Focus = Results

CELEBRATING FIVE YEARS OF RESEARCH PROGRESS

Cure Alzheimer's FUND

ANNUAL REPORT 2009

Celebrating Five Years of Focused Research with Major Milestones Achieved

- Identified more than 100 genes that affect risk for or prevention of the disease through the Alzheimer's Genome Project™.
- Named a Major Medical Breakthrough of 2008 by *TIME* magazine and CNN.
- Created breakthroughs in understanding the underlying mechanisms of Alzheimer's disease.
- Sustained the No. 1 online scientific knowledge database for Alzheimer's researchers, Alzgene.org.
- Pushed ahead the understanding of the mechanism behind the disease in major ways through better understanding of the functionality of high-priority Alzheimer's genes, oligomers, synaptic function, gamma secretase modulators and a paradigm-changing perspective on Abeta as an anti-microbial agent.
- Supported more than 30 high-quality papers published in major, peer-reviewed journals.

To end Alzheimer's, we believe it is imperative to focus on and fund research that is innovative, speed-driven and results-oriented. Our funded work, upholding these values, has drastically changed the research landscape of Alzheimer's and is making great progress toward therapeutic intervention and an end to the disease.

"Over the five years of its existence, Cure Alzheimer's Fund and the Alzheimer's Genome Project have done more to advance our knowledge of the complex genetics of Alzheimer's disease than prior studies using less-sophisticated techniques. These studies have identified new targets for pharmacological or genetic therapies."

—Anne B. Young, MD, Ph.D.

Chief of the Neurology Service at Massachusetts General Hospital

Julieanne Dorn Professor of Neurology at Harvard Medical School

Founder and Scientific Director of MIND, the MassGeneral Institute for Neurodegenerative Disease

LETTER FROM THE CHAIRMAN

Jeff Morby

Dear Friends,

Now that Cure Alzheimer's Fund has completed its first five years of existence, it is appropriate to review our progress and the assumptions underlying the activities of the foundation during its initial history.

Alzheimer's—A Pandemic That Could Bankrupt Our Health Care System by 2015.

When we first established the foundation, we projected that the annual cost of Alzheimer's care to the U.S. Medicare and Medicaid budget would climb from $120 billion in 2005 to $188 billion by 2015, causing a major financial crisis in our country. We were far too optimistic—Alzheimer's care in 2010 already is at least $172 billion, representing a compound growth rate of about 11 percent (and equal to approximately 20 percent of combined Medicare/Medicaid costs).

Consequently, the cost of Alzheimer's care within the national health care budget has far exceeded our projections. Even assuming more modest growth of 8 percent per year, the cost of Alzheimer's will be more than $290 billion by 2015. In other words, the crisis may occur sooner than we had anticipated. And, of course, the figures do not include any of the costs of Alzheimer's care to members of individual families who are taking care of their loved ones. The bottom line: We must do something about Alzheimer's as soon as possible—which is why we are working so hard to find preventatives and cures.

There is Far Too Little Government Funding Of Alzheimer's Research.

At the time of our projections, the budget of the National Institutes of Health (NIH) for Alzheimer's research was approximately $650 million a year and dropping. The budget has continued to drop, and more recently NIH officials have discovered they were miscalculating the amount of Alzheimer's funding. They have revised their estimates down to approximately $400 million as of last year. This $400 million is a paltry sum, less than 1 percent of the annual cost of Alzheimer's to the country. Clearly, an inadequate amount.

A Small Foundation with a Focused Strategy Can Make a Significant Difference.

Cure Alzheimer's Fund is that small foundation, and as you will read in the pages that follow, within a five-year period, we have made a significant difference in science's understanding of the causes and potential cures for Alzheimer's. Rudy Tanzi, the chairman of our Research Consortium, will lead you through some of the tremendous insights and breakthroughs resulting from our funding activities.

The Key to Success—The Best Scientists In the World.

With the help of Dr. Tanzi, Cure Alzheimer's Fund, over a five-year period, has assembled a group of the top Alzheimer's scientists in the world (the "Research Consortium") to work cooperatively and collectively on the task of finding a cure for the disease. They are doing so in the context of a focused strategic document—the "Roadmap." The Roadmap is the fundamental guide we use to make

decisions concerning which research projects we will fund. Research projects are brought to us by the Research Consortium and must be approved by the Scientific Advisory Board for quality and consistence with the Roadmap before the Executive Committee and Board of Directors will approve any given project.

Finding All the Alzheimer's Genes Is Essential to the Discovery of Cures.

One initial and continuing focus has been to analyze, and engage in, "translational analysis" and drug development for known Alzheimer's genes, and we have made considerable progress in this regard. However, when we began our research, only four genes had been unequivocally identified as being Alzheimer's genes, and those genes represented only about 30 percent of the entire genetics of Alzheimer's. Virtually all scientists and pharmaceutical researchers at the time were attempting to understand those four genes; whereas, the bulk of genetic information pertaining to Alzheimer's (the 70 percent) was not available to them because no other genes had been discovered.

To remedy that problem, we undertook the Alzheimer's Genome Project™. This is the first genomic screen of Alzheimer's disease and the largest single disease-related genomic project ever undertaken. As a result of the project, we have identified approximately 100 genes that are highly correlated with the incidence of, and protections from, Alzheimer's disease. The important point to understand is that Alzheimer's is a disease of multiple genes—that is, the genes (some deleterious, some protective) interact to create a net impact from the disease. Therefore, every person will have a different mix of Alzheimer's genes, positive or negative, and to truly protect a given individual, one needs to understand the makeup of his Alzheimer's genes. This can be done only when science has a complete understanding of all the Alzheimer's genes and their causes and impacts.

Dr. Tanzi will describe to you in more detail the implications of the Alzheimer's Genome Project, but I want to point out that at the current stage of our history, we believe we have more genetic information on Alzheimer's than any other single organization in the world.

On to Further Translation Analyses and Drug Discovery.

