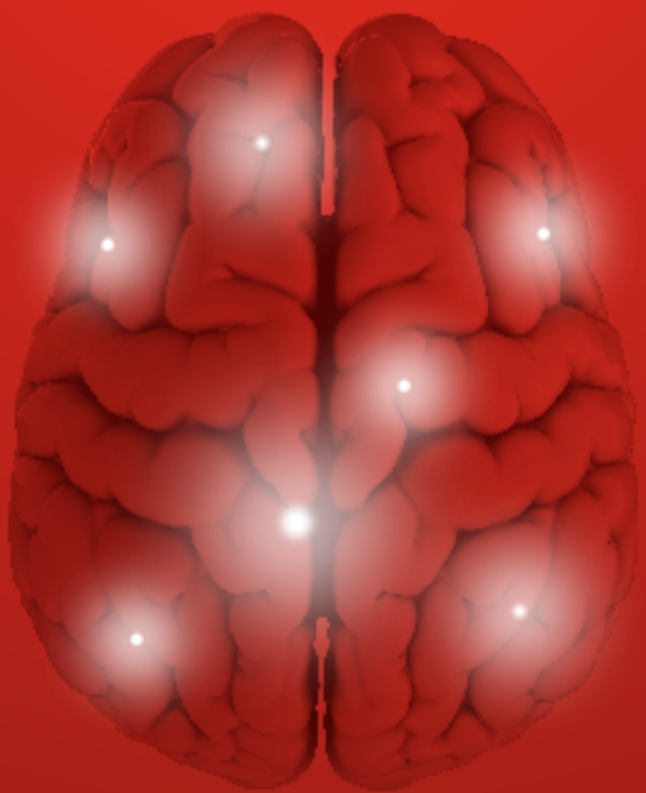
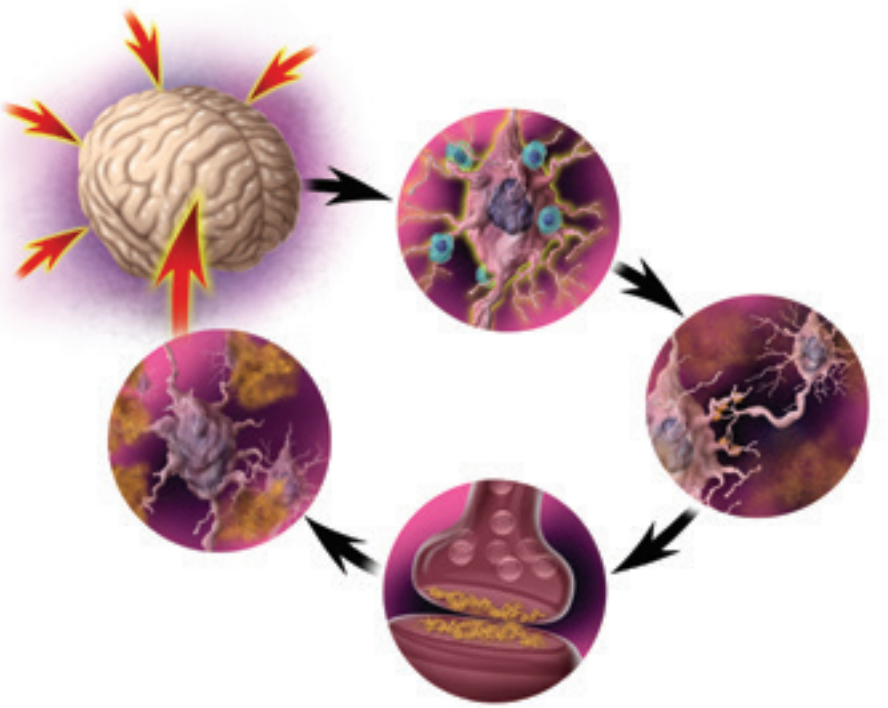
Annual Report 2011

PROGRESS THROUGH RESEARCH



Cure Alzheimer's FUND

ON OUR COVER: We have abstractly depicted, with pinpoints of light, points of insults or injury to the brain. As described below in this detailed illustration from our 2011 publication, "Alzheimer's Disease: The Science," such events can set off a chain reaction and a vicious cycle that is key to understanding Alzheimer's pathology.



▲ When the brain experiences any form of injury (red arrows), such as exposure to neurotoxins, stroke, transient ischemia, traumatic brain injury or an infection, excess Abeta is produced and accumulates in the brain. This can lead to inflammation and proliferation of glial cells (blue spheres). While glial cells can help clear Abeta, inflammation can increase Abeta production and, consequently, the formation of excessive Abeta oligomers (yellow squiggles), which then can impair neurotransmission at synapses (right and bottom circles) where nerve cells communicate as part of the brain's neural network. The oligomers go on to form fibrils and amyloid plaques (left circle). Excess beta-amyloid can act as an insult that once again triggers the brain's immune system, Tau aggregation, inflammation, and, thus, more Abeta production. This leads to a vicious cycle of continued insult to the brain, leading to neurodegeneration and dementia.

More key points of understanding Alzheimer's disease are illustrated and explained in the publication. Visit www.curealz.org/the-science for more information on the report.

2011

Annual Report

LETTER FROM THE CHAIRS

Jeff Morby, chairman and co-founder, Cure Alzheimer's Fund
Rudy Tanzi, chairman, Cure Alzheimer's Research Consortium

Dear Friends

Dear Friends,

On behalf of the Board of Directors and the Research Consortium, we want to thank all the donors, researchers and academic institutional partners supporting Cure Alzheimer's Fund research for your help in making 2011 such a successful science year. Guided by leading scientists in the field, Cure Alzheimer's Fund-supported research continues to make breakthrough progress toward our goal of eradicating Alzheimer's disease.

Research supported by Cure Alzheimer's Fund has helped reshape the current view of the pathological processes underlying Alzheimer's disease. Not long ago, it was thought that beta-amyloid plaques in the brain, made up of the protein called "Abeta," were the main causes of the disease. Though beta-amyloid continues to be an important factor in the Alzheimer's picture, we now have progressed to a more sophisticated understanding of Alzheimer's pathology—one that will allow us to develop much more effective therapies and early interventions.

A quick summary of this current and more sophisticated view is as follows:

1. We now know genetic mutations and "insults" to the brain (e.g., undetected mini-strokes, head bangs, chemical toxins and other harmful impacts) cause excessive amounts of Abeta to accumulate in the brain.
2. While a good deal of Abeta is found in the toxic, beta-amyloid, senile plaques, most of the Abeta floats around nerve cells in toxic clumps known as "oligomers." In excess, these clumps of Abeta somehow trigger the clumping of another protein, Tau, which produces toxic tangles inside the nerve cells of the brain.
3. The toxic tangles then can spread to other brain cells, causing more tangles. In this process, the tangle-bearing nerve cells ultimately die. The combination of both dead nerve cells and beta-amyloid plaques triggers inflammation in the brain.
4. Inflammation then becomes a major "insult" to the brain and causes even more Abeta production, tangle formation and nerve cell death.
5. A vicious cycle ensues.

Adding to this picture is the very new discovery made by our researchers that Abeta, the peptide that begins this whole process, may be part of the brain's innate immune system, and as such, attacks and attempts to eliminate toxic bacteria, fungus and viruses that enter the brain as we age. In fact, Cure Alzheimer's Fund is actively funding research into the possibility the initial accumulation of excess Abeta in the brain may be triggered by the brain's own immune system trying to fight a chronic infection of various origins.

Cure Alzheimer's Fund has played a major role in the development and confirmation of each piece of the above-described emerging understanding of the process of generation of Alzheimer's pathology. 2011 has been a particularly important year. Genetic studies conducted as a consequence of our Alzheimer's Genome Project™ have taught us, in particular, that this whole process is triggered when, over one's lifetime, too much Abeta accumulates in the brain. This is usually due to poor clearance of Abeta in the form of plaques and clump-like oligomers. This then leads to the tangles, nerve cell death and inflammation as part of a vicious cycle. Once enough nerve cells and their connections, called synapses, are lost, cognitive impairment and, ultimately, dementia, is the result, causing Alzheimer's disease.

Since the inception of the Cure Alzheimer's Fund, nearly $15 million dollars has been distributed to more than 50 projects in 24 of the top Alzheimer's research laboratories in the world. As a result, more than 100 research publications in top-tier scientific journals have acknowledged Cure Alzheimer's Fund for support. It is safe to say our understanding of the causes of Alzheimer's disease and how to more effectively treat this devastating disease have been profoundly impacted by Cure Alzheimer's Fund-supported research efforts, with 2011 hitting new highs.

A summary of these achievements is provided below.

The Alzheimer's Genome Project (AGP) and Novel Animal Models

The flagship project of the Cure Alzheimer's Fund is the AGP, begun in 2007 and carried out in Dr. Tanzi's laboratory at Massachusetts General Hospital. It also includes the AlzGene database maintained by Dr. Lars Bertram at the Max Planck Institute in Berlin. The AGP has successfully completed Phase I, resulting in the identification of more than 100 new candidate genes affecting susceptibility for Alzheimer's disease. We now are actively engaged in sharing this information in public databases, including those maintained by the National Institutes of Health and the Cure Alzheimer's Fund-supported database AlzGene.org. The identification of these genes has implicated several new biological pathways and systems in the Alzheimer's disease process that previously were not known to be involved.

In the second phase of the AGP, we have been analyzing the DNA of the many new Alzheimer's gene candidates to pinpoint the human gene variants that directly influence one's susceptibility for the disease. Introduction of these human gene variants into mice already is accelerating the creation of new animal models for the disease and new drug screening programs. In fact, over the past year, we have created four new animal models for Alzheimer's based on discoveries made in the AGP. The generation of these new animal models is paving the way for the development of new therapies aimed at more effectively preventing and treating Alzheimer's from novel angles. The ultimate goal of the AGP is to use the dozens of validated Alzheimer's genes to predict one's risk for the disease, and then treat to prevent the disease from striking before symptoms appear.

Novel Therapeutics for Alzheimer's Disease

Currently available therapies only treat the symptoms of Alzheimer's but do not stop the disease from progressing. They generally provide modest and only temporary benefit from the ravages of this terrible disease. To effectively treat and prevent this disease, we will need therapies that directly slow down, stop or reverse the disease process. This means we must first fully understand how the disease progresses and then develop therapies that intervene. Cure Alzheimer's Fund has been supporting numerous drug programs from bench to bedside. Over the past year, Cure Alzheimer's Fund has made significant progress in novel drug discovery for Alzheimer's.

Some examples are listed below.

Bexarotene

Cure Alzheimer's Fund supported the groundbreaking work of Dr. Gary Landreth and colleagues at Case Western Reserve University, who showed in a mouse model for Alzheimer's that the FDA-approved lymphoma drug bexarotene was able to stop the accumulation of beta-amyloid (made up of Abeta and more particularly, its most toxic form, Abeta42) in the brain and, to some extent, reverse beta-amyloid-induced pathology and cognitive deficits. The researchers found bexarotene could rapidly clear beta-amyloid deposits in the mice, and that this process depended

on the Alzheimer's risk gene known as *APOE*. While the results in the mice were nothing short of remarkable, the leap from mouse to man does not guarantee success in humans. However, as a result of this landmark study, bexarotene is now beginning to undergo testing in human clinical trials for efficacy and safety for the potential treatment and prevention of Alzheimer's disease. Cure Alzheimer's Fund has supported Dr. Landreth and his collaborator, Dr. David Holtzman of Washington University, St. Louis, to explore the effects of bexarotene on Alzheimer's pathology, and also plans to help support pivotal clinical trials.

Gamma Secretase Modulators

Preventing the accumulation of toxic Abeta in the brain is currently the goal of thousands of academic and pharmaceutical laboratories attempting to discover effective new drugs for Alzheimer's disease. One approach involves trying to curb the production of Abeta by inhibiting the enzyme called gamma secretase, which is required for the production of the toxic material. Previous attempts to do this used drugs called "gamma secretase inhibitors." However, in a recent clinical trial by Lilly, these drugs caused major side effects, including skin cancer.

Dr. Steve Wagner, University of California, San Diego, in collaboration with Dr. Tanzi's laboratory, has been supported by the Cure Alzheimer's Fund since 2009 to develop safer versions of these drugs, which we call "gamma secretase modulators." We were able to avoid what is thought to cause the toxic side effects of the original drugs and made new drugs that slow down the production of Abeta in the brain.

