

PROGRESS THROUGH RESEARCH



2012

Annual Report

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ON OUR COVER: Our cover highlights the DNA double helix and its nucleotides (bases). Cure Alzheimer’s Fund 2012 funded research includes the recording of these bases, called Whole Genome Sequencing. Research Consortium Chair Rudy Tanzi discusses the details of Whole Genomg Sequencing on page 6.



It's All About the Science

Message from the Chairman

Jeff Morby, Chairman and Co-founder, Cure Alzheimer's Fund

Introducing a New Era in the Field of Alzheimer's Research

Dear Friends,

On behalf of the Board of Directors and the Research Consortium, I want to thank all the donors, researchers and academic institutional partners supporting Cure Alzheimer's Fund research for your help in making 2012 such a successful science and fundraising year. We welcomed new board member Robert F. Greenhill and quickly benefited from his guidance and wisdom, and we thank outgoing founding board member John S. Lazo, Ph.D., for his years of scientific oversight and service on the board. To the newest members of our community, I welcome you.

2012 was a fantastic year for us in three respects:

1. We are entering into a new era in Alzheimer's research as a result of our \$5.4 million commitment to Massachusetts General Hospital to fund the first and largest Whole Genome Sequencing Project for Alzheimer's disease.
2. In 2012 we carried out a vast array of impactful research projects, all of which are moving us closer and closer to our goal of finding a preventative or cure for Alzheimer's disease.
3. The quality and scope of our research now is being recognized by an ever-larger group of supporters. This year we increased the number of our supporters by more than 1,300, to a total of 6,900. And we increased our funding receipt to \$6.7 million, an increase of 53 percent over last year's total of \$4.34 million. As always, the founders/directors pay all of the operating costs of the foundation so that 100 percent of donor funds go into research.

Message from the Chairman (continued)

Largest and Most Advanced Alzheimer's Database in the World

As many of you know, we have led the way in genomic analysis of Alzheimer's genes, in all cases using the newest technologies available. With the results in hand from Phases I and II of the Alzheimer's Genome Project™, we, through our funding of Whole Genome Sequencing at Mass General (AGP III), will have one of the largest and most comprehensive databases of Alzheimer's genes in the world. AGP III is important for three reasons:

- It greatly speeds up the process of understanding the “mechanism of action” of the genes we are studying. The AGP III will allow us to sequence the entire 3 billion base pairs of the human genome, something that never was possible to do. Prior to the AGP III, we only could look at select genes, one at a time, which misses most of the genome and is not very cost effective. Whole Genome Sequencing will greatly speed up our ability to understand the Alzheimer's genes and develop potential cures for forms of Alzheimer's disease caused by various gene defects.
- The AGP III also will facilitate our further understanding of Alzheimer's genes. With AGP III we will be able for the first time to understand the contribution of what is called “junk DNA” to disease processes. The “junk DNA” is formally called “intergenic” DNA, since it resides in between the genes. While genes represent only 2 to 3 percent of the DNA in the human genome, 97 percent of human DNA is “intergenic.” The recent release of data from the ENCODE Project (described later by Dr. Tanzi) now is allowing the scientific community to begin understanding the functions of the “intergenic” DNA in health and disease, including Alzheimer's disease. Thus, with the initiation of AGP III, we now are in a position to take the final genetic step in our understanding of Alzheimer's genes. As Dr. Tanzi will tell you, for many of the Alzheimer's genes, we have discovered it was impossible to identify the mechanisms of actions that caused the deleterious effects of specific Alzheimer's genes. The ENCODE Project revealed that intergenic DNA has an important regulatory function *vis-à-vis* genes. Therefore, with the new Whole Genome Sequencing methodologies and bioinformatic analyses, we will have a powerful vehicle for truly understanding the basic causes of the malfunctions of the various Alzheimer's genes we have discovered in the AGP.

- Finally, because intergenic DNA does perform regulatory functions, one can potentially eliminate certain functions within intergenic DNA and emphasize others, etc., in order to regulate or impact the underlying genes. Therefore the AGP III will lead us to further potential therapies for Alzheimer's disease.