The task ahead is to enlarge the scope of our efforts from the four previously known genes to the most important of the newly found genes in order to understand what the genes do, what they do wrong in Alzheimer's disease and how they interact together, with the objective of developing medicines to prevent and reverse the disease as soon as possible. We already are well into those tasks, but given the number of genes and their interrelationships, significant funding will be required for this final and important phase.

As you know, the founding families of Cure Alzheimer's Fund have made substantial financial commitments to this project, and we will continue to do so for the benefit of all. We are now at a critical stage in the evolution of our research, at a key inflection point. Now that we have the required genetic material, we need to push ahead rapidly to develop appropriate cures. We very much hope you will continue to support us in our efforts.

Thank you very much for your support and interest.

Sincerely yours,
Jeff Morby

Major Milestones Achieved!

Now the Hard Work Begins

Rudolph E. Tanzi, Ph.D.

CAF Research Consortium Chair

Joseph P. and Rose F. Kennedy Professor of Neurology, Harvard Medical School

Director, Genetics and Aging Research Unit, MassGeneral Institute for Neurodegenerative Disease, Massachusetts General Hospital

It has been five years since the inception of Cure Alzheimer's Fund and its flagship research project, the "Alzheimer's Genome Project™." This bold and unprecedented scientific endeavor sought to identify the entire complement of human genes that influence one's lifetime risk for Alzheimer's disease. We are proud to announce that we have achieved the first major milestone in this project by identifying the vast majority of novel Alzheimer's gene candidates in the human genome. In other groundbreaking studies sponsored by Cure Alzheimer's Fund, we also reached a major milestone regarding how neural network impairment in the brain leads to nerve cell degeneration, cognitive deficits and ultimately dementia. These monumental accomplishments allow us to forge ahead toward the arguably more daunting and laborious task of translating these discoveries into effective new therapies for treating and preventing Alzheimer's disease. We are ready for this challenge.

Our First Five Years—Monumental Progress

Over the past five years, the Cure Alzheimer's Fund Research Consortium emphasized the use of genetic studies to lay the foundation for ultimately curing Alzheimer's disease.

Between 1987 and 1995, my laboratory co-discovered three of the four genes known to carry defects that cause Alzheimer's disease. Virtually every Alzheimer's research project in academic and industrial sectors over the past two decades have in some manner used the four known Alzheimer's genes to gain crucial insights into the biological underpinnings of Alzheimer's disease and to devise strategies aimed at hindering or even reversing this dreaded neurological disease. Thus, we selected two major priorities in our genetic studies of AD. Firstly, we continued investigating the four original Alzheimer's disease genes to better understand the process of neurodegeneration in Alzheimer's disease. This knowledge then is translated into the search for novel therapeutics. Secondly, we were mindful of the fact that while the four original Alzheimer's genes have taught us the vast majority of what we know *so far* about the causes of Alzheimer's disease, these four genes account for only 30 percent of the genetics of the disease. Therefore, we placed a very high priority on identifying the remaining 70 percent of the genes influencing one's susceptibility for Alzheimer's disease. This entailed combing through the entire human genome, and all ~30,000 human genes it encompasses, to find that small subset of genes that contain DNA mutations and variations that can confer either increased risk for or protection from Alzheimer's disease. During a period in which federal research funding for Alzheimer's disease research has decreased with each new year for the past several years, Cure Alzheimer's Fund courageously stepped up to fund this critically important research, identifying all human genes influencing one's risk for Alzheimer's, while concurrently funding studies of the

four original Alzheimer's disease genes to extract data necessary to devise novel, more effective therapies.

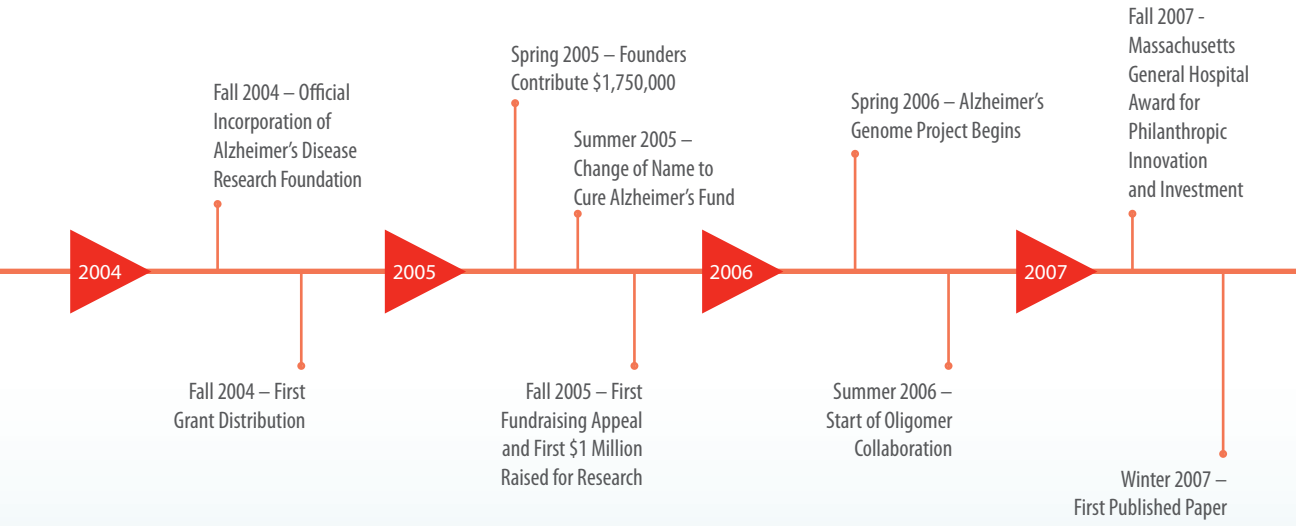
Cure Alzheimer's Fund-sponsored studies of the four known Alzheimer's disease genes have led to dramatic new insights into how stroke, traumatic brain injury and certain inhalant anesthetics increase risk for Alzheimer's disease. In other studies, the role of these genes in the synaptic dysfunction observed in the AD brain has been elucidated. Specifically, a consortium of Cure Alzheimer's Fund investigators carried out groundbreaking experiments in which they showed that the major component of senile plaques, beta-amyloid, is most dangerous in the brain when it is *not* sequestered in the plaque but floating around freely in the brain as small aggregates called "oligomers." In excess, these beta-amyloid oligomers can "short-circuit" communication between nerve cells in the synapses where neural signals are conveyed. Cure Alzheimer's Fund investigators around the country are attempting to determine exactly how oligomers disrupt synapses and neural transmission, which leads to cognitive deficits and ultimately, dementia. These studies also included pre-clinical development of several novel drug classes that now are being tested in Alzheimer's animal models for the safe ability to rescue synapses and preserve cognition in Alzheimer's disease patients.