As a major validation of the promise of these new drugs made possible by Cure Alzheimer's Fund, Dr. Wagner recently was awarded a multimillion-dollar National Institutes of Health "Blueprint" Neurotherapeutics grant for the fast-track development of these drugs. Drs. Wagner and Tanzi serve on the lead development team for the five-year NIH project, which brings together 15 agencies that will help shepherd these new drug candidates into human clinical trials by 2014.

Tangle Therapies

Cure Alzheimer's Fund also has been engaged in supporting a number of promising new therapies for Alzheimer's in 2011. In the pathological cascade of Alzheimer's, toxic clumps of Abeta drive the formation of tangles, which choke the inside of nerve cells in Alzheimer's patients' brain. Dr. Charles Glabe, University of California, Irvine, and Dr. George Bloom, University of Virginia, received Cure Alzheimer's Fund funding to discover exactly which forms of Abeta cause tangles to form in nerve cells.

Over the past several years, tangles were shown to "spread" from one nerve cell to another, causing serial nerve cell death in the brains of Alzheimer's patients. In addition to curbing beta-amyloid deposition, we also will need therapies for stopping the formation and spread of tangles. In pursuit of better understanding of how this works, Cure Alzheimer's Fund has been funding Dr. Dennis Selkoe and Dr. Dominic Walsh, Harvard Medical School, in 2011 as well as Dr. Virginia Lee (University of Pennsylvania) in 2010 to devise therapies that can prevent Abeta from triggering tangles and prevent the spread of tangles from dying nerve cells to healthy ones.

Cholesterol-Targeted Drugs and Other New Alzheimer's Therapeutics

Several other new Alzheimer's therapies are being developed by other investigators with Cure Alzheimer's Fund money. For example, some cholesterol-lowering drugs carry the potential to lower Abeta levels and are being developed as new therapeutics for Alzheimer's in the laboratory of Dr. Dora Kovacs, Massachusetts General Hospital (MGH). Dr. Kovacs has been funded by Cure Alzheimer's Fund to develop drugs known as "ACAT inhibitors," which she has shown dramatically reduce Abeta levels in Alzheimer's animal models. Other 2011 Cure Alzheimer's Fund-supported projects aimed at drugs that can lower Abeta levels in the brain include compound being developed by Dr. Phillip Haydon, Tufts University (UDP analogs), Dr. Nicholas Seeds, University of New Mexico (neuroserpin inhibitors), and Dr. Gal Bitan, UCLA, (molecular tweezers).

Understanding Alzheimer's Disease Pathology

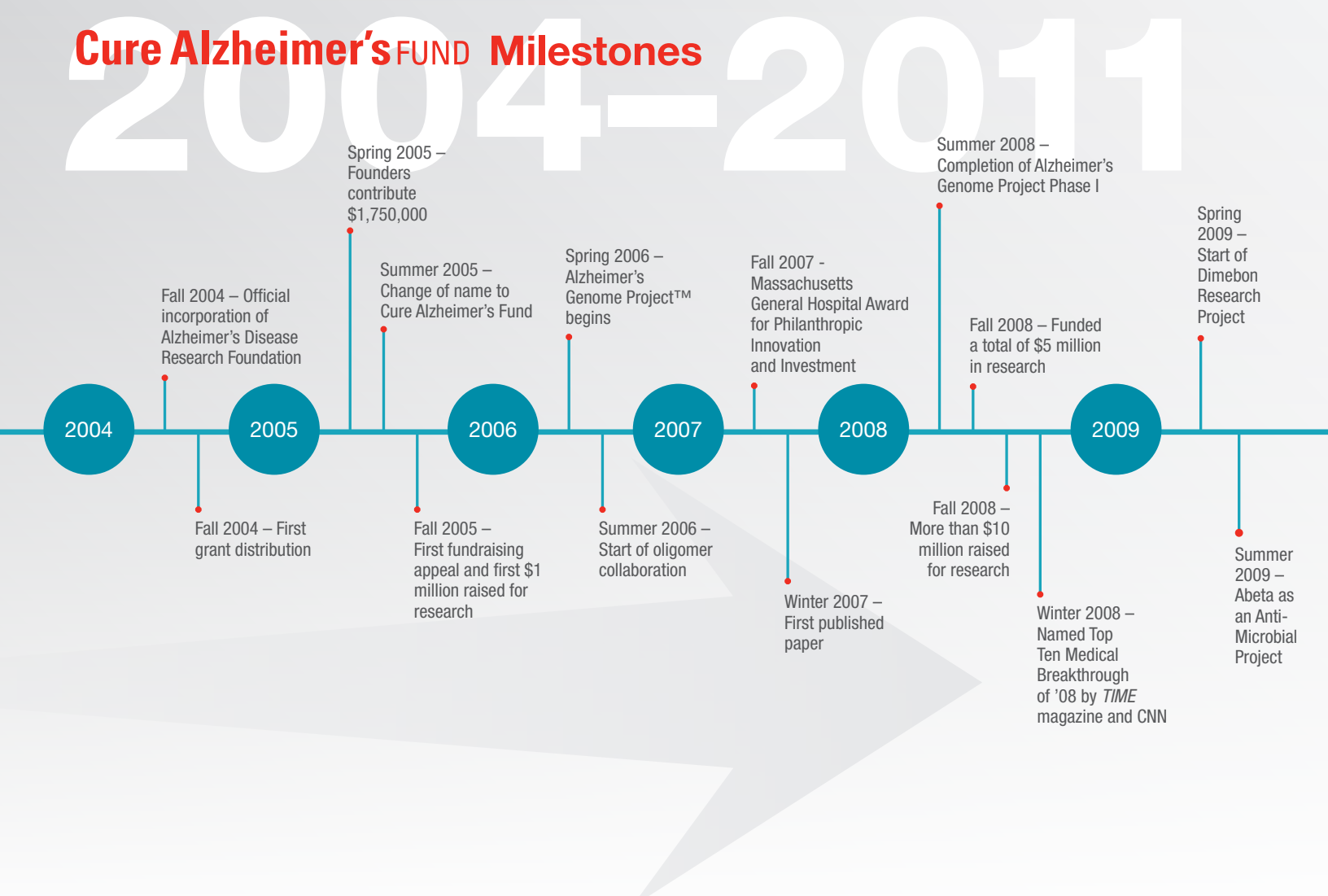
In addition to the very exciting work that has been supported by Cure Alzheimer's Fund in genetics and drug discovery, we also are supporting critical research aimed at further understanding the pathological process in Alzheimer's disease. In a revolutionary study, Dr. Robert Moir (MGH) was supported by Cure Alzheimer's Fund to uncover the normal role of Abeta, showing it may protect the brain from microbial infections. He now is being funded to investigate whether amyloids in other diseases such as diabetes and Parkinson's disease carry out similar roles. These studies carry profound implications for the causes of these diseases and especially whether infections by certain microbial pathogens may initially trigger the formation of beta-amyloid as well as other amyloids, such as amylin in the pancreas of diabetes patients. Dr. Moir's studies also call for much more careful consideration as we develop therapies

to lower Abeta levels, in view of the small protein's potential "normal" role in the brain.

In other studies, Dr. Paul Greengard, Rockefeller University, Nobel Laureate, is studying why only certain sets of nerve cells die in the brains of Alzheimer's patients, while others are spared. Similarly, Dr. Lee Goldstein, Boston University, is performing state-of-the-art mapping of metal (zinc and copper) distributions in the brain to investigate their contribution to disease pathology. Dr. Sam Sisodia, University of Chicago, was funded to search for factors in the brain that drive the generation and toxicity of Abeta. Dr. Doo Yeon Kim and Dr. Sehoon Choi (MGH) are being supported to explore how the propagation of new nerve cells in the brain and delivery of neural stem cells (made from skin cells) into the brain can ameliorate Alzheimer's pathology. And finally, Dr. Giuseppina Tesco, Tufts University, and Dr. Zhongcong Xie (MGH) were funded in 2011 to explore how traumatic brain injury and surgery-induced brain inflammation contribute to risk for Alzheimer's pathology, respectively.

In summary, 2011 has been a tremendously successful and busy year for Cure Alzheimer's Fund. The groundbreaking work described above would not have been possible without the

Cure Alzheimer's FUND Milestones 2004–2011



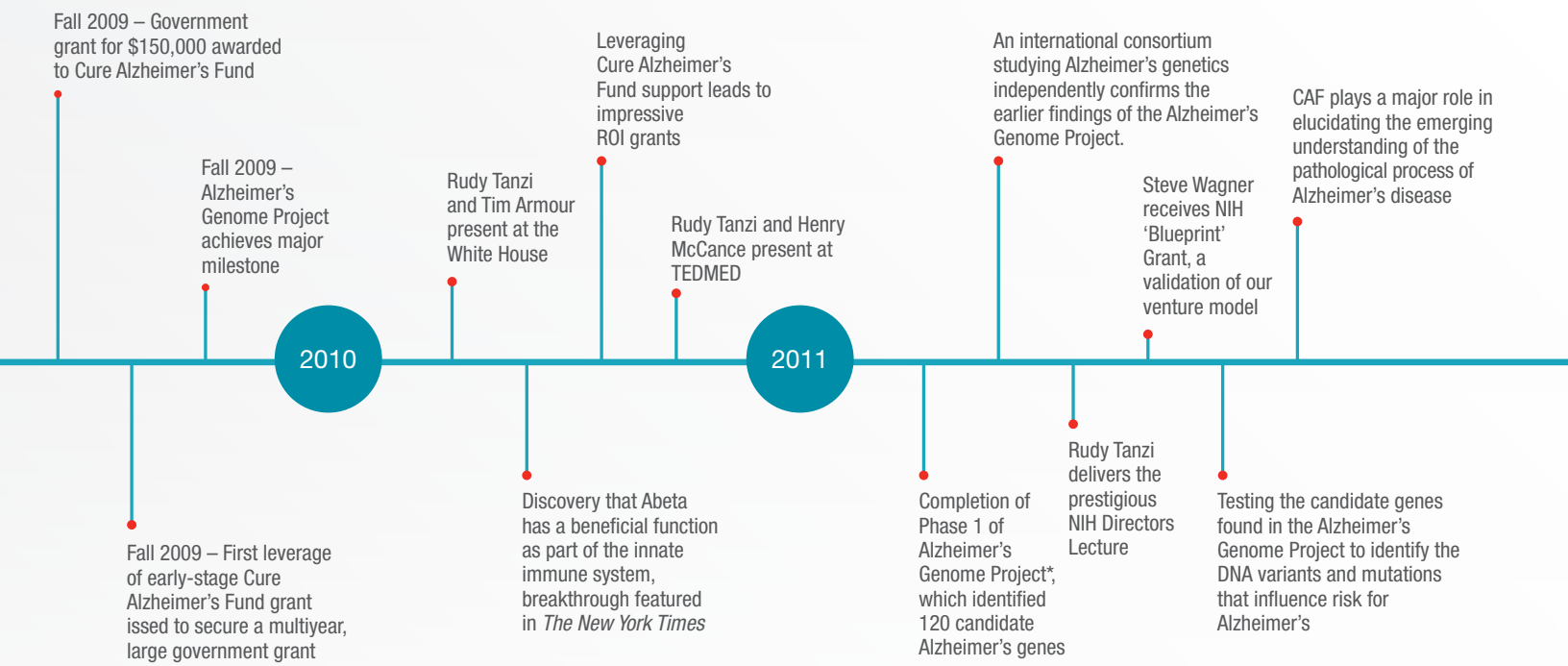
generous support of more than 4,000 supporters, including the founding families and board members who provide both financial and personal support on so many levels. While there is still a great deal of work to be done before we achieve our overarching goal of eradicating Alzheimer's disease through early prediction-early prevention, huge strides were made in 2011 toward this end.

On behalf of the Cure Alzheimer's Fund, we thank you all for your devotion, perseverance and passion in supporting the research necessary to end this devastating disease in our lifetimes.

Sincerely yours,

Jeffrey L. Morby
Chairman and Co-Founder
Cure Alzheimer's Fund

Rudolph E. Tanzi, Ph.D.
Chair, Cure Alzheimer's Fund Research Consortium
Joseph P. and Rose F. Kennedy Professor
of Neurology, Harvard Medical School
Director, Genetics and Aging Research Unit,
Massachusetts General Hospital



*The first large-scale study of the human genome performed on the world's largest collection of families affected by Alzheimer's and the first genome-wide study for Alzheimer's in the world to discover novel Alzheimer's gene candidates with statistically significant results and confirmation in thousands of subjects from families with a high incidence of Alzheimer's disease.

