimer’s disease, both to describe the natural history of the disorders as well as to provide objective, noninvasive and quantifiable estimates of the efficacy of experimental therapies.

Prof. Mazziotta joins a distinguished panel of senior scientists which Cure Alzheimer’s Fund is honored to have as its Scientific Advisory Board. Other members include:

- Caleb Finch, Ph.D.
  Professor of Gerontology and Biological Sciences, University of Southern California

- Paul Greengard, Ph.D.
  Nobel Prize in Physiology and Medicine, 2000; Head of the Laboratory of Molecular and Cellular Neuroscience; Vincent Astor Professor, The Rockefeller University

- John Lazo, Ph.D.
  (Chairman of Cure Alzheimer’s Fund Scientific Advisory Board and member of the Board of Directors) Allegheny Foundation Professor and Director of the Fiske Drug Discovery Laboratory; Department of Pharmacology, University of Pittsburgh School of Medicine and the Co-Director of Molecular Therapeutics/Drug Discovery Program, Pittsburgh Cancer Institute

- Marsel Mesulam, M.D.
  Director of the Cognitive Neurology and Alzheimer’s Disease Center, the Ruth and Evelyn Dunbar Distinguished Professor, Northwestern University

**Thanks!** Cure Alzheimer’s Fund thanks our summer intern, Laura Simon, for her dedicated work. Laura helped us with our online presence (check out our Wikipedia page) and helped expand our marketing reach. Laura has returned to her junior year at the University of Southern California in Los Angeles. We wish her the best of luck as she heads toward her Bachelor of Arts in Anthropology degree.
**Financial Report**

**How much money have we raised this year?**
*Current Year, January 1, 2008, to September 30, 2008 (to nearest $1,000)*

Funds raised from donors and founders:  $1,325,000
- No funds from Cure Alzheimer’s Fund may be used for overhead or indirect costs by receiving researchers or institutions.

Funds contributed by founders for operations:  $416,000
- Founders contribute funds for all expenses of Cure Alzheimer’s Fund; all non-founder contributions go directly to research.

**Research Update**

Funds distributed to research for 2008:  $1,436,000
See www.curealzfund.org/research for research detail.

Total research funded since inception—$6,234,000 funding 21 projects at nine major research labs.

$2,451,000 in reserve for follow-up projects based on results of the Alzheimer’s Genome Project™ and some reserve for plausible “wild-card” paradigm-changing discovery emerging from recent findings.

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

**Scientific Advisory Board**
- Caleb Finch, Ph.D., University of Southern California
- Paul Greengard, Ph.D., The Rockefeller University
- John S. Lazo, Ph.D., University of Pittsburgh
- John C. Mazziotta, M.D., Ph.D., UCLA
- Marsel Mesulam, M.D., Northwestern University

**Board of Directors**
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- William E. Trueheart, Es.D., Pittsburgh, PA
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*Founder

**Administration**
- Tim Armour, President
- Katie Cutler, Director of Development
- John Epeneter, Controller
- Laurel Lyle, Manager, Fundraising Programs
- Karen Robertson, Accountant

**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.

**How much money have we raised and distributed since our inception?**

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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 or sent directly to our office.

For gifts of securities or direct wire transfers, please contact Tim Armour at 877-CURE-ALZ (287-3259) for further information.
Hay Harbor hosts Ladies Tennis Tournament to Benefit Cure Alzheimer’s Fund

The Hay Harbor Tennis Tournament raised more than $6,000 this July. Many thanks to all who competed in and donated to the tournament this year. The event raised almost three times more than last year! Special thanks to Diana Fiske for her organizational work and to the Hay Harbor Tennis Club.