Breakthrough Research Projects—Attacking AD from a Variety of Perspectives

Alzheimer's is thought to be caused or influenced by three related phenomena: excessive accumulation of beta-amyloid in the brain; neurofibrillary tangles made of the protein, Tau, which damage and kill neurons and spread rapidly through the brain; and finally, inflammation, which is induced by beta-amyloid and neurodegeneration associated with tangle formation. In the detailed descriptions that follow, you will read about a variety of exciting approaches we are taking to deal with these three problems. These approaches include:

- reducing the production of beta-amyloid;
- creating a mechanism that “crunches up” beta-amyloid and removes it from the brain;
- creating mechanisms that improve the clearance of beta-amyloid from the brain;
- stopping the formation of tangles;
- preventing the spread of tangles throughout the brain; and
- protecting the brain from excessive inflammation.

There are a great many potential ways of dealing with the above problems, as you will see from reading the individual reports that follow.

An Extremely Important Insight into a Fundamental Cause of Many Neurological Diseases

In the process of trying to understand the function of abeta amyloid in the brain, Rob Moir of Massachusetts General Hospital, supported by us, performed research that led to an extremely important insight, namely, that beta-amyloid is actually a component of our innate immune system and performs important protective functions within the brain.

So, beta-amyloid is good, and only bad when in excess, e.g., due to genetic mutations or lifestyle choices that cause too much beta-amyloid to remain in the brain. Excess beta-amyloid triggers tangle formation and nerve cell death followed by inflammation and more nerve cell death. These findings suggest that in new drug development programs, we must take into account that we do not want to wipe out beta-amyloid in the brain!

Perhaps equally interestingly is the fact that within the etiology of other neurological diseases, such as Parkinson's and diabetes, there are "amyloid equivalents" that perform the same protective functions as beta-amyloid. But these substances (such as Lewy bodies made of alpha-synuclein in the case of Parkinson's and amylin (pancreas) in the case of diabetes) also are involved in a major way in the causes of those diseases. We actually have done some research on Parkinson's and diabetes and have found the amyloid substances of both to be protective at normal levels of concentrations and harmful at higher levels—quite similar to that which occurs with Alzheimer's. Consequently, we think we may have discovered at least one universal cause of these neurological diseases (and perhaps others as well). Obviously, this insight again could result in a mantra for drug development—modulate, not wipe out.

Scientific Impact of Our Work

In the Our Research Influence section that begins on page 27, we have summarized the number of scientific papers we have financed that have appeared in major scientific journals. The list is extremely long and impressive in terms of the impact, quality and depth of the work. As an indication of the scientific impact of our work, we have identified within the literature more than 4,000 references made by other researchers to our work. We think this is a record relative to other research groups.

Sharing Information With Others: Alzgene.com

We continue to maintain the Alzgene database on the Internet, which is freely available to scientists who would like to interrogate that database. The database contains up-to-date information on all research projects undertaken anywhere in the world on Alzheimer's disease. Since its inception in 2006, there have been about 150,000 hits on the Alzgene website, which is an indication of the impact our research is having on the scientific community.

Leveraging Our Efforts: The Multiplier Effect of Our Funding

One of our strategies at the very outset of the formation of Cure Alzheimer's Fund was to attempt to leverage our own resources with the resources of others. The basic idea is that if we can do that, we will have greater chances of finding a cure as quickly as possible. Over the last eight years we have been able to generate more than \$23 million in additional funding for Alzheimer's-related efforts as a consequence of our involvement. This number incorporates co-funding projects with others, as well as research projects initially funded by us and taken over by others either as co-funders or absolute funders. One example is the gamma-secretase project that will be discussed in the pages to follow. In that particular instance, we carried out all the basic research for the gamma-secretase modulator, but the results were so spectacular the National Institutes of Health (NIH) basically worked with us to significantly increase the funding of the project by putting millions of dollars into it and by committing substantial scientific resources to it. We continue to work on the mechanisms of action related to the project, but NIH is now providing the bulk of the funding.

To Conclude, a Great Year

We at the Cure Alzheimer's Fund have had a wonderful year both in terms of our science and our funding. Now, with the Whole Genome Sequencing project under way, we are moving the science of Alzheimer's into a totally new technological arena, one that should result in the acceleration of our quest to find a cure.

Thank you very much for your generous support.