Our Research Roadmap

FOUNDATIONAL GENETICS

Alzheimer's Genome Project (AGP)™
Phase 1 Rudy Tanzi, Ph.D.
Phase 2 Rudy Tanzi, Ph.D.

AlzGene Database

TRANSLATIONAL RESEARCH

Alzheimer's Genome Project (AGP)
Phase 2 Rudy Tanzi, Ph.D.

****Anti-Microbial Peptide (AMP)**
Robert Moir, Ph.D.
Rudy Tanzi, Ph.D.

Stem Cells
Doo Yeon Kim, Ph.D.

Neurogenesis
Se Hoon Choi, Ph.D.

Brain Vulnerability
Paul Greengard, Ph.D.

Abeta Oligomers and Tau
George Bloom, Ph.D.

****Surgery/Anesthesia**
Zhongcong Xie, M.D., Ph.D.

Head Trauma
Giuseppina Tesco, M.D., Ph.D.

Metallomic Mapping
Lee Goldstein, M.D., Ph.D.

Abeta Deposition
Sangram Sisodia, Ph.D.

Amyloid Pathology
Charles Glabe, Ph.D.

DRUG DISCOVERY

Molecular Tweezers
Gal Bitan, Ph.D.

***Tau Immunotherapy**
Virginia M.-Y. Lee, Ph.D., M.B.A.

****Abeta Oligomers and Tau Aggregation**
Dominic Walsh, Ph.D.
Dennis Selkoe, M.D.

Neuroserpin Inhibitor
Nicholas Seeds, Ph.D.

DRUG DEVELOPMENT

Gamma Secretase Modulators (GSM)
Steven Wagner, Ph.D.

Bexarotene
David Holtzman, M.D.

ACAT Inhibitors (Enzyme of the Cholesterol Pathway)
Dora Kovacs, Ph.D.

****UDP Analogs (Glial Activation for Therapeutic Opportunities)**
Phillip G. Haydon, Ph.D.

Retinoid X Nuclear Receptor and Bexarotene
David Holtzman, M.D.
Gary Landreth, Ph.D.

*extension from 2010
**2011 grant funded in 2012

2011 Research Projects

In 2011 Cure Alzheimer's Fund distributed $2,050,000 for research supporting 15 projects.

The Alzheimer's Genome Project™

Rudolph Tanzi, Ph.D.,
Professor of Neurology,
Harvard Medical School

Director, Genetics and
Aging Research Unit,
Massachusetts General Hospital

$600,000

The goal of this project is to evaluate Alzheimer's disease gene candidates for effects on APP processing, Abeta generation, Tauopathy and cell death as part of the Alzheimer's Genome Project.

This Alzheimer's Genome Project (AGP) progress report summarizes activities from October 2010 to March 2011 and also incorporates a research plan for April 2011 to September 2011. In the past funding period, Dr. Tanzi and his fellow researchers continued Phase II of the AGP focusing on follow-up of AD gene candidates from their Genome Wide Association Study (GWAS), which includes fine-mapping, replication genotyping and re-sequencing of top candidates coming from their various AD GWAS. They also have continued functional studies of *ADAM10* and *ATXN1* in cell-based and animal models and begun genetic follow-up and functional studies for AD-associated copy number variants (CNV) identified in the National Institute of Mental Health (NIMH) and National Cell Repository of Alzheimer's Disease (NCRAD) Affymetrix 6.0 GWAS datasets. As in the past, functional follow-up includes RNAi and overexpression of AD gene candidates in primary neurons and various cell lines to test for effects on APP processing, Aβ generation, Tauopathy and cell death.

"In the Alzheimer's Genome Project, Ataxin 1 came up as one of our strongest hits as an Alzheimer's risk factor. Martin Zhang, Ph.D., who works in my lab, then found that it directly affects the production of amyloid beta protein. He received an NIH grant to explore the mechanism underlying that effect and is attempting to find mutations in the gene."

—Rudy Tanzi, Ph.D.

Alz Research Forum for AlzGene Maintenance

www.alzforum.org
$2,500

The AlzGene Database:
Cure Alzheimer's Fund is funding the upkeep and continued development of a revolutionary Web-based database.

AlzGene is a fantastic resource for Alzheimer's researchers, providing data and meta-analyses from hundreds of genetic association studies in an easy-to-use, searchable database. Scientists interested in a particular gene can search for it in AlzGene to see what previous studies have reported, receiving a wealth of information in a very short amount of time.

Family history is the second greatest risk factor for Alzheimer's disease after age, and the growing understanding of AD genetics is a critical part of the science behind the disease. In the past decade, literally hundreds of reports have been published claiming or refuting genetic association between AD genes and disease risk, onset-age variation or other phenotypic variables. Presently, more than a half-dozen AD association studies are being published monthly from research groups worldwide. For the AD genetics research community (and for the public as well), this wealth of information is becoming increasingly difficult to follow, evaluate and—most importantly—to interpret. The AlzGene database has been developed to manage this huge amount of information and to allow it to be used productively.

The Amylin Protein of Diabetes Mellitus is an Antimicrobial Peptide

Robert Moir, Ph.D.

Rudolph Tanzi, Ph.D.

Harvard Medical School/
Massachusetts General Hospital

$300,000

The goal of this project is to determine whether the amylin (IAPP) protein has a role in innate immunity (similar to Abeta) in order to significantly advance our understanding of the origins of diabetes pathology and its possible linkage to Alzheimer's disease.

The underlying cause of Type 2 diabetes mellitus remains unclear. In 1987, researchers found an important clue to the pathological mechanisms underpinning the disease—insoluble deposits of a small protein called amylin (IAPP) that form in pancreatic islets of those with diabetes. Proteinaceous deposits of this kind are known as amyloid and are a pathological hallmark of a number of common diseases, including Alzheimer's disease (AD). Different amyloid-forming proteins are associated with different diseases. However, amyloid-forming proteins often share physiochemical properties and their associated diseases overlapping pathologies. The similarities between IAPP and Abeta are particularly striking. Abeta is present in the brains and pancreatic islets of patients with diabetes. Both IAPP and Abeta are small, amphipathic molecules generated by cleavage of larger membrane-associated precursor proteins and bind the molecular chaperone apolipoprotein E. Abeta and IAPP also share another important similarity—despite two decades of intensive study, the normal non-pathogenic functions of these proteins are poorly understood. Our laboratory recently advanced the novel idea that Abeta is part of the innate immune system and belongs to a family of proteins called antimicrobial peptides (AMPs). AMPs function as natural antibiotics to protect against invading pathogens. *In vitro* Abeta can inhibit the growth of at least eight clinically important pathogens. In addition, homogenates prepared from the brains of AD patients have specific Abeta-mediated antimicrobial activity. Preliminary data from our latest experiments show IAPP also has antimicrobial activity and inhibits the growth of the important human pathogens *Candida albicans* and *Listeria monocytogenes*. In initial tests, IAPP antimicrobial activity was equivalent to Abeta, although the peptide may target a narrower microbial spectrum.

Our discovery of Abeta's role in immunity identifies pharmacological manipulation of the innate immune system as a new and promising therapeutic strategy for treating AD. Strong epidemiologic evidence suggests an association between AD and Type 2 diabetes, but the critical pathological mechanism common to both diseases has yet to be identified. Our preliminary findings link, for the first time, the amyloid-forming proteins of these two disorders with a common non-pathological function as innate immune effector molecules. We propose a project to investigate IAPP for a role in innate immunity using an experimental paradigm similar to that used in the study of Abeta. We think findings from this new line of inquiry may significantly advance our understanding of the origins of diabetes pathology and is potentially the basis for a new therapeutic strategy for curbing the rising diabetes epidemic.

Alzheimer Disease Models Based On Human Neural Progenitor Cells

Doo Yeon Kim, Ph.D., Assistant Professor of Neurology, Harvard Medical School

$100,000

The goal of this project is to develop genetically modified human neural progenitor cells that can replicate Alzheimer's disease pathology in *in vitro* and *in vivo* conditions in order to develop and test Alzheimer disease drugs in human brain cells.

This work represents a potential major breakthrough in the use of stem cells for Alzheimer's research. Various therapeutic applications are under development in many laboratories to treat this tragic disease. However, the lack of fast and reliable Alzheimer's disease model system slows down the validation of laboratorial trials that could lead to the final clinical stage. Current Alzheimer disease mouse models fail to fully replicate the disease pathology, possibly due to lack of human-specific physiological pathways of the brain.

Dr. Doo Yeon Kim and his team plan to develop Alzheimer's disease models based on human neural progenitor cells. Human neural progenitor cells are multipotent stem cells that can differentiate to brain cells in *in vitro* and *in vivo* conditions. Recent reprogramming technology makes it possible to generate human neural progenitor cells easily from skin cells of normal and Alzheimer's disease patients. In this study, they will develop genetically modified human neural progenitor cells that can replicate Alzheimer's disease pathology in *in vitro* and *in vivo* conditions. Their study will provide a novel Alzheimer's disease model system that can be used to develop and test Alzheimer's disease drugs in human brain cells and it will provide a human Alzheimer's disease model for basic researchers.

Exploring Adult Neurogenesis as a Therapeutic Target for Alzheimer's Disease

Se Hoon Choi, Ph.D., Research Fellow, Genetics and Aging Unit, Department of Neurology, Massachusetts General Hospital

$100,000

The goal of this project is to test whether the strategy of stimulating endogenous stem cells in the AD brain is safe in order to find treatment for Alzheimer's patients.

Recent evidence shows the adult brain contains discrete populations of stem cells that retain the capacity to generate new neurons through the process of neurogenesis. Dr. Se Hoon Choi will test whether the strategy of stimulating endogenous stem cells in the AD brain is safe and effective ultimately to find treatment for Alzheimer's patients.

Selective Cell Vulnerability in Alzheimer's Disease

Paul Greengard, Ph.D.,
Vincent Astor Professor, The Rockefeller University

$100,000

The goal of this project is to identify cells that are both most vulnerable and most resistant to Alzheimer's disease in order to develop drugs that will protect the most vulnerable.

At the early stages of Alzheimer's disease (AD), neurofibrillary tangles (NFT) and neurodegeneration occur only in very specific regions, while many regions remain virtually unaffected. Paul Greengard's lab at the Rockefeller University recently developed a new procedure to compare the molecular profiles of very specific cell types inside the brain. They will apply this technology to mice in order to compare vulnerable regions with more resistant regions that don't show any pathology until late stages of the disease. They will establish the molecular profiles of the different regions of interest, try to find genes that are common to all vulnerable regions or to all resistant regions and verify the region-specific expression of these genes in human brain tissue. Important differences between vulnerable and resistant cells might not be obvious at a normal physiological state, but might become obvious only in a pathological environment. They will apply the bacTRAP technology (a platform to identify novel targets in specific cell types) to different AD mouse models, and study the molecular profile of the different regions in an AD-like environment. Then they will try to find genes that are modulated region-specifically in the context of AD and verify their findings in brain tissue of patients at different stages of AD.

These comparisons will yield lists of vulnerability genes that could potentially explain why vulnerable cells are vulnerable, or why resistance genes protect resistant cells from the pathology. By comparing these genes with AD susceptibility genes, they have the potential to identify genes that are crucial for AD pathogenesis. In future studies, they will modulate the expression level of the best candidates in neurons, and test the vulnerability of the cells thereafter. If these genes are indeed vulnerable or resistance genes, they could be very good drug targets aimed at protecting vulnerable cells.

Structural and Functional Analysis of Novel Abeta and Tau Oligomers Using Conformation-Specific Monoclonal Antibodies

George Bloom, Ph.D.,
Professor of Biology and Cell Biology, University of Virginia

$100,000

The goal of this project is to determine which oligomers of Abeta and Tau are most damaging and whether specific antibodies can prevent formation of those oligomers.

Two types of abnormal structures, amyloid plaques and neurofibrillary tangles, have long been known to accumulate in the brains of Alzheimer's disease (AD) patients, but recent advances point to the building blocks of these structures as the actual disease-causing agents. The building blocks of plaques are small clusters, or "oligomers" of Abeta peptides, which represent small pieces of a larger protein and are aggregated into densely packed, insoluble fibers in the plaques. Tangles arise by an analogous process and also comprise densely packed, insoluble fibers, but their building blocks are oligomers of the protein known as Tau. There are many structurally distinct versions of both Abeta and Tau, and the oligomers they form vary in size and shape. It follows naturally that development of procedures for early diagnosis and effective treatment of AD depend on learning exactly which oligomers of Abeta and Tau are most damaging.