In our first major victory for the Cure Alzheimer's Fund Alzheimer's Genome Project,™ we reported four new Alzheimer's gene candidates in a study that was named by *TIME* Magazine a "Top Ten Medical Breakthroughof 2008." We now proudly announce that in the first five years of Cure Alzheimer's Fund research, we have uncovered more than 100 genes that, when inherited in certain forms, play significant roles in determining one's susceptibility for Alzheimer's disease. We think these genes represent the vast majority of genetic risk factors for Alzheimer's disease in the human genome. With these genes in hand, we now shift our focus to the even more challenging task of determining the exact defects in the DNA of these genes that lead to Alzheimer's disease. Elucidation of these genetic aberrations will allow us to tease out precisely how they perturb the normal functioning of the brain. This level of understanding will, in turn, enable us to devise smart therapies for Alzheimer's disease based on precisely what is going wrong at the very roots of the disease process.

Next Steps—Now the Hard Work Begins

In accord with the Cure Alzheimer's Fund Roadmap, the next phase of the Alzheimer's Genome Project involves prioritizing more than 100 novel Alzheimer's disease candidate genes for intensive efforts aimed at discovering the exact gene mutations and DNA variants that are at fault in genomes of Alzheimer's patients. Molecular and biochemical studies of these gene defects then will be used to drive novel drug discovery. Moreover, these genes, together with

Cure Alzheimer's FUND Milestones



previously known Alzheimer's genes, are being used to create new animal models of the disease. These animal models will be used to better understand causes of Alzheimer's disease, test novel drugs for potential for treatment and prevention, and better understand biological activities of Alzheimer's drugs currently in clinical trials. We already made considerable progress in this process. For example, we discovered two mutations in a novel Alzheimer's gene called ADAM10 and have used them successfully to create transgenic mice that serve as animal models for novel drug discovery and for experiments aimed at better understanding the pathological process in Alzheimer's disease.

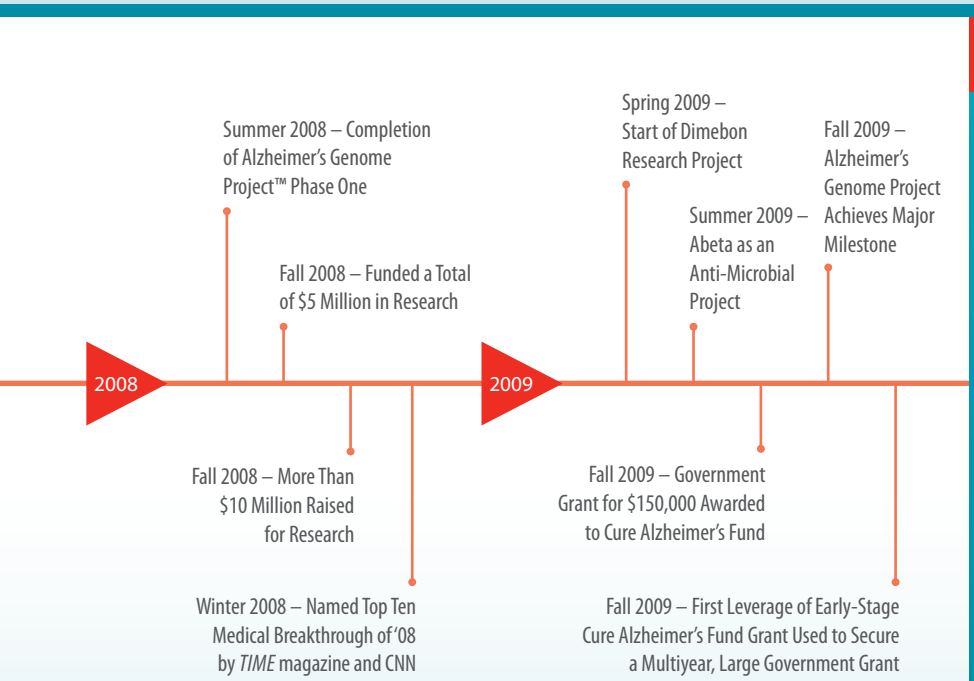
Since the majority of novel drugs in discovery seek to reduce levels of beta-amyloid in the brain, Cure Alzheimer's Fund also is researching what normal roles beta-amyloid may play in the brain. The major component of beta-amyloid is a small protein called "amyloid beta protein." We know that the amyloid beta protein is neurotoxic when present in excessive amounts in the brains of Alzheimer's patients. However, we recently found that when present at normal levels, amyloid beta protein can help the brain fight microbial pathogens, thereby preventing potentially serious bacterial and fungal infections. Our discovery was covered in depth by *The New York Times* shortly after we published our results in March 2010.

We now proudly announce that in the first five years of Cure Alzheimer's Fund research, we have uncovered more than 100 genes that, when inherited in certain forms, play significant roles in determining one's susceptibility for Alzheimer's disease.

We think that only by fully understanding the normal role of the amyloid beta protein in the brain can anti-beta amyloid therapeutics developed by us and other researchers someday be employed in the safest manner possible for treatment and prevention of Alzheimer's disease. In addition, we will be actively searching for microbial pathogens (bacterial, viral or fungal) that may trigger excessive amyloid deposition in the brain, increasing risk for AD. If we can identify such a trigger, remedial steps then could be taken to prevent the infection as means for mitigating AD risk. We already have made considerable progress in this exciting new research endeavor, thanks to support from Cure Alzheimer's Fund.