Best wishes,

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

It's All About the Research

Message from the Research Consortium Chairman

Rudolph E. Tanzi, Ph.D.
Chairman, Research Consortium, Cure Alzheimer's Fund



Dear Cure Alzheimer's Fund Supporters,

On behalf of the Cure Alzheimer's Fund Research Consortium, it is my pleasure to share with you some of our key research findings in 2012. Last year was a stellar one for Cure Alzheimer's Fund and arguably unprecedented in terms of the quality and quantity of research progress made. It seems like every new year brings us a treasure trove of valuable findings thanks to your support, but this year was particularly special. Below, I summarize some of the highlights of the achievements in Alzheimer's research made possible by Cure Alzheimer's Fund in 2012.

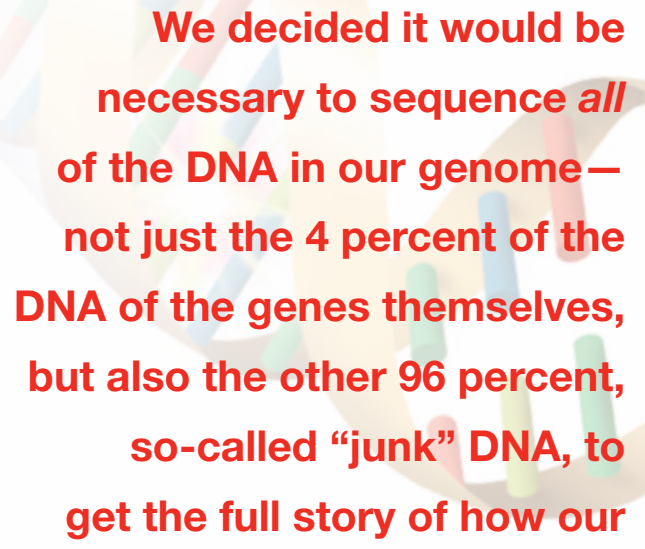
1. Alzheimer's Genome Project™

The goal of the Alzheimer's Genome Project is to elucidate all of the genetic factors that influence risk for Alzheimer's disease. We then use this information to guide the development of novel therapies while also being able to more reliably predict lifetime risk for Alzheimer's. The completion of Phase I of the Alzheimer's Genome Project (AGP) in 2008 informed us as to "where," in the human genome, there lie stretches of DNA that influence risk for Alzheimer's disease (either positively or negatively). The study describing several new Alzheimer's risk genes was named a Top Ten Medical Breakthrough of 2008 by *TIME* magazine. In Phase I, we focused only on the DNA in our genome that makes up the actual genes. But genes make up only 4 percent of our genome, and as you will see later

in this letter, we now have found it necessary to tackle the other 96 percent of the DNA in the genome, since it recently was shown to regulate the activity of our genes.

Beginning in 2009, we embarked on Phase II of the AGP, functional studies asking how the new Alzheimer's genes identified in Phase I of the AGP impact risk for Alzheimer's. For example, we asked how novel Alzheimer's genes impact beta-amyloid (plaque) deposition in both cell-based and disease animal models. Three Alzheimer's genes that we have focused on using Alzheimer's disease transgenic mouse models are CD33, ATXN1 and ADAM10. All of these were found to increase the accumulation of beta-amyloid in the brain owing to specific mutations and/or lack of activity. Phase II also has targeted certain Alzheimer's disease candidate genes for "DNA sequencing," with the goal of identifying DNA variants that alter the function of the genes, directly affecting one's risk for Alzheimer's.

To understand the concept of "DNA sequencing," we need to first review some basic genetic concepts. Approximately 35,000 genes provide the blueprints for the roughly 350,000 proteins made in the human body. Genes are chemically made of deoxyribose nucleic acid (DNA), first described by Jim Watson and Francis Crick in the late 1950s. The structure of DNA resembles a double helix consisting of chemicals called



We decided it would be necessary to sequence *all* of the DNA in our genome—not just the 4 percent of the DNA of the genes themselves, but also the other 96 percent, so-called “junk” DNA, to get the full story of how our genome influences risk for Alzheimer’s disease.

nucleotides (bases). The bases are named by letters: A (red), T (green), C (blue) and G (yellow). A on one strand always binds to T on the other, and C always to G. These are called “base pairs.” The human genome consists of 3 billion of these base pairs of DNA. This sequential determination of the base pairs is called “sequencing” of the DNA.