This project builds on recent discoveries made in the labs of Dr. George Bloom at the University of Virginia and Dr. Charles Glabe of the University of California, Irvine. Bloom's lab identified a new class of exceptionally toxic Abeta oligomers that are self-propagating, like the infectious particles that cause mad cow disease, and they also have been studying how Abeta oligomers can seed formation of Tau oligomers. Concurrently, the Glabe lab developed a new and intriguing collection of antibodies that were made by immunizing rabbits with Abeta. Collectively, these antibodies stain a variety of abnormal structures in post-mortem brain tissue removed from the brains of AD patients and mice that are genetically engineered to develop AD. Most notable among these structures are "aggrodegrosomes," or "ADsomes," which were seen in the human tissue, had never been observed earlier and represent a brand new type of brain lesion associated with AD. Remarkably, several of the Glabe lab antibodies recognize multiple proteins in addition to Abeta. We will see if any of the Glabe lab antibodies recognize the Abeta or Tau oligomers that the Bloom lab is studying, and whether the antibodies can prevent formation of those oligomers. Completion of this work could lead eventually to new diagnostic and therapeutic tools for AD.

General Anesthetics and Alzheimer's Disease

Zhongcong Xie, M.D., Ph.D., Associate Professor of Anesthesia, Harvard Medical School, Director, Geriatric Anesthesia Research Unit, Massachusetts General Hospital

$100,000

The goal of this project is to test the hypothesis that desflurane is a safer anesthetic than isoflurane for AD patients in order to find safer anesthetics that won't worsen AD symptoms.

Age is one of the most important risk factors for Alzheimer's Disease (AD), with an incidence of 6.8 percent in people older than 65 years. One-third of all anesthetics are administered to people older than 65. Therefore, it is inevitable that many older patients who present to anesthesiologists will have AD. Just as the anesthesia specialty became intimately involved with the management of coronary artery disease (CAD), it is time for the anesthesiology specialty to develop guidelines for safer anesthesia care for AD patients. As the first step of these efforts, Dr. Zhongcong Xie and his fellow researchers will set out to identify anesthetics that will exacerbate the AD pathology, such as neuronal death, increases of Abeta levels, learning/memory impairment and synapse loss.

In their preliminary studies, they found the inhalation anesthetic isoflurane, but not desflurane, can induce cell death and increase Abeta levels in the cultured cells. In this application they will repeat these experiments in the mice having AD pathology (Aim #1) and in real human AD patients (Aim #3). In addition, they will study the up-stream mechanism of the anesthetics-induced cell death and increases in Abeta levels (Aim #2). The hypothesis they will test is *desflurane is a safer anesthetic than isoflurane for both AD patients and normal patients*. The anticipated results from the proposed studies will finally help them find safer anesthetics, which may not worsen the AD symptoms (e.g., learning/memory impairment). These efforts are consistent with the goals of Cure Alzheimer's Fund research grant program in identifying the risk factors of AD and in finding the prospects and strategies for the prevention of AD, which, ultimately, will help AD patients.

Understand the Role of ADAM10 in the Pathogenesis of Alzheimer's Disease After Head Trauma

Giuseppina Tesco, M.D., Ph.D., Assistant Professor of Neuroscience, Tufts University School of Medicine

$100,000

The goal of this project is to determine whether increased sAPPα levels are capable of reducing the production of neurotoxic Abeta following head trauma in order to reduce the risk of developing Alzheimer's disease following brain injury.

Traumatic brain injury (TBI) is the strongest environmental risk factor for the development of Alzheimer's disease (AD). AD is characterized by the accumulation and deposition of Abeta in the form of senile plaques. Abeta is a neurotoxic peptide (small protein) derived by the sequential cleavage of the amyloid precursor protein (APP) by beta and gamma secretase enzymes. In addition to the amyloidgenic processing of APP, which gives rise to the production of Abeta, an alternative non-amyloidgenic pathway exists in which APP is cleaved by α-secretase, which inhibits the production of the neurotoxic Abeta. In addition, cleavage of APP by α-secretase gives rise to the production of the secreted alpha cleaved APP fragment (sAPPα), which has been shown to have neuroprotective properties. A recent study has shown that when synthetic sAPPα is administered to mice following experimental head trauma, it appears to be protective, reducing neuronal death and axonal injury. If the neuroprotective properties of sAPPα following head trauma can be confirmed, this provides a potential therapeutic strategy for improving a patient's clinical outcome and reducing the potential for the development of AD following head trauma. More importantly, mutations in the gene ADAM10 have been associated with an increased risk of developing AD by reducing the production of sAPPα. This project aims to prove whether increased production of sAPPα is protective following experimental traumatic brain injury by using genetically engineered mice that overexpress the α-secretase gene (ADAM10) and whether reduced levels sAPPα in mice expressing ADAM10 AD-associated mutations results in a worse functional outcome following levels of head trauma. These mice will be bred with a well-characterized mouse model of AD to generate mice that express increased levels of sAPPα and also develop key characteristics of AD, such as amyloid plaques and impaired learning and memory. These mice will be subjected to experimental traumatic brain injury at 3 months of age (young adult mice). One group of mice will be analyzed shortly after injury to determine whether increased expression of α-secretase and hence sAPPα reduces the production of neurotoxic Aβ and improves learning and memory compared with control mice that have decreased levels of sAPPα. A second group of mice will be allowed to age following TBI and will be analyzed at 12 months of age (when they would normally develop symptoms of AD, such as amyloid plaques and impaired memory) to determine whether the increased levels of sAPPα are protective against AD by reducing the number and size of amyloid plaques and improving learning and memory compared with a control group of mice that have decreased levels of sAPPα. If they are able to prove that over-expression of α-secretase and hence increased sAPPα levels are capable of reducing the production of neurotoxic Aβ peptides and Aβ plaques and improving learning and memory in these mice following head trauma, this provides an important therapeutic strategy to pursue to reduce the risk of developing AD following brain injury.

Metallomic Mapping of the Aging Brain in Trg2576 Transgenic Mouse Model

Lee E. Goldstein, M.D., Ph.D., Associate Professor in Psychiatry, Neurology, Pathology & Laboratory Medicine, Ophthalmology, Biomedical Engineering, Electrical & Computer Engineering, Boston University School of Medicine, College of Engineering & Photonics Center

$100,000

The goal of this project is to perform the first high-resolution metallomic brain maps of key biometals (copper, zinc, iron) during normal brain aging and in Alzheimer's disease in order to develop disease-modifying treatments that target normalization of biometal distribution and metal-protein interactions in the brain.

In this project, Dr. Lee Goldstein's lab will deploy unique analytical resources at the Boston University Center for Biometals & Metallomics studying zinc and other key brain biometals and show how they play a critical role in normal brain function and, when altered, lead to the development of Alzheimer's disease. Recent clinical trials strongly support developing drugs targeting brain biometals and metal-protein interactions as a promising therapeutic strategy for this devastating neurodgenerative disease. However, little is known about the role and distribution of key biometals and essential micronutrients (including copper, zinc and iron) in brain aging and Alzheimer's disease. This information is critical for rational development of disease-modifying treatments that target normalization of biometal distribution and metal-protein interactions in the brain. In this project, Goldstein and his colleagues will deploy unique analytical resources at the Boston University Center for Biometals & Metallomics to perform the first high-resolution metallomic brain maps of key biometals (copper, zinc, iron) during normal brain aging and in Alzheimer's disease. These studies will be performed in a well-characterized Alzheimer's disease transgenic mouse model and validated in human brain specimens.

Modulation of Abeta Deposition by Cell-Specific Mechanisms

Sangram Sisodia, Ph.D.,
Professor of Neurosciences
Director, Center for Molecular Neurobiology, The University of Chicago

$100,000

The goal of this project is to determine which types of cells and factors in the brain influence excess Abeta deposition in Alzheimer's patients, using animal models of the disease.

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by impairments in memory and cognition, neuronal loss and deposition of Abeta peptides that are derived from larger amyloid precursor proteins (APP). Rare, familial, early-onset autosomal dominant forms of Alzheimer's disease (FAD) are caused by mutations in genes encoding APP, presenilin-1 (PS1) and presenilin-2 (PS2), polypeptides that are expressed ubiquitously in all central nervous system cell types and in peripheral organs. Transgenic animal (mouse) models for Alzheimer's recapitulate the histological, synaptic and memory deficits that are classically associated with the human disorder. The goal of this project is to employ genetic and molecular strategies to test for the effects of FAD mutations in specific types of cells in the brains of Alzheimer's animal models. The *hypothesis* is that deposition of Abeta in the brain can be influenced by various factors that are secreted not only by nerve cells, but other cells, e.g. glial cell in the neighborhood of the nerve cells. If they can identify which cell populations influence Abeta deposition, future studies will be aimed at identifying the exact factors that mediate Abeta deposition in animal models of Alzheimer's disease. These factors then could guide novel drug discovery efforts to treat and prevent Alzheimer's disease.

"I can't wait to go to work every day. I know I'm going to learn something new each time. That's what drives me—studying the science of the brain in order to stop this devastating disease. I'm grateful to Cure Alzheimer's Fund for the funding they've provided. This work requires a lot of people and resources."

—Sangram Sisodia , Ph.D.

Cellular and Animal Models of Amyloid Pathology in Early Alzheimer's Disease

Charles Glabe, Ph.D.,
Professor of Molecular Biology
and Biochemistry
University of California, Irvine

$100,000

The goal of this project is to evaluate the pathological significance of a new type of Abeta deposits in the brain (at the onset of Alzheimer's disease) in order to develop a novel mechanism for amyloid pathogenesis to help convince the FDA to approve and support early clinical trials.

Although the genetics of Alzheimer's disease (AD) implicates Abeta as a causal agent of pathology, the potential mechanisms of amyloid pathology are numerous, and there is no consensus about which mechanisms are critically important. The simple formulations of the "amyloid hypothesis" have a number of weaknesses, including the fact that amyloid plaques do not correlate well with disease and that cognitively normal individuals can have the same amount of plaque amyloid as patients with dementia. This has led to a reformulation of the amyloid hypothesis where other types of amyloid aggregates, such as soluble oligomers, are postulated to be the primary pathogenic species. If this is the case, there is considerable disagreement about which specific oligomers are toxic and why they are pathological. Dr. Charles Glabe's previous work established that Abeta can form a variety of structurally and immunologically different types of oligomers. In work that was partially funded by Cure Alzheimer's Fund, he and his team have recently produced a battery of monoclonal antibodies by immunizing rabbits with Abeta. The goal of this effort was to obtain as many different antibodies as possible with the hope they might reveal new types of amyloid aggregates in the brain. Most of these antibodies are conformation dependent and specifically recognize Abeta aggregates and not Abeta monomer or the amyloid precursor protein, APP. One of these antibodies, Mab78, identified a new type of Abeta pathology in an aged human and AD brain. Analysis of more than 20 different human brain samples suggests this new pathological accumulation of Abeta is a very early event in aging of AD pathogenesis and disappears as plaques accumulate in later stages of AD.

In order to experimentally evaluate this relationship and the pathological significance of this new type of Abeta deposits, researchers need a living system they can study over time and manipulate experimentally. The potential significance of this work may be the identification of the earliest type of amyloid pathology at the onset of the disease and the discovery of a novel mechanism for amyloid pathogenesis. This may provide a new target for therapeutic development and provide evidence for the early initiation of the disease before cognitive impairments. This evidence could be instrumental in convincing the FDA to approve and support early clinical trials, which may have a much better chance of preventing or curing the disease.

Molecular Tweezers—Novel Inhibitors of Amyloidogenic Proteins and Promising Drug Candidates for Alzheimer's Disease

Gal Bitan, Ph.D., Associate Professor of Neurology, David Geffen School of Medicine at UCLA

$100,000

The goal of this project is to plan expanded *in vivo* characterization of the efficacy of "molecular tweezers" toward development of disease-modifying therapy for AD and related diseases.