Thank You and Reach for a Cure with Us

In closing, the first five years of Cure Alzheimer's Fund have led to scientific victories and seminal discoveries that far exceeded our high expectations



5 Years!

Fundraising Total
$15,067,000

Total Number of Donors
4,311

Total Distribution for Research
$9,575,000

Total Number of Research Projects
35

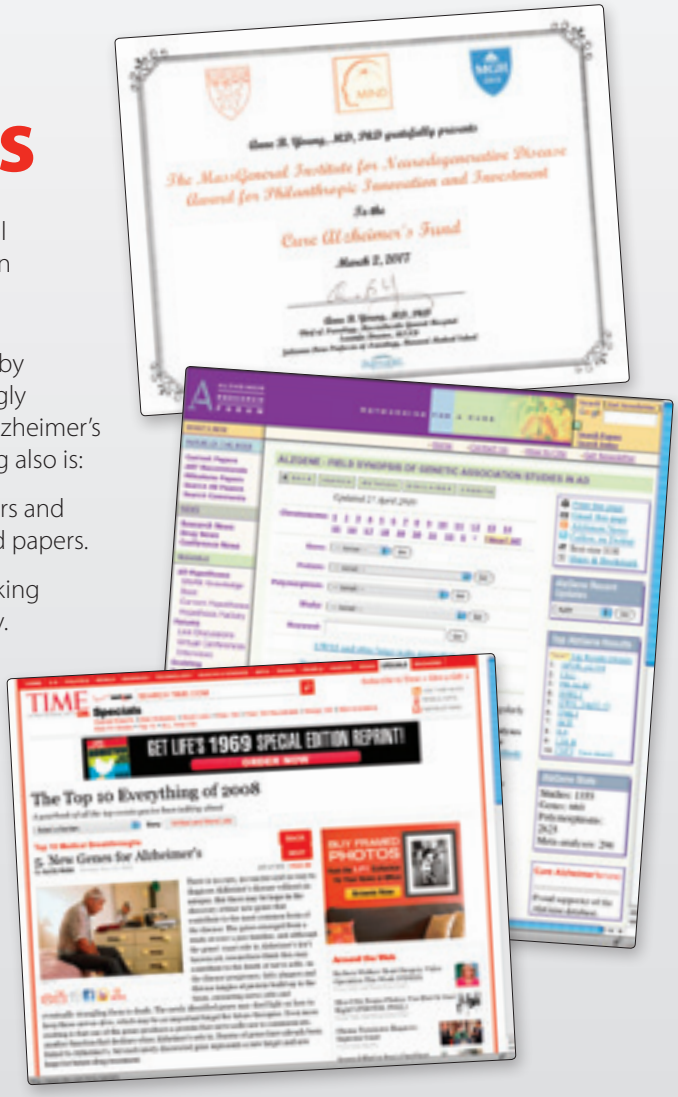
Total Number of Published Papers
32

when first starting the foundation. For example, we reached a monumental milestone by completing the first phase of the Alzheimer's Genome Project™. As a result, we now know of 100 different genes that significantly influence susceptibility for Alzheimer's disease at the levels of both risk and protection. The difficult task of determining exactly what goes wrong with these genes and how that information can be exploited to drive novel drug discovery lies directly ahead. Cure Alzheimer's Fund and its Research Consortium embrace this task with equal parts excitement and trepidation, similar to how we initially approached the Alzheimer's Genome Project at its inception five years ago. However, we are fully confident that just as we met our first major milestone within budget and ahead of schedule, we will do the same as we enter this next major segment of our Roadmap in the race toward a cure.

On behalf of the entire Cure Alzheimer's Fund Research Consortium, thank you for your kind and generous support over the past five years. We could not possibly have reached our first major milestone in the Alzheimer's Genome Project and gotten such a tremendous head start on the next steps of the Roadmap without your support. We sincerely hope you will join us as we forge ahead in pursuing the next steps to cure this devastating and unforgiving disease. ■

Special Recognitions

- First recipient of the Massachusetts General Hospital Award for Philanthropic Innovation and Investment, 2007.
- Alzgene.org, which is sustained exclusively by Cure Alzheimer's Fund support, is increasingly recognized as the authoritative source of Alzheimer's genetic information worldwide. Alzgene.org also is:
  - Increasingly cited in peer-reviewed papers and lists all genes published in peer-reviewed papers.
  - Features meta-analysis to determine ranking of genes' affect on Alzheimer's pathology.
  - A template for tracking genes of other diseases, including schizophrenia, Parkinson's and others.
- Named one of the Top Ten Medical Breakthroughs of 2008 by *TIME* magazine and CNN.
  - Awarded for work done in the Alzheimer's Genome Project to identify genes not previously associated with Alzheimer's disease.



Foundations for Success

How is Cure Alzheimer's Fund making a difference?

We take a bold approach.

Dare to be great—not incremental; go for transformational change!

Find the leaders in the field, the best people in the world and support their success.

Use the venture and entrepreneurial experience of founders and key supporters for a fresh approach to funding research.

—***Henry McCance***, *co-founder, Cure Alzheimer's Fund, and chairman emeritus, Greylock Partners*

We move research forward faster.

Cure Alzheimer's Fund focuses on results, not process.

Cure Alzheimer's Fund's grants leverage leading-edge ideas into much bigger grants from government and major foundations.

As in venture capital funding, focus is a key to success. For Cure Alzheimer's Fund, this is the Research Roadmap.

—***Jacqui Morby,*** *co-founder, Cure Alzheimer's Fund, and senior advisor, TA Associates*

We are cutting-edge science and world-class talent.

Science conducted and reviewed by leading researchers, including a Noble laureate.

Focus on facilitating the best proposals for moving knowledge ahead and understanding the cause of the disease.

Minimal process plus high integrity and due diligence lead to maximum results.

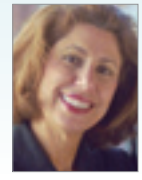
—***John Lazo, Ph.D.***, *University of Pittsburgh, chair, Cure Alzheimer's Fund Scientific Advisory Board*

We are changing the course of history.

Like the generation before us ended the threat of polio, we want to end Alzheimer's for future generations.

We are rising to a challenge that has existed for 100 years and are making progress to end the disease.

We think finding the cause will lead to the cure.



—***Phyllis Rappaport***, *Cure Alzheimer's Fund co-founder, chair of the Jerome Lyle Rappaport Charitable Foundation, director of New Boston Fund, Inc.*

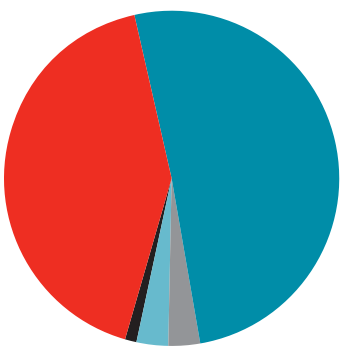
Fundraising

In 2009, Cure Alzheimer's Fund (CAF) received financial support from individuals, corporations and foundations in the amount of $3,372,398 from 1,006 donors in cash and in-kind revenues.

Source of Funds

	2009	% of 2009 Funds Raised	2005–2009	% of 2005–2009 Funds Raised
Non-Founder Individuals	$1,262,000	37%	$6,370,000	42%
Founders	1,555,000	46%	7,757,000	51%
Foundations	350,000	10%	378,000	3%
Bequests	157,000	5%	395,000	3%
In-Kind Donations	32,000	1%	127,000	1%
Corporations	16,000	~1%	40,000	0%
Government	—	—	—	0%
Total	**$3,372,000**		**$15,067,000**	

Note: Funds do not include investment income or unrealized gain (loss) or donor-advised funds.



Source of Funds, 2005–2009

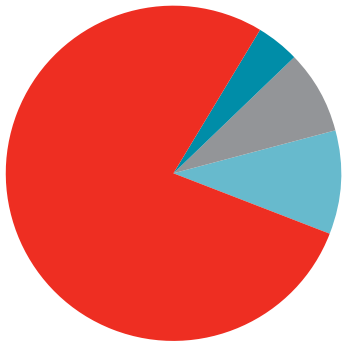
Funding Our Vital Research

- Founders pay for all Cure Alzheimer's Fund (CAF) expenses as well as contribute to research.
- 100 percent of non-founder contributions go to research.
- CAF does not support overhead or indirect costs at recipient institutions.

Use of Funds 2009

	$	%
Distribution to Research (grants)	2,388,000	78
Grant Support/Programs	135,000	4
Management and General	239,000	8
Fundraising	298,000	10
Total Expenses	**3,060,000**	**100**

Source: IRS Form 2009 990, now posted on CAF website.



Use of Funds, 2009

"While Cure Alzheimer's Fund is driven to fund research leading to a cure and *not* by traditional philanthropic ratios of efficiency—particularly because our founders pay all the expenses—our ratios are excellent. For 2009, 'program expenses,' including funds distributed to research, were 82 percent of total expenses; 'management and general' was 8 percent; and fundraising another 10 percent of expenses."

—Timothy W. Armour, president and CEO, Cure Alzheimer's Fund

- CAF has no endowment and passes all funds raised directly to researchers.
- CAF keeps all funds in cash equivalents; there is no endowment or investment fund as the objective is to move money from donors to research as quickly as possible.
- A corollary of the "no endowment" policy is that CAF suffered virtually no loss of assets during the recent financial crisis. Donor money was safe and deployed to research as planned.
- CAF funds only projects approved by its Scientific Advisory Board. While proposal approval is as streamlined as possible to facilitate a focus on results rather than process, there is a high premium on the integrity of the science.
- CAF has its IRS Form 990 online at its website, www.curealzfund.org; audited financial statements are available upon request. CAF has a history of "clean" audits.

Financials (Year Ended Dec. 31, 2009, Rounded to the Nearest $1,000)

Statement of Financial Position

ASSETS	
Cash and cash equivalents	$2,934,000
Contributions receivable and undeposited funds	23,000
Pledges receiveable	72,000
Deposits, donor-advised funds	22,000
Fixed asset, net	34,000
Other assets	8,000
TOTAL ASSETS	$3,093,000
LIABILITIES AND NET ASSETS	
Liabilities	
Accounts payable and accrued expenses	$34,000
Net assets	
Unrestricted	2,987,000
Temporarily restricted (pledges receivable)	72,000
TOTAL NET ASSETS	3,059,000
TOTAL LIABILITIES AND NET ASSETS	$3,093,000

Statement of Activities

REVENUE AND OTHER SUPPORT	
Contributions	$3,235,000
Donated services	32,000
Investment income	9,000
Realized gain (loss) on sale of stocks	11,000
Unrealized gain (loss) on donor-advised funds	2,000
Pledges collected	104,000
TOTAL REVENUE AND OTHER SUPPORT	3,393,000
EXPENDITURES	
Program expenses	
Grants distributed	2,388,000
Other program expenses	135,000
Management and general	239,000
Fundraising	330,000
	3,093,000
INCREASE IN UNRESTRICTED NET ASSETS	300,000
TEMPORARILY RESTRICTED NET ASSETS	
Pledges–current year	-
Pledges collected	(104,000)
Net discount/amortization of pledges	11,000
DECREASE IN TEMPORARILY RESTRICTED NET ASSETS	(94,000)
CHANGES IN NET ASSETS	207,000
NET ASSETS, beginning of year	2,852,000
NET ASSETS, end of year	3,059,000

Adapted from the 2009 audited statements; available upon request.
Please note that the IRS Form 990 is available online at www.curealzfund.org.

Research Projects

In 2009, Cure Alzheimer's Fund distributed $2,388,000 in research supporting 10 research projects.

Alzheimer's Genome Project (AGP)™

Gene Characterization: Alzheimer's Genome Project (AGP): Massachusetts General Hospital—The primary objective for the AGP in 2009 was to prioritize more than 100 candidate Alzheimer's genes identified in 2008 and 2009 as affecting risk for Alzheimer's disease, to find those with both the highest genetic impact and those within biological pathways most amenable to drug treatment. This approach resulted in concentration on at least five genes so far that have the potential to point the way to effective treatments.