This project addresses Alzheimer's disease (AD) in the larger context of diseases caused by aberrant protein folding and self-assembly, which leads to formation of toxic oligomers and aggregates. In the last several years, Dr. Gal Bitan's lab has been studying novel compounds called "molecular tweezers," which modulate the aberrant assembly process using a previously unexplored "process-specific" mechanism. Their current lead compound effectively prevents formation of toxic aggregates of several disease-related proteins, including those involved in AD, Abeta and Tau. Initial *in vivo* experiments show peripheral administration of low doses of this compound lead to significant reduction of Abeta and Tau in the brain of transgenic mice.

In view of these promising data, they are poised to explore further the mechanism of action of the molecular tweezers and answer critical questions about their pharmacokinetics and safety.

Passive Tau Immunology*

Virginia M.-Y. Lee, Ph.D., M.B.A., The John H. Ware III Professor in Alzheimer's Research, Dept. of Pathology and Laboratory Medicine; Director, Center for Neurodegenerative Disease, University of Pennsylvania

*Extension from 2010

Neurofibrillary tangles (NFTs) are biomarkers for Alzheimer's disease and are the products of a breakdown in part of the structure of cells (Tau), leading to neural cell death. The goal of this project is to establish the first cellular system that develops authentic NFT-like Tau aggregates to provide mechanistic insights into NFT pathogenesis and a potential tool for identifying Tau-based therapeutics.

Over the past year, we have firmly established a cell-based model of neurofibrillary tangle formation. NFTs in Alzheimer's disease and related Tauopathies are comprised of insoluble hyperphosphorylated Tau protein, but the mechanisms underlying the conversion of highly soluble Tau into insoluble NFTs remain elusive. Dr. Lee has, with Cure Alzheimer's Fund funding, conducted a series of experiments demonstrating that introducing minute quantities of misfolded preformed Tau fibrils (Tau pffs) into Tau-expressing cells will rapidly recruit large amounts of soluble Tau into filamentous inclusions (resembling NFTs) with unprecedented efficiency. This suggests a "seeding" recruitment process as a highly plausible mechanism underlying NFT formation *in vivo*. Consistent with the emerging concept of prion-like transmissibility of disease-causing amyloidogenic proteins, we found that spontaneous uptake of Tau pffs into cells is likely mediated by endocytosis, suggesting a potential mechanism for the propagation of Tau lesions.

Abeta Oligomers and the Pathogenic Spread of Tau Aggregation: Implications for Alzheimer's Disease Mechanism and Treatment

(not pictured)

Dominic M. Walsh, Ph.D.,
Associate Professor, Center
for Neurologic Diseases

Dennis Selkoe, M.D.,
Coates Professor
of Neurologic Diseases,
Brigham and Women's Hospital

$125,000

The goal of this project is to conduct a series of experiments designed to elucidate the role of Abeta and exosomes (vesicles involved in "cell-to-cell signaling") in the transfer of Tau clumps from nerve cell to nerve cell.

Two proteins are known to be critically involved in Alzheimer's disease: Abeta and Tau. Both are prone to "self-associate," such that in the Alzheimer brain clumps of Abeta, known as amyloid plaques, are found in the spaces in between nerve cells and clumps of Tau, known as neurofibrillary tangles, are found within nerve cells. Until recently it was assumed that Abeta had to form plaques to be toxic; however, it is now clear that smaller, mobile clumps of Abeta (referred to as oligomers) are also damaging. When Dr. Walsh's lab isolated an oligomer from a human brain composed of just two Abeta molecules (referred to as Abeta dimer) and injected it into rats, it caused amnesia. Studies also show that lowering Tau levels can protect nerve cells against the toxic effects of Abeta oligomers. These data indicate that Abeta oligomers cause changes in Tau that harm brain cells. In parallel, evidence has emerged that clumps of Tau can be passed from one nerve cell to another. Indeed this process may explain why neurofibrillary tangles appear to spread through the brain as the disease progresses.

Thus understanding how Tau pathology is "transmitted" and, if Abeta is involved, should identify novel targets for therapeutic intervention. For instance, if Abeta is found to cause the release of Tau via small membranous vesicles known as exosomes, it should be possible to prevent either the release of Tau-containing exosomes or their uptake by unaffected recipient cells. If this is possible, drugs designed to prevent the spread of Tau pathology should halt further cognitive deterioration. Accordingly, this project will include a series of experiments designed to elucidate the role of Abeta and exosomes in the transfer of Tau clumps from nerve cell to nerve cell.

DRUG DISCOVERY

Understanding the Up-Regulation of Neuroserpin in the Alzheimer's Brain and Isolating a Potential Therapeutic Inhibitor of its Action: Continued

Nicholas W. Seeds, Ph.D., Professor of Cell Biology and Physiology, University of New Mexico School of Medicine

$50,000

The goal of this project is to determine if there is a strong correlation between Alzheimer's patients with high neuroserpin and high thyroid hormone levels (for both males and females).

Since our initial proposal in Spring 2010, several papers have appeared making the association between thyroid hormone levels and dementia. Thyroid hormones are associated with poorer cognition in mild cognitive impairment. (Dementia Geriatrics & Cognitive Disorders 30:205-11. Bensenor, IM et al. 2010, Subclinical hyperthyroidism and dementia. BMC Public Health 10:298.)

Interestingly, the latter publication only found a correlation among males. We have not assayed enough samples to see whether there is a gender difference with thyroid hormones and neuroserpin among Alzheimer's disease males. In contrast, there are publications relating hypothyroidism and Alzheimer's disease; however, this is not surprising since there are probably a number of insults that may trigger Alzheimer's disease in different individuals.

Still, if we can establish a strong correlation between those Alzheimer patients with high neuroserpin levels and high thyroid hormone levels, treatment of their hyperthyroidism may be a rapid and effective means to diminish neuroserpin levels. Thus, such treatment may delay the progression and extent of cognitive decline, plaque formation and neuronal death in those individuals.

DRUG DEVELOPMENT

Novel Soluble Gamma-Secretase Modulators for the Treatment of Alzheimer's Disease Identification of the Molecular Target of Potent Gamma-Secretase Modulators

Steven Wagner, Ph.D., Principal Investigator/Project Scientist, University of California, San Diego, Neurosciences

$150,000

The goal of this project is to identify a series of highly potent gamma-secretase modulators able to lower Abeta$_{42}$ and Abeta$_{40}$ production while concomitantly increasing the less toxic production of Abeta$_{38}$ without measurably affecting gamma-secretase-mediated processing of the Notch 1 receptor (which is very important in a variety of cellular processes for cell-to-cell communication).

Dr. Steven Wagner and his fellow researchers recently discovered two structurally related series of gamma-secretase modulators (AGSMs and SGSMs) with potencies more than a thousandfold superior to tarenflurbil and many of the NSAID-like carboxylic acid-containing GSMs. The first series of these aryl 2-aminothiazole GSMs (AGSMs) are small molecules that bind directly to gamma-secretase, decreasing Abeta$_{42}$ and Abeta$_{40}$ levels while concomitantly increasing Abeta$_{38}$ and Abeta$_{37}$ levels without affecting gamma-secretase-mediated enzymatic processing of other known substrates, such as Notch-1. >

(continued)

AGSMs were shown to be efficacious *in vivo* for lowering the levels of $Abeta_{42}$ and $Abeta_{40}$ in both the plasma and brain of APP transgenic mice. Chronic efficacy studies revealed that one AGSM (compound 4) dramatically attenuated AD-like pathology in the Tg2576 APP transgenic mouse model. In addition, unlike the GSIs, the AGSMs, by virtue of the fact they do not inhibit gamma-secretase, do not show Notch-related side effects that invariably appear in rodents and mice when treated chronically with GSIs (e.g., no evidence of intestinal goblet cell hyperplasia). However, the very poor aqueous solubility of these AGSMs (<0.1 micromolar at neutral pH) may significantly compromise their further preclinical development due to the difficulties in achieving the escalated supraefficacious exposures necessary for safety and toxicity studies required for advanced preclinical development with such poorly soluble compounds.

More recently, the researchers discovered a second series of highly potent GSMs that have significantly improved physicochemical properties (e.g., aqueous solubilities at neutral pH) compared to the previously described AGSM series. These two structurally related series, as may be expected, behave similarly with respect to their effects on APP processing in steady-state cell-based assays. Both GSM series are able to lower $Abeta_{42}$ and $Abeta_{40}$ production while concomitantly increasing $Abeta_{38}$ production without measurably affecting gamma-secretase-mediated processing of another known gamma-secretase substrate, namely, the Notch 1 receptor.

As a result of my CAF funding on gamma-secretase modulators, I received a five-year NIH-sponsored Blueprint Neurotherapeutics U01 award beginning in 2011.

—Steve Wagner, Ph.D.

The Blueprint Neurotherapeutics program was launched in 2011 as part of the National Institutes of Health's heightened emphasis on translational medicine. It enables award recipients access to 15 agency institutes and centers, and Steve Wagner's project was the perfect candidate. I'm very optimistic about the prospects for this series of drugs, given the very promising preliminary data generated in Steve's lab and my own.

—Rudy Tanzi, Ph.D.

Effect of Bexarotene on Abeta in APP Tg Mice Expressing ApoE3 and ApoE4

David M. Holtzman, M.D.,
Professor and Chairman,
Deptartment of Neurology,
Washington University School
of Medicine

$100,000

The goal of this project is to determine the effects of bexarotene on both Abeta and ApoE metabolism in the presence of human Abeta and human ApoE isoforms (any of two or more functionally similar proteins that have a similar but different amino acid sequence) because it is relevant to potential effects of similar drugs in humans.

A large amount of data strongly suggests the aggregation and deposition of the Abeta peptide in the brain is the initiating event in the pathological cascade known as Alzheimer's disease (AD). This event appears to initiate a series of events, including exacerbation of Tau-related pathology, direct damage to neurons and synapses and damage to blood vessels from cerebral amyloid angiopathy (CAA). ApoE is the strongest genetic risk factor for AD, and is an important component of amyloid plaques that plays a direct role in determining whether, when and how much Abeta deposits accumulate in the brain (for review, see (Kim et al., 2009a)). The laboratory of Gary Landreth has found that activation of the retinoid X receptor (RXR) pathway, by a drug called bexarotene, strongly alters the levels of several proteins linked to lipid metabolism in the brain, including ApoE, ABCA1 and others. His lab also has found that bexarotene has very strong effects in decreasing soluble Abeta levels over hours as well as clearing amyloid plaques over days.

This finding has important treatment implications for AD. The Landreth lab data shows the effects of bexarotene on Abeta require ApoE; however, the experiments were done in mice that express murine ApoE. While murine ApoE is homologous to human ApoE, it is not identical at the amino acid level and some properties are different. For example, in APP transgenic mice that develop Abeta deposition, murine ApoE is much more amyloidogenic than any of the human ApoE isoforms (Fagan et al., 2002; Holtzman et al., 2000; Holtzman et al., 1999). Thus, it is important to determine the effects on bexarotene on both Abeta and ApoE metabolism in the presence of human Abeta and human ApoE isoforms, as this is more relevant to potential effects of this or similar drugs in humans. In these experiments, they will utilize 5XFAD mice, which express human mutant APP that leads to Abeta deposition beginning at around 4 months of age. The 5X FAD mice express human ApoE3 and human ApoE4. They will assess the effects of bexarotene on interstitial fluid Abeta levels over hours as well as its effects on behavior and Abeta deposition and associated pathology over weeks and months.

Optimization of Novel ACAT Inhibitors for Alzheimer's Disease

Dora Kovacs, Ph.D., Associate Professor, Department of Neurology, Harvard Medical School, Massachusetts General Hospital

$150,000

The goal of this project is to test three novel ACAT inhibitors to determine whether they will prevent development of amyloid pathology and alter APP processing in AD mice in order to prevent and treat AD.

High cholesterol is associated with cardiovascular disease and also regulates the production of the toxic Abeta peptide in Alzheimer's disease (AD). Professor Kovacs previously found that drugs specifically targeting an enzyme of the cholesterol pathway, acyl-coenzyme A: cholesterol acyltransferase (ACAT) inhibitors reduce generation of the toxic Abeta peptides in cells and animal models of AD. Most importantly, she and her team recently used a potentially clinically relevant ACAT inhibitor, CI-1011, in aged mice after abundant amyloid deposition. CI-1011 has previously reached phase III clinical trials for prevention of atherosclerosis (but was later discontinued). In aged mice, CI-1011 dramatically decreased diffuse amyloid, which is most toxic for neuronal function (Huttunen, 2010).