Grant Amount: $1.2 million
Lead Researcher: Dr. Rudy Tanzi

Micro RNAs: Drexel University—Micro RNAs (miRNAs) play a fundamental role in normal cell and organism development and are present in a variety of human diseases. The hypothesis of this project is that miRNAs regulate APP protein levels and Alzheimer's disease risk genes expression as identified through Genome Wide Association Screens (GWAS).

Grant Amount: $100,000
Lead Researcher: Dr. Aleister Saunders

Techniques for Real-Time Study of Potential Treatments for Alzheimer's Disease

Researchers at Washington University in St. Louis have developed technology and techniques for testing potential drug compound therapies in live Alzheimer's disease-affected mice. Cure Alzheimer's Fund has helped to underwrite development of this unique technology.

Microdialysis Core Facility: Washington University in St. Louis—Cure Alzheimer's Fund has joined another foundation in funding the development of this technology to speed analysis of proposed compounds for treatment of Alzheimer's disease. This represents the third and final payment in this series.

Grant Amount: $87,914
Lead Researcher: Dr. David Holtzman

Abeta Elucidation

The Abeta peptide (small protein) is at the heart of Alzheimer's pathology, but too little is known about *how* it is involved in the cause of the disease. Several Cure Alzheimer's Fund projects sought further clarification of this critical and very-high-priority issue.

Specificity and Mechanism of Abeta Oligomers Through Prion Protein: Yale University—Understanding the relationships among Abeta oligomers (certain configurations of aggregated Abeta molecules), the prion protein and neuronal synaptic responsiveness.

Grant Amount: $100,000
Lead Researcher: Dr. Stephen Strittmatter

Rescue of Synapses in Rodent Models: University of California at San Diego—Testing the hypothesis that synaptic loss as seen in Alzheimer's disease-affected animals (mice) can be rescued (stopped or reversed) by blocking synaptic receptor endocytosis.

Grant Amount: $100,000
Lead Researcher: Dr. Roberto Malinow

Design Synthesis and Characterization of Novel and Potent Gamma Secretase Modulators: University of California at San Diego—Gamma secretase is an enzyme that controls production of Abeta. By modulating the enzyme in certain ways, Abeta production theoretically can be kept within ranges of "normal" activity. Gamma secretase modulators are a class of compounds that have the potential to do this, but finding the right mix to allow for only the normal amount of Abeta production has proven exceedingly difficult. This project seeks to explore new compounds to achieve this objective.

Grant Amount: $200,000
Lead Researchers: Dr. Stephen Wagner and Dr. William Mobley

Brain Penetant Thromboxane Antagonist for Alzheimer's Therapy: University of Pennsylvania—A target-directed drug discovery program aimed at reducing Abeta levels in the Alzheimer's-diseased brain.

Grant Amount: $100,000
Lead Researcher: Dr. Virginia M.-Y. Lee

Tau Exploration

In addition to the peptide Abeta, another important protein implicated in Alzheimer's disease is tau.

Development of Tau Microdialysis as a Method to Study Tau Metabolism Pathophysiology and Response to Treatments: Washington University in St. Louis—Further development of the microdialysis technique, this time for study of tau and compounds that potentially may disrupt its role in Alzheimer's pathology.

Grant Amount: $100,000
Lead Researcher: Dr. David Holtzman

New Perspective on the Role of Abeta in the Healthy Brain

Abeta has been thought to be a completely toxic substance, particularly in its Abeta42 allele or genetic variant. However, new evidence supported by Cure Alzheimer's Fund suggests there may be a profoundly positive use for Abeta in the brain.

Potential for Host Cell Cytotoxicity from Microbially Delivered Abeta Oligomers: Massachusetts General Hospital and University of California at Irvine—Test the proposition developed from new evidence about Abeta that in its "normal" proportions it serves as an anti-microbial agent in the brain and only becomes toxic when its normal proportions are changed by prolonged microbial attack or by malfunction of the production process.

Grant Amount: $250,000
Lead Researchers: Dr. Rudy Tanzi, Dr. Rob Moir and Dr. Charlie Glabe

Drug Development

Investigation of Dimebon: Mount Sinai Medical School—A drug originally developed in Russia as an antihistamine has demonstrated positive results against certain Alzheimer's symptoms, although the basic mechanism of action of the drug is unknown. This research aims to understand that mechanism to determine the true nature of the effect of the drug on Alzheimer's disease pathology.

Grant Amount: $150,000
Lead Researcher: Dr. Sam Gandy

Funded Research 04-09

Researcher	Institution	Project	Date	Amount
Alzheimer's Genome Project (AGP)™				
Rudolph Tanzi	Mass General/Harvard	Identifying Novel Candidate Genes. Special Chip Purchase for GWAS	March '06 – October '09	$4,641,400
Bradley Hyman	Mass General/Harvard	Relating AD Brain Morphology to AD Genotype	November '06	150,000
Deborah Blacker	Mass General/Harvard	Longitudinal Study of AD Genotypes	November '06	100,000
Lars Bertram	Max Planck Institute	Fine Mapping of Prioritized GWAS Results	December '08	127,880
Alistair Saunders	Drexel University	miRNA's in AD Pathology	March '09	100,000
Oligomer and Snyaptic Toxicity Studies				
Rudolph Tanzi, et al.	Mass General/Harvard	Identification of Agents That Inhibit the Generation and Neurotoxicity of Cross-linked B-amyloid Protein Species	June '06	$100,000
		Support of Greengards' Synaptic Transmission	June '07	50,000
Tanzi and Robert Moir	Mass General/Harvard	Identification of Agents. . . Year 2	August '07	100,000
Paul Greengard	Rockefeller University	The Role of Oligomeric Abeta in Synaptic Transmission and Plasticity	June '06	100,000
		Effects of Abeta Oligomers on Neurotransmisson Across the Neuronal Synapse	June '07	100,000
		The Role of Oligomeric Abeta in Synaptic Transmission and Plasticity, Year 2	August '07	100,000
Sangram Sisodia	University of Chicago	Molecular Analysis of *56 Structure and Function	June '06	100,000
		Molecular Analysis of *56 Structure and Function, Year 2	August '07	100,000
		Molecular Mechanism Underlying Hippocampal Neurogenisis by Familial AD-linked Presenilin-1 Variants	September '08	100,000
Virginia Lee	University of Pennsylvania	Abeta Oligomers in Mouse Models of AD	June '06	100,000
		Abeta Oligomers in Mouse Models of AD, Year 2	August '07	100,000
		Abeta Oligomers in Mouse Models of AD, Year 3	August '08	100,000
		Brain-Penetrant Thromboxane Antagonists for AD Therapy	July '09	100,000
Charles Glabe	University of California, Irvine	Role of Oligomeric Abeta in AD	June '06	100,000
		Role of Oligomeric Abeta in AD, Year 2	August '07	100,000
		Abeta's Role as an Antimicrobial Agent	May '09	50,000
David Holtzman	Washington University, St. Louis	Role of Synaptic Activity and Neurotransmitter Modulation in the Dynamic Regulation of Inter-stitial Fluid Amyloid and Oligomer Formation	July '06	100,000
		Role of Synaptic Activity and Neurotransmitter Modulation, Year 2	August '07	100,000
		Defining the Effects of Physiological Synaptic Activity on Abeta Levels: Implications for AD	September '08	100,000
Tae Wo Kim	Columbia University	Role for Phosphoinositides in Abeta Oligomer-associated Synaptic Dysfunction	August '07	100,000

Researcher	Institution	Project	Date	Amount
Sam Gandy	Mount Sinai School of Medicine	Mouse Models of Abeta Oligomers and Vasculopathy	August '07	$100,000
Wm. Van Norstrand	SUNY, Stonybrook	Modulation of Abeta Assembly and Cytotoxicity by a Fragment of Myelin Basic Protien	September '08	100,000
Roberto Malinow	UC San Diego	Understanding the Cell Biology Underlying the Effects of Abeta on Synapse	September '08	100,000
		Rescue of Synapses in AD Rodent Models	November '09	100,000
Stephen Strittmatter	Yale University	Specificity and Mechanism of Abeta Oligomer Action Through Prion Protein	March '09	100,000
ACAT Inhibitor Study				
Dora Kovacs	Mass General/Harvard	Effect of Avasimibe (C-1011) on AD Pathology in Mice	September '04	100,000
		Effect of Avasimibe (C-1011) on AD Pathology in Mice, Year 2	June '06	100,000
		ACAT Inhibition Regulates Protein Binding to APP	October '08	100,000
Tools to Enhance AD Research				
Lars Bertram	Max Planck Institute MassGeneral/Harvard	Sustaining Support for the AlzGene Identification and Meta-analysis Website	November '06	142,000
		Sustaining Support for the AlzGene, Year 2	December '08	124,836
David Holtzman	Washington University, St. Louis	Core Facility for Optimal Management of Abeta Microdialysis Drug Discovery Platform	May '07	104,212
		Core Facility for Optimal Management, Year 2	April '08	86,112
		Core Facility for Optimal Management, Year 3	March '09	87,914
		Development of Tau Microdialysis as a Method to Study Tau Metabolism, Athophysiology, and Response to Treatment.	November '09	100,000
Biomarkers				
AD Neuroimaging Initiative	National Institutes of Health	Support of Add-on CSF Biomarker Study	December '07	100,000
Collaborative Award				
James Lah	Emory University	Partnering with Alzheimer's Association and Ruvo Institute for Outstanding Contribution to AD Research	April '08	100,000
Traumatic Brain Injury				
Giuseppina Tesco	MassGeneral/Harvard	Role of BACE in the Pathogenisis of AD Following Traumatic Brain Injury	September '08	50,000
Drug Development				
Sam Gandy	Mount Sinai School of Medicine	ADAM10 and Dimebolin	March '09	100,000
		Dimenon Follow-up	September '09	50,000
Steven Wagner and William Mobley	University of California, San Diego	Design, Synthesis, and Characterization of Novel and Potent Gamma Secretase Modulators: Physiochemical and Pharmacokinetic Properties	September '09	200,000
New Perspective on Abeta as an Antimicrobial Agent				
Tanzi and Moir	MassGeneral/Harvard	Investigation of Certain Properties of Mitochondria Membranes Related to AD	June '08	200,000
		Abeta as an Anti-microbial Agent	May '09	200,000

Special Events

Grampy's Golf Tournament

Following a festive evening including a raffle, cocktails and hors d'oeuvres, golfers hit the links at Foxwoods Casino in Connecticut for this exceptional outing that raised money for Cure Alzheimer's Fund.

Buenos Aires Marathon

Maria Pugliese logged 26.2 miles in the Buenos Aires Marathon in support of Cure Alzheimer's Fund.

"My grandmother suffers from the disease and every day is a challenge for her and those around her," Maria says. "As genetics plays a key role in the disease, it is likely that this will continue to affect my family. I want to do everything possible to try and advance the research so fewer and fewer people suffer."

Hay Harbor Tennis Tournament

For the third year in a row, this ladies tennis tournament raised funds to help end Alzheimer's disease. Creative rules, like paying for an extra serve, made this event a winner as it raised money for research. Many thanks to all the participants, the Hay Harbor Tennis Club and Diana Fiske!