Their data show that ACAT inhibition can reverse existing amyloid pathology, not just prevent novel pathology from forming. ACAT inhibitors are not yet marketed against cardiovascular disease. Dr. Kovacs and associates have recently designed and screened a library of 45 novel ACAT inhibitors, based on the structure of CI-1011. From this screen, they identified three novel ACAT inhibitors that reduce Abeta generation. They will optimize these three inhibitors by screening a novel library of compounds based on their structure and determine whether the novel inhibitors prevent development of amyloid pathology and alter APP processing in AD mice in absence of toxicity. These studies should result in one or more novel ACAT inhibitor with the potential to prevent and treat AD.

Cure Alzheimer's Fund funded my original study of ACAT inhibitors as drug candidates for *reversing* existing amyloid pathology in Alzheimer's disease. Thanks to their seed funding, I was able to generate the data needed to successfully obtain the financing needed to continue the development of these drugs with an RO1 grant from the NIH. Thank you, Cure Alzheimer's Fund.

—Dora Kovacs, Ph.D.

The Development of UDP Analogs for the Treatment of Alzheimer's Disease

Philip G. Haydon, Ph.D., Tufts University School of Medicine

$100,000

The goal of this project is to collaborate with a medicinal chemist to design, synthesize and test the efficacy of third-generation small molecules that will activate glial receptors. The most efficacious molecules then will be tested for their ability to reverse plaque burden in mouse models of Alzheimer's disease.

The brain is composed of two classes of cells, electrically active neurons and electrically silent glia. Over the past 20 years, Dr. Philip Haydon's lab has focused its research efforts on understanding the role of glia in brain function. As a consequence, the scientists made a breakthrough discovery that these often-neglected cells offer new therapeutic opportunities for the treatment of disorders of the brain. In particular, they demonstrated that the activation of a glial receptor leads to the clearance of amyloid plaques and restores learning and memory in Alzheimer's mouse models.

The goal of this project is to collaborate with a medicinal chemist to design, synthesize and test the efficacy of third-generation small molecules that will activate these glial receptors. The most efficacious molecules then will be tested for their ability to reverse plaque burden in mouse models of Alzheimer's disease. Success in this project will allow Dr. Haydon and associates to leverage private and federal funds to develop a small biotech spin-off focused on glial cells, and will prepare this study for IND-enabling studies as well as Phase I clinical trials of compounds developed in this project.

Mechanisms of Retinoid X Receptor-mediated Abeta clearance in Alzheimer's disease

Gary Landreth, Ph.D.,
Professor of Neurosciences,
School of Medicine, Case
Western Reserve University

David M. Holtzman, M.D.,
Professor and Chairman,
Deptartment of Neurology,
Washington University
School of Medicine

$100,000

The goal of this project is to investigate the mechanisms through which RXRs (retinoid x nuclear receptor) promote amyloid clearance from the brain.

There is now persuasive evidence that sporadic, late-onset forms of AD arise from impaired clearance of Abeta from the brain. Moreover, the elevated risk associated with possession of an ApoE4 allele is correlated with a reduced capacity to remove Abeta from the brain. These findings are consistent with the ability of ApoE to facilitate the proteolytic degradation of Abeta, and ApoE4 is less efficient in doing so. These data argue that elevation of ApoE levels in the brain would enhance the physiological mechanisms that aid Abeta clearance. ApoE expression and subsequent lipidation is transcriptionally regulated through the coordinated actions of the nuclear receptors PPARg and LXR. These ligand-activated receptors form obligate heterodimers with RXRs to create a functional transcription factor. Preliminary data demonstrating the oral administration of the RXR-specific agonist, bexarotene, results in the rapid, ApoE-dependent clearance of soluble Abeta in the interstitial fluid within hours. Moreover, bexarotene treatment provokes the loss of more than 60 percent of amyloid plaques from aged APP/PS1 mice within 72 hours, coincident with the appearance of amyloid-laden, phagocytic microglia. This latter effect is postulated to arise from the ability of the nuclear receptors to stimulate the conversion of microglia into M2 or "alternative activation" states associated with suppression of inflammatory gene expression and induction of genes promoting phagocytosis.

Thus, the effects of the activation of RXRs on AD pathology arise from two distinct transcriptional programs that operate in different cell types. The genetic targets of RXR action in the brain are largely unknown. This application represents a collaboration between the laboratories of Drs. David Holtzman, Rudolph Tanzi and Gary Landreth that is focused on investigating the mechanisms through which RXRs promote amyloid clearance from the brain.

Cure Alzheimer's FUND finances high-potential research, some of it in the "proof of concept" stage, which might not be funded initially by the National Institutes of Health or other, more conservative funders. This "pump priming" is proving increasingly successful as more of our early-stage grants are leveraged into more substantial and longer term funding.

Our approach works.

2011 Grant Recipients Include*:

- Can Zhang, M.D, Ph.D. (Tanzi lab) AGP Phase II Project, received NIH/ NIA K99 Grant
- Steven Wagner, Ph.D., GSM Project received NIH Blueprint Neurotherapeutics UO1 Award
- Sangram Sisodia, Ph.D., Abeta Deposition Project received NIH Grant
- Dora Kovacs, Ph.D., ACAT Inhibitor Project received NIH R01 Grant

*As reported by Cure Alzheimer's Fund-funded researchers

About Cure Alzheimer's Fund

The Founders

left to right: Henry F. McCance, Phyllis Rappaport, Jacqueline C. Morby, Jeffrey L. Morby

In late 2004, three families—the McCances, the Morbys and the Rappaports—came together to inject new life into finding a cure for Alzheimer's disease.

They were all frustrated with the pace of research. The drug pipeline was coming up dry. Research funding was risk averse and slow to respond to new discoveries. Even the most prominent Alzheimer's scientists were spending a *third* of their time filling out lengthy grant applications. Meanwhile, both the prevalence and costs of Alzheimer's were skyrocketing. Already, the disease afflicts 5 million Americans and costs $180 billion each year in the United States alone; those figures will nearly triple by 2050.

Leveraging their experience in venture capital and corporate start-ups, Henry McCance, Phyllis Rappaport, and Jacqui and Jeff Morby built a new venture-based Alzheimer's research fund designed to dramatically accelerate research, make bold bets and focus deeply on finding a cure.

In just seven years, with just $20 million spent, Cure Alzheimer's Fund has an unparalleled track record. Its Alzheimer's Genome Project (AGP)™ was the largest single disease scan of all time and was considered one of the "Top 10 Medical Breakthroughs in the world in 2008" by *Time* and CNN. Its funded research work has also been noted by *The Wall Street Journal*, NPR and the White House. And one of its star researchers, Steve Wagner from the University of California, San Diego, has just been chosen for a pilot project for the prestigious new "Blueprint" drug discovery program at the National Institutes of Health.

Cure Alzheimer's Fund focuses the best scientific minds in the industry. It does so scrupulously, and without any financial gain for its founders, donors or researchers. And since the founders cover **all** administrative costs, every dollar donated is guaranteed to go straight to funding new research.

Join us! **www.curealz.org**

“immeasurable pa and great skill”

LETTER FROM THE PRESIDENT

Dear Friends,

Thanks to thousands of supporters and the tireless efforts of researchers across the country, Cure Alzheimer’s Fund saw solid advances in 2011 to end Alzheimer’s disease. We thank all of those who have contributed their money, dedication and skill to this enterprise and assure you your efforts have made a huge difference.

That difference has come from 15 projects funded by Cure Alzheimer’s Fund for 16 researchers from 12 institutions in 2011, all profiled here in our 2011 Annual Report. The total grant support from Cure Alzheimer’s Fund for 2011 is $2,050,000. Overall, since our inception in the fall of 2004, Cure Alzheimer’s Fund has supported 47 projects for 35 researchers from 22 institutions, totaling $14,700,000.

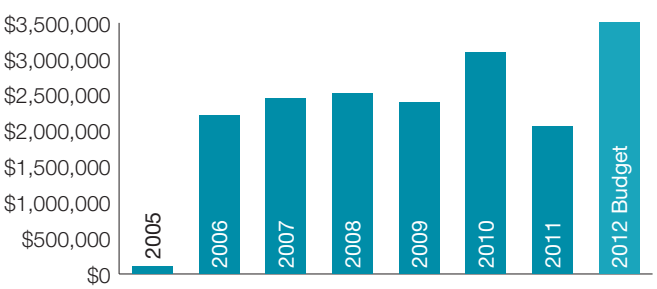
As only one index of success, Cure Alzheimer’s Fund researchers have published more than 100 peer-reviewed papers since inception in highly respected science journals.

To support this breakthrough research, the founders and more than 4,000 other donors, large and small, contributed $4,346,000 in 2011 and have given almost $25,000,000 since inception.

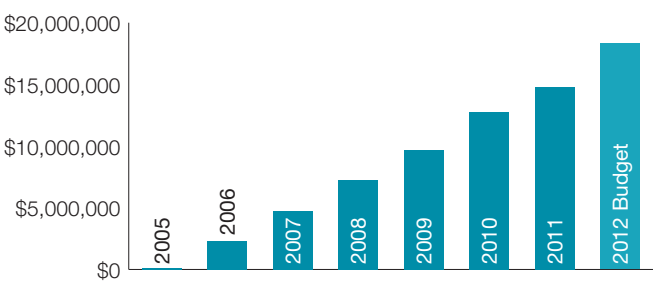
Our bank balance shows a larger than usual “profit” at the end of 2011. This resulted from several proposals submitted in late November or December 2011 not being funded until early 2012, thus reducing the Program Grants section of our expenses by almost $1 million. This money was awarded in the first quarter of 2012.

With the founders continuing their commitment to pay for all operating expenses for Cure Alzheimer’s Fund, we have invested in our organization in 2011 to generate more support for the challenging research agenda before us. We were most pleased to welcome Sally Rosenfield, former managing director of Hadassah in the Northeast Region, and Mike Curren, formerly senior vice president of the Massachusetts Hospital Association and a senior manager of the American Diabetes Association and March of Dimes, as senior vice presidents of Cure Alzheimer’s Fund in the summer of 2011. Both have served as executives in large, complex nonprofit organizations that depend on sophisticated fundraising to support their missions. Similarly, we are delighted to have Toni Carbone join us as office manager after 20 years as director of planning and administration for Harvard Business School’s external relations area.

Annual Research Grants



Cumulative Grant Totals



In addition to the funds raised for research in 2011and to strengthening our ability to increase that support, Cure Alzheimer's Fund also saw a marked advance in our outreach and awareness efforts. We published four quarterly reports, the 2010 Annual Report, the well-received Alzheimer's Disease: the Science (available through our website, www.curealz.org) and multiple support pieces.

Volunteer events profiled elsewhere in this 2011 Annual Report featured runs, walks, tennis tournaments, mountain climbing and other activities on behalf of Cure Alzheimer's Fund that brought additional and most welcomed funding to the research effort. Each of the people involved in conceiving and executing these events brought immeasurable passion and great skill to Cure Alzheimer's Fund in pursuit of our mission, and we are deeply grateful for their commitment.

All of this activity has combined to strengthen our ability to support the research that will lead to the eradication of Alzheimer's. Thanks to more than 4,000 donors, many of whom have been with us since inception, and others who are just joining, our ability to sustain our commitment to the mission continues to grow.

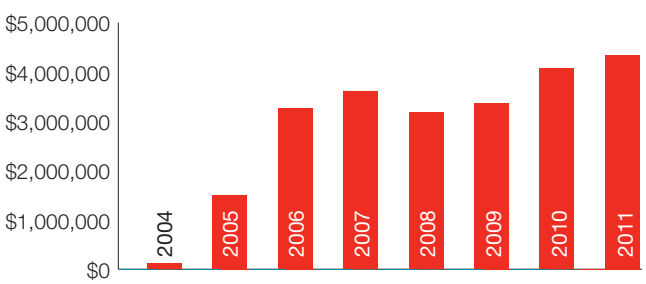
But the challenge is great. As the curve of the dollars we raise and the dollars we contribute to research raise appreciably, so does the curve of the number of those suffering from the disease. Together we have made great progress. We have heard from grateful researchers that without Cure Alzheimer's help, the search to end the disease undoubtedly would take longer. All of that, plus the knowledge that more of our family members, friends and loved ones fall victim to this disease every day, provides the incentive to work harder to provide the resources these world class researchers need to achieve their mission.