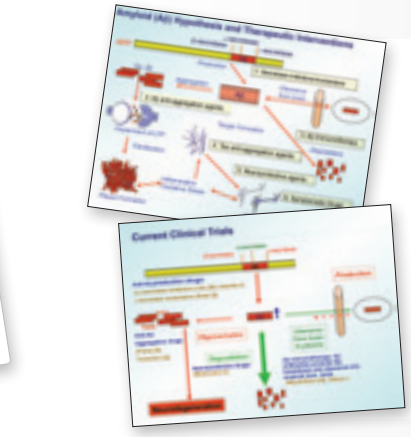
Rock Stars of Research

In September, top scientists and rock stars joined forces in Washington, D.C., to urge Congress to increase research funding. The event, which included such rock celebrities as Grammy Award-winning singer Sheryl Crow and Aerosmith's Joe Perry, was a success, as it highlighted the need for funding and featured scientists and rock stars playing together! Organized by the Geoffrey Beane Gives Back Alzheimer's Initiative, the Rock Stars of Science also featured a designer menswear shoot in *GQ* magazine.

(Top photo, L to R) Rudy Tanzi, Joe Perry, Francis Collins (Photo at left, L to R) Ronald Petersen, will.i.am, Steven Dekosky and Sam Gandy

The Alzheimer's Genome Project™: From Genes to Therapies presented by Dr. Rudy Tanzi

A collaborative event hosted by Cure Alzheimer's Fund and Massachusetts General Hospital featured Dr. Tanzi's research on new genes that are revealing information about Alzheimer's and significantly aiding researchers worldwide in the search for a cure.

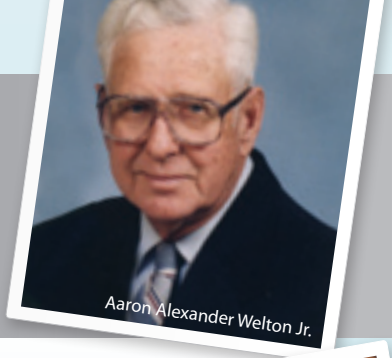


Webinar: Progress in the Search for an Alzheimer's Cure

Our first live webinar was conducted over the Internet and featured Dr. Rudy Tanzi's recent work and progress on the path to a cure. The event was attended by 75 people, who also particpated in the live question-and-answer session with Dr. Tanzi.

In Memoriam

Many families choose to honor loved ones by making and requesting donations in memory or honor of a family member. We are grateful to the more than 1,050 families who have honored Alzheimer's patients and friends with a donation to Cure Alzheimer's Fund over the last five years.

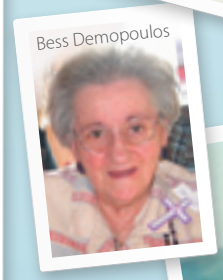

Aaron Alexander Welton Jr.


Mavis Martin


Robert Moniz


Merril L. Claire


Edna Frances 'Tookie' Watts


Bess Demopoulos


Elaine Engleberg


Fred Hauswirth


John McKiernan


Barbara M. Osborne

The Future

PRIORITIES FOR CURE ALZHEIMER'S FUND-SUPPORTED RESEARCH FOR 2010

Our Research Agenda for the next year will follow three tracks:

1. Identify genes that contribute to risk for Alzheimer's disease (AD).

The Alzheimer's Genome Project™ has identified more than 100 candidate genes thought to contribute to or guard against Alzheimer's pathology. Our immediate focus will be to confirm and prioritize those genes to yield approximately the top two dozen genes that both a) have a high genetic impact (are both prevalent in the general population and play a significant role in AD); and b) influence biological pathways that are most susceptible to drug treatment.

2. More completely characterize the role that Abeta plays in AD pathology.

The peptide (small protein) Abeta, and particularly its variant Abeta42, clearly plays a key role in Alzheimer's disease. Exactly how it initiates or helps to initiate AD pathology remains unclear, but it is critically important to understand if effective therapies are to be developed to stop or prevent the disease from starting. Specific targets of investigation will include more exploration of Abeta "oligomers" (aggregations of the Abeta molecule); the effect of Abeta on the neuronal synapses of the brain; gamma secretase modulators and their delivery systems; the role of Abeta as an antimicrobial agent; and investigation of specific compounds or drugs already available for other purposes that may address causes of AD.

3. New initiatives for old questions.

Cure Alzheimer's Fund's Research Consortium has posed two projects, the resolution of either of which could be immensely important to accelerating progress toward a cure.

- Firstly, the APOE4 gene variant is the most prevalent AD-related gene in people developing late-onset Alzheimer's disease. However, little is known about its "mechanism of action" or how it actually drives the disease pathology. Uncovering this process will speed the development of effective therapies to block or counter what the powerful APOE4 gene type does to initiate AD.
- Secondly, we will investigate the protein Tau. It is increasingly clear that while Abeta may be involved in initiating AD pathology, the disease really takes hold when Abeta interacts with the Tau, which causes the tangles so characteristic of AD. The relationship between the two proteins has been shown to exist, but exactly how one leads to the other to propel the pathology is not clearly understood. This understanding could be critical in order to interrupt the progress of the disease before it can do its damage.

New Paradigm for Exploration

A paper by colleagues Robert Moir, Ph.D., and Rudy Tanzi, Ph.D., of Mass General Hospital titled *The Alzheimer's Disease-Associated Amyloid β-protein is an Antimicrobial Agent* has appeared in the March issue of the online journal *PLos One*. The paper shows that the Abeta protein, previously thought to have no value to the human body and in fact thought only to be a primary instigator of Alzheimer's pathology, may be part of the body's natural defense against infection. This is truly breakthrough research and could possibly change the way the entire Alzheimer's research field looks at modulating this protein to affect prevention and cure of the disease.

We Care!

Alzheimer's affects about 10 percent of people older than 65, and almost half of those 85 and older. In 2009, the federal government spent more than $185 billion on care for Alzheimer's patients through Medicare and Medicaid. At the same time, the federal government through the National Institutes of Health spent less than $450 million on research.

We cannot rebalance this equation ourselves, but we can use the financial support from more than 2,500 donors to target truly breakthrough research that has and will accelerate progress toward a cure.

We think the best way to express our care and concern for those already afflicted and those millions more sure to be afflicted without significant interruption of this epidemic is to fund the research that will make "care" obsolete.

Please join the pioneers of these first five years in supporting focused, targeted research to accelerate progress toward a cure.

To make a gift or for more giving information, please visit our website, www.curealzfund.org

Cure Alzheimer's FUND

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.

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