With the deepest gratitude to those who have helped us accelerate this progress in 2011, we thank you in advance for your continued support and welcome those new to Cure Alzheimer's Fund who share our commitment to ending Alzheimer's disease.

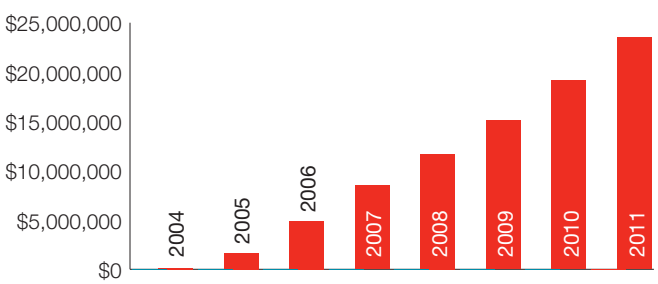
Sincerely,

Tim Armour
President and CEO

Annual Donation Trends



Cumulative Donation Totals



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.
- 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.
- 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 and audited financial statements online at its website, www.curealz.org. CAF has a history "clean" audits.

2011 Fundraising

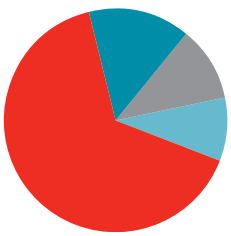
In 2011, Cure Alzheimer's Fund (CAF) received financial support from individuals, corporations, foundations and government in the amount of $4,346,016 from 2,100 donors in cash and in-kind revenues.

Source of Funds	$	%
Founders	1,641,475	37.8%
Non-Founder	2,335,236	53.8%
Foundations	300,000	6.9%
Government	0	0%
Corporations	30,979	0.7%
In-Kind Donations	32,575	0.7%
Bequests	5,751	0.1%
Total	**$4,346,016**	**100%**

Source of Funds

Use of Funds	$	%
Distribution to Research (grants)	$2,052,500	66%
Grant Support/Programs	473,427	15%
Management and General	330,292	10%
Fundraising	267,051	9%
Total Expenses	**$3,123,270**	**100%**

Source: IRS Form 2011 990, now posted on www.curealzfund.org.



Use of Funds

Financials (Year Ended Dec. 31, 2011, Rounded to the Nearest $1,000)

Statement of Financial Position

ASSETS	
Cash and cash equivalents	$4,198,098
Restricted cash, documentary project funds (temporarily restricted)	159,677
Contributions receivable, documentary project (temporarily restricted)	147,000
Contributions receivable and undeposited funds	45,900
Deposits—donor-advised funds	22,013
Fixed assets, net	26,520
Other assets	2,163
TOTAL ASSETS	$4,601,371
LIABILITIES AND NET ASSETS	
Liabilities	
Accounts payable and accrued expenses	$50,903
Net assets	
Unrestricted	4,243,791
Temporarily restricted, documentary project	306,677
TOTAL NET ASSETS	4,550,468
TOTAL LIABILITIES AND NET ASSETS	$4,601,371

Statement of Activities

REVENUE AND OTHER SUPPORT	
Contributions	$4,307,457
Donated services	35,075
Investment income	1,132
Realized gain (loss) on sale of stocks	3,952
Unrealized gain (loss) on donor-advised funds	(314)
Net assets released from restrictions, pledges collected	80,823
TOTAL REVENUE AND OTHER SUPPORT	4,426,993
EXPENDITURES	
Program expenses	
Grants distributed	2,052,500
Documentary program expenses	65,323
Other program expenses	408,104
Management and general	330,292
Fundraising	267,051
	3,123,270
(DECREASE) INCREASE IN UNRESTRICTED NET ASSETS	(1,304,855)
TEMPORARILY RESTRICTED NET ASSETS	
Documentary project contributions	372,000
Net assets released from restrictions	(80,823)
Net discount/amortizations of pledges	233
INCREASE IN TEMPORARILY RESTRICTED NET ASSETS	291,410
CHANGES IN NET ASSETS	1,596,265
NET ASSETS, beginning of year	2,954,203
NET ASSETS, end of year	$4,550,468

Adapted from the 2011 audited statements which, along with IRS Form 990, is available online at www.curealz.org

2011 Special Events

Second Annual Running 4 Answers Road Race

On April 2, founders Carolyn Mastrangelo and Barbara Geiger held the second annual Running 4 Answers road race/ fun run/fitness walk in Roseland and Essex Fells, N.J., to raise money toward finding a cure for Alzheimer's. The event was even more successful than last year and we thank Mastrangelo and Geiger for their tireless dedication to our cause. Check out www.curealzfund.org for more information.

'80s Night

For the second time, Robyn Kasper organized a "Back to the '80s Night" fundraiser in March to honor the memory of her mother, Rosemarie McDonough, her father, James Kelly, and her uncle, Albert Drinkwater—who all passed away last year from Alzheimer's disease. We greatly appreciate Robyn's dedication to Cure Alzheimer's Fund and thank her for her efforts.

Run for CAF

Brian Gray chose to run his first marathon—the Vermont City Marathon—alongside his dad as they honored the memory of his maternal grandmother, who suffered from Alzheimer's and passed away in 2003. We thank Brian for his commitment to our cause.

Alan Arnette

After two previous attempts to summit Mount Everest, the highest peak on Earth, Alan Arnette finally succeeded on May 26, 2011. Everest was the third stop on his 7 Summits Climb for Alzheimer's: Memories are Everything campaign—in which he climbed the highest peak on each continent to raise money to fight Alzheimer's. Summiting Everest is a significant milestone that Arnette now can look back on with a smile.

"It has been a wonderful experience that can be summarized in one word—humbling," says Arnette. "The summit was nice, but my climbs are all about the cause. I want to thank my followers for their support, and more importantly for their generous donations."

Hay Harbor Tennis Tournament

For the last five years, Diana Fiske has organized a round-robin tennis tournament for 44 women—ranging in age from their 30s to their 70s—at Fishers Island's Hay Harbor Club to raise money for Cure Alzheimer's Fund.

"I felt like we should have some sort of a charity tournament where we give to others," says Fiske. "And pretty much everyone I know knows a parent or friend who has been afflicted with Alzheimer's." Hay Harbor Club member Alison McCance had been diagnosed with Alzheimer's, and Fiske learned about CAF through Alison's husband, Henry McCance, co-founder of CAF, where "every single penny goes directly to research."

So five years ago Fiske rallied a group of women to support the cause, and every July they take to the courts to play. Every uttered "sorry" means $1 toward research, and expletives garner $10 each, in addition to the $25-per-person entry fee.

"Everyone is welcome to play," says Fiske. "You don't have to be a member of the club to participate."

At the start of the tournament Fiske reminds everyone why they are there—to raise money for Alzheimer's research. "I'm really proud of the fact that we've been going strong for five years and it's been a real team effort, from our pro Ramsey Hoehn donating his time to the club providing refreshments. It's a lot of fun, too," says Fiske.

"Over the years, the tournament has raised nearly $20,000 for CAF," says Tim Armour, president and CEO of CAF, "and we thank Diana for her tireless efforts on our behalf."

Cure Alzheimer's Fund Symposium

Thanks to a dynamic panel and more than 175 supporters, our Fall Symposium, *Taking Control of Alzheimer's Through Research*, was a huge success. Out-of-towners were able to watch it live on the Web. The symposium was moderated by Robert Bazell, chief science and health correspondent, NBC News, and included Drs. Rudy Tanzi and Rob Moir from Harvard Medical School/Massachusetts General Hospital and David Shenk, author of *The Forgetting*. An exhibition from ARTZ: Artists for Alzheimer's®, an initiative of the I'M STILL HERE Foundation, was on display.

Softball

On Oct. 16, members of both the Wellesley Police Department and the Wellesley/Weston Chabad Center joined forces for a charity softball game in Wellesley, Mass., CAF's headquarters. The event raised almost $500 for CAF. We thank them for their contribution and commitment to our cause.

Hair Salon

Barbara Canty sees hundreds of clients weekly in her salon, The Color Studio, in Wellesley, Mass. Five years ago, her father was diagnosed with Alzheimer's disease, and her experience caring for him made her realize that education and funding are critical to finding a cure.

Putting the professional and the personal together, Canty thought of Colin Walsh, vice president of L'Oréal, and Dr. Lew Losoncy, who co-wrote ***On***, an inspirational book that Canty says encouraged her to turn her life "on," when Alzheimer's patients are forced to live their lives in "off" mode. As a passionate advocate for finding a cure for Alzheimer's, Canty reached out to Walsh, who donated 100 copies of his book so Canty could sell them in her salon. Fellow hairdresser Karen Ricci, who also has a parent with Alzheimer's, joined Canty in this effort. We thank The Color Studio for its support.

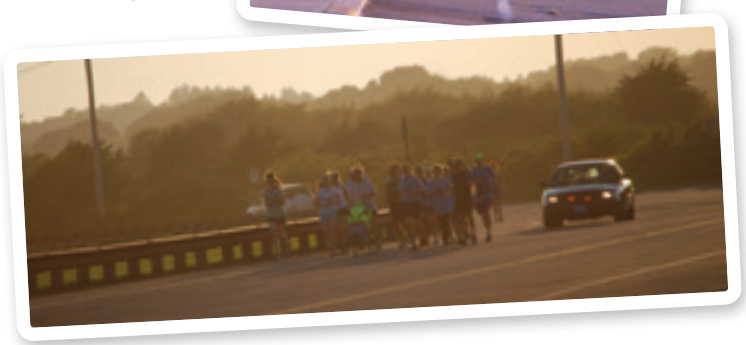
Glenn Caffery Finishes Run Across U.S.

Glenn Caffery completed his 3,200-mile run across the United States on Wednesday, Aug. 17, 2011, on the shores of the Atlantic in Westerly, R.I. Caffery, a University of Massachusetts Amherst professor and veteran distance runner, began his Cure Alzheimer's Run in Seaside, Ore., on May 19 to raise money and awareness for Alzheimer's disease research and treatment.

His father, Dick Caffery, passed away in 2002 after battling the disease for 13 years, and Caffery said his goal was to raise $20,000 to donate to finding a cure for the disease. Since starting his run, Caffery has raised nearly $25,000.

"It feels so good when someone makes a donation because then I know it's going directly toward curing this disease," said Caffery. "I am amazed by the generosity of the donations and so excited that people have been making them. Research is the solution."

"What's been essential is that so many people have brought so much meaning to this run beyond me because they really believe in doing something for Alzheimer's disease," Caffery said. "The folks who have experienced Alzheimer's in their family know how much this run means. They know what it feels like to be so powerless when someone in their family is suffering from it. My run was a way to bring people together to make a statement. It didn't feel like a solo effort."



Swimming for a Cure

On Oct. 22, Jessica Wellman swam her second annual 5K in 2½ hours to support Cure Alzheimer's Fund.

"My decision to swim for CAF is both professional and personal," Wellman says. She spends most of her workday caring for elderly patients, helping them and their caregivers find ways to best remember their medicines and cope with their diseases. "On the personal side," says Wellman, "my mother and her siblings visit my grandmother, who has Alzheimer's, weekly. They have put their lives on hold to care for someone who at times forgets their names, and nearly always forgets that they were there in the first place."

While it's heartbreaking for Wellman to hear the stories, she does not endure it daily, since she lives 400 miles away. But she still wanted to do something to help. She chose to swim for CAF because "its sole purpose is to fund ongoing research for the prevention and cure of Alzheimer's disease." Wellman exceeded her goal and raised $1,600 for CAF. We are very grateful to her for her support and congratulate her on her achievement.

Media and Recognition

New York Times Online Columnist Cites CAF Leadership—May 2011

Helping New Drugs out of Research's 'Valley of Death'

"Cure Alzheimer's Fund['s] … approach departs from the standard model employed by the National Institutes of Health and major medical foundations. These groups are intensely goal-directed and collaborative; they see the creation of new cures as a process that needs to be managed; and they bring a sense of urgency to the task."

USA Today Online Features Nobel Prize for Paul Greengard, Member of CAF's Scientific Advisory Board—May 2011

Charity news highlights: A week in review

NBC Interviews Dr. Sam Gandy—July 2011

Dr. Sam Gandy's article, titled "Prevention is Better than Cure," was featured in the journal *Nature*. NBC highlighted Dr. Gandy's perspective and research in an interview on the nightly news and on its website.

Nature Article Features Dr. Sam Gandy—August 2011

Alzheimer's therapy: a BACE in the hand?

CNN Video Features Dr. Rudy Tanzi—August 2011

Music clears mind for Alzheimer's researcher

Dana Foundation Website Profiles Dr. Rudy Tanzi—September 2011

The Arts of Neuroscientists: Rudolph Tanzi

WBUR Alzheimer's Series Features Cure Alzheimer's Fund—October 2011

Weeklong series

Fade to Darkness: The Age of Alzheimer's

Cure Alzheimer's Fund's Tim Armour and Henry McCance were both interviewed for the series and are featured in the section on Alzheimer's research funding.

Los Angeles Times Publishes Letter by Dr. Rudy Tanzi and George Vradenburg—November 2011

In response to the editorial, "Is Alzheimer's Inevitable?" published Nov. 21

"Currently, 5.4 million Americans suffer from Alzheimer's, a number that is expected to triple over the next decade. Of the 10 most deadly diseases, only Alzheimer's has no cure, treatment or other means of prevention. However, with the right leadership we can develop an aggressive plan of action to enhance research funding and stop this disease."

Capital Hill Briefing—November 2011

Presentation made to members of Congress and staff by Cure Alzheimer's Fund researchers Rudy Tanzi, Ph.D., David Holtzman, M.D., and Pfizer Inc.'s Michael D. Ehlers, M.D., Ph.D.

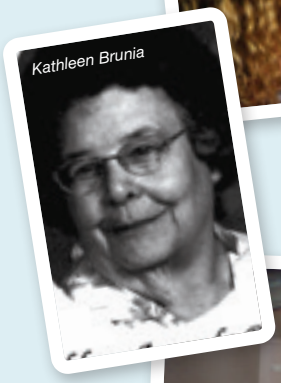
In Memoriam

Cure Alzheimer's Fund received gifts in honor or in memory of the following in 2011:

Gerald Adams
Charlotte Alexander
Frank Alfonso
Barbara Burr Allegaert
Joyce Allen
Eileen Altieri
Virginia Amoroso
Diana Anderson
Roland Arguin
John Asgeirsson
Harold Aster
Mary Ellen Auer
Alice Baird
Ann Ewing Baird
Jack Baker
Arvil Ball
Colin Bannister
Anne Barber
Suzanne Barnes
Rosalyn Baron
Joan Baughman
Maria Baylis
Pauline Bays
Mary Elizabeth Bebel
Simone Belanger
William Hardie Bender
Carol Benson
Robert Beveridge
Emilio Biagioni
Frances Bienert
Jack Black
Norman Blumeno
Eileen Bolger
Joan Borrie
Betty Jean Bowe
Abraham Braha
Edd Brand
Betty Brannen
Hector Brena
Virginia Brenner
Betty Brewer
Mary Brooks
Mary Louise Brown
Susan Talley Brown
Kathleen Brunia
Bernice Buczek
Anthony Cafarelli
Dick Caffery
Joan Calatayud
Sheila Callender
Elvira Cenci
Marion Chadwick
Mrs. Chaffins
Veronica Chris
Melvin Chrisco
Barbara Christy
Howard Chu
Patricia Holmes Clark
Adeline Cohen
Clare Cole
Megan Contreras
Arthur Cooper
Mark Corradini
Tinisha Cosme
Eloise Craige
Merle Daniels
Ron Daniels
Gloria Debow
Nadine DeLay
Billie Deneau
Matthew DiBenedetto
Anthony DiNocco
Norma Distler
Edna Dodge
Judy Duggan
J. Dunetz
Pete Eastman
John Egan
Galen Enochs
Bettyann Enright
Mollie Epstein
Betty Eresh
Marilyn Erwin
Helen Ethell
Mary Fahnestock
Bernadine Farnell
Bernie Farrington
Anne Faubert
Evelyn Faulkner
Mary Ann Ferguson
Stephen Fiorito
Woody Floyd
Valerie Fogoros
Steven Friedberg
James Fuller
Peg Furey
Ersilia Galli
Anne Gardner
Tozia George
Jo Lynn Gershon
Thelma Gevanter
John Richard Golden
Jack Gough
Brian Gray
Joanie Green
Iosif Gringauz
Roger Haag
Betty Hagelstein
Electra Haggis
Irene Haney
Gary Harris
Virginia Harris
Joy Hart
Jean Healy

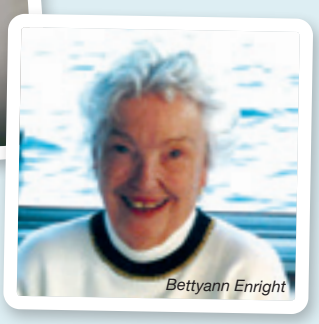

Jack Gough

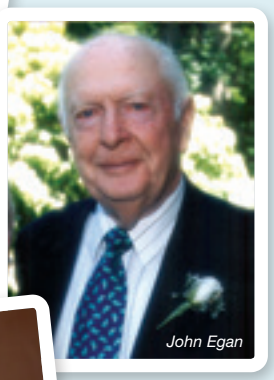

Joan Borrie

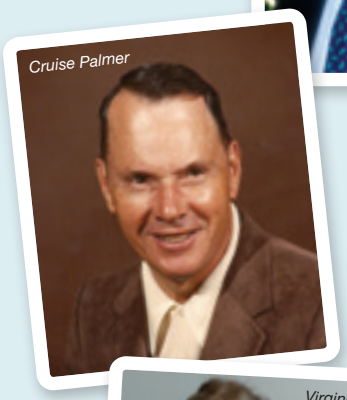

Kathleen Brunia


Jo Lynn Gershon


Anthony Cafarelli


Bettyann Enright





In Memoriam (continued)

Ellen Hebert
Marilyn Heise-Helmke
Miriam Herr
John Higley
Nicholas Van Hoose
James Hope
Don Hoven
George Howe
Bill and Marsha Hughes
Nancy Elizabeth Hughes
Ruthann Huston
Betty Jo Hutchinson
Sandra Hyllengren
Ed Ioccopetti
Jim Iverson
Erna Jansen
Charles Jenison
Catherine Jenkins
Fred Johnson
Gerald Johnson
Margaret Lynch Johnson
Elsie Johnston
Judi Jones
Veronica Jordan
Jean Juleff-Roy
Lillian Jutkiewicz
Frances Kamlay
Zenowiy Kassaraba
Monica Kayko
Elizabeth Keating
Elizabeth Keegan
Cora Mae Stickney Kinzer
Lloyd Knudson
Harley Kovall
Edith Krantz
Sharad Kulkarni
Trudy Kuzniacki
Grace Lass
Elizabeth Lee
Eunice Maybelle Lee
Patsy Lerfald
Alvin Levy
Frances Liptak
Veda Long
Rosemary Loop
Eutiquia Lopez
Marty Loquvam
Rita Loupe
Anne Lowe
Virgil Lynch
Jeanne Mache
Lori Mandeville
Donavan St. Marie
Patricia Markowski
Mary Marr
Natalie Maxwell
Esther Maze
A. Vernon McCormack
James McDonnell
Mary Elizabeth McGee
Grace McIntyre
Shirley Meaux
Angelina Meli
Areline Mercer
Vera Merrifield
Harriet Mesh
Marge Miller
Mae Monsen
Sharon Moore
Thomas Moore
Carma Morgan
Rodney Moseley
Shirley Mueller
Mervin Mull
Nancy Munson
Lois Murdock
Madeline Naser
Josefina Natera
David Navias
Florence Nick
Anne O'Connor
Joy O'Mahony
John O'Neal
Shirley O'Neal
Fanny Ortiz
Didi O'Toole
Joseph Ottaviani
Ann Ovington
Cruise Palmer
Lorraine Parker
Mike and Judy Parrish
R. Larry Paul
Maxine Pennick
Frances Perfetto
Ira Phillips
Bettilou Pierce
George W. Pierce
Lesley Leroy Pipkin
Richard Pittala
Judith Poretz
Rose and Sam Portnoy
Walter Prelle
Margaret Provenzano
Irving Rabb
Earl Reddick
Joanie Reutten
Malcolm Reventlow Jr.
Bea Rhodes
Robert Rhubart
Edwin Richards
Mrs. Charles Riott
Edna Ritter
Agnes Robertson
W.C. and Fannie Robison
Francisca Ortiz Rodriguez
Phil Roettinger
Catherine Rogers
Ralph and Melissa Rogers
Barbara Rooney
Lew Ross
Dorothy Phelps Rugg
June Ruggiero
Joan Sale
Nellie Salm
Leonardo Santini
Gladys Scheyer
Darrel Schiebel
Robert Schmitt
Elizabeth Schnieders
Dave and Dorothy Schroeder
Siv Schuch
Sarah Selders

Mack and Juanice Settle
Clarence Shapiro
Esther Shearouse
Richard Shenk
Barbara Sherratt
Jacqueline Henry Shirley
Ruth and Arnold Siegle
Madalyn Smith
Tresi Smyth
Doris Snow
Stan and Ann Southall
Charlie Spears
Ozell Spears
Melvin Sprowl
James Stacy
Jeannette Stavro
Lorraine Steiner
Bill Stillman
Walter Sturgis
Douglas Surgenor
Virginia Susarrey
John Suttinger

Bonnie Tarr
Robert Taub
Suzy Tauer
Edward Teltser
Joseph and Elizabeth Tevald
David Thomas
Earl Thomas
Marion Tiger
Leonard Tindell
Burton Tischer
Guy Tropeano
Carl Trovato
Robert Trunick
Jack Tucker
Garry Ustach
Lorraine Ustach
Dillard Vernon
Philip Verrier
Alphonse Vigliotti
William Wade
Norbert Wagner
Roberta Wagner

Ila Wallace
Julie Walterhoefer
Tom Warczak
Bernard Waterway
Ruth Wathen-Dunn
Janet Werkmeister
Angela White
David Wile
Percy Williams
Rose Williard
Grover Willis
Christina Boden Wilson
Gordon Wilson
Nancy Wilson
Frances Winter
Lee Wright
W.A. Wright
Martha Wysor
Kwok Wai Yee
June Young
Jenny Ziccardi
Lyle Zimmer

What better way to pay your respects to your loved one than to give a life-affirming gift in their memory to research into the cause of Alzheimer's disease?

If you would like to designate memorial gifts to come to Cure Alzheimer's Fund, please let us know whom to notify when we receive donations.

Whether gifts are made online, by mail or by phone, we will gratefully acknowledge each donation by notifying the person or family member designated (no gift amount is disclosed).

Photos sent to us are posted on our website under "In Memory."
www.curealz.org/who-we-remember

Each donation will honor your loved one and help sustain our research projects.
Thank you for designating charitable contributions to Cure Alzheimer's Fund!

If you have any questions about our In Memory program, please contact Laurel Lyle, Director–Fundraising Programs at llyle@curealz.org or 781-237-3800.

Why Give?

To end Alzheimer's, we believe it's imperative to focus on and fund research that is innovative, collaborative and results-oriented. Our funded work, upholding these values, has made tremendous progress in the search for an Alzheimer's cure. But there is more work to be done.

We invite you to join our ongoing effort to support the most promising, speed-driven, productive research to end Alzheimer's disease. We are targeting truly breakthrough work that is accelerating the efforts to reach a cure.

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

Or call: 877-CURE-ALZ (287-3259).

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 #52-239-6428.

CHARITY NAVIGATOR ★★★★ Four Star Charity

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GUIDESTAR

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Wellesley Hills, Mass. 02481
Telephone: 877-CURE-ALZ (287-3259)
Fax: 781-658-2399
www.curealz.org

Henry W. Oliver Building
535 Smithfield St., Suite 625
Pittsburgh, Pa. 15222
Telephone: 412-261-2785

2011

Research Consortium

***Rudolph E. Tanzi**, Ph.D., Chairman, Research Consortium, Cure Alzheimer's Fund; Harvard Medical School/ Massachusetts General Hospital*

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

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

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

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

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

***Robert Malinow**, M.D., Ph.D., University of California, San Diego*

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

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

***Robert Vassar**, Ph.D., Northwestern University*

***Steven L. Wagner**, Ph.D., University of California, San Diego*

***Berislav Zlokovic**, M.D., Ph.D., University of Rochester*

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**In Memory*

Full bios available online at www.curealz.org/about/people

Report design by Winking Fish

Cure Alzheimer's FUND

MISSION

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

www.curealz.org