On average, the DNA in two different individuals contains about 3 million variations in the DNA sequence. Some variants have no effect on disease, while others may increase risk or cause the disease, and still others may protect against disease. When a DNA variant directly impacts one’s risk for disease, it is called a “functional DNA variant.” In Phase II of the AGP, we have been sequencing the DNA of the specific genes shown in Phase I to be associated with Alzheimer’s risk, with the goal of identifying functional DNA variants responsible for risk. Identifying these functional variants is essential for accelerating our understanding of “how” a particular Alzheimer’s-associated gene directly increases or decreases risk for Alzheimer’s disease at the biological level. This is critical information needed for translating the genetic information into ideas for novel therapies and to someday carry out reliable genetic testing for one’s lifetime risk for Alzheimer’s, so that early prevention measures can be taken once effective disease-modifying drugs are available.

Surprisingly, as we sequenced the DNA of the new Alzheimer’s genes found in Phase I of the AGP, we found very few obvious functional DNA variants that could explain how the genes influence risk. As an exception, we found rare risk-enhancing mutations in the gene ADAM10 and protective mutations in the gene CD33 (see more below). But for most of the genes that had been confirmed by us (and others) to be *bona fide* novel Alzheimer’s disease genes, we could not find the functional variants to explain how they influenced risk for Alzheimer’s!

At this point, we decided it would be necessary to sequence *all* of the DNA in our genome—not just the 4 percent of the DNA of the genes themselves, but also the other 96 percent, so-called “junk” DNA, to get the full story of how our genome influences risk for Alzheimer’s disease. Meanwhile, the eagerly awaited and groundbreaking “ENCODE” project results were published in late 2012, validating the new direction we already had decided on—once again, we were ahead of the curve! ENCODE showed that, indeed, most of the action when it comes to inherited disease risk resides in

“junk” DNA (more formally known as “intergenic” DNA) and not necessarily in the DNA of the genes! This intergenic DNA appears to affect the gene activity across long distances in the genome.

We’ve now formally launched Phase III of the AGP, known as “Whole Genome Sequencing,” in which we will sequence the entire genomes of the subjects in our Alzheimer’s families to search for functional DNA variants influencing risk for Alzheimer’s. It is the largest project of its type focusing on families. It’s also amazingly cost-effective: While it cost billions of dollars to obtain the first whole genome sequence of a human being at the turn of the century, we now can do so for \$2,000 per human genome. Most importantly, Whole Genome Sequencing ensures we will not miss the bulk of functional DNA variants that most likely reside in the intergenic DNA between the genes. (See page 6, “What is Whole Genome Sequencing (WGS)?”)

So very exciting days lie ahead for the AGP. Whole Genome Sequencing is the final stop, the “Holy Grail,” in this journey to elucidate the entire genetic profile of Alzheimer’s disease risk in terms of both susceptibility and protection. We look most forward to analyzing the new data in 2013! Meanwhile, in other aspects of the AGP, we are submitting a series of research reports describing the other groundbreaking discoveries

Message from the Research Consortium Chairman (continued)

made in Phase I and II of the AGP. These include papers presenting (1) The analyses of the ADAM10 mutations in animal models of Alzheimer's disease; (2) Elucidation of 100 or so genes (or stretches of junk DNA) found to influence risk for Alzheimer's disease based on our genomewide association studies (GWAS); and (3) Large structural aberrations in the human genome (copy number variants), including large deletions, duplications and rearrangement of DNA that we found to directly cause Alzheimer's disease in subsets of our Alzheimer's families. While these results are all very exciting, the best is yet to come with Whole Genome Sequencing. And we are ready!

2. CD33: Novel Alzheimer's Disease Gene

One of the new Alzheimer's disease genes we reported in our 2008 AGP study that was named a top breakthrough by *TIME* magazine is called "CD33." At the time, all that was known about CD33 was that this gene was involved in the brain's innate immune system. This finding helped inspire parallel studies demonstrating a role for the amyloid beta protein (Abeta) as an anti-microbial peptide, fighting infection in the brain. (See 5. Understanding Alzheimer's Pathology, page 8.) In line with the Cure Alzheimer's Fund Roadmap, we reached out to investigators who had been studying CD33, (but not as

What is Whole Genome Sequencing (WGS)?

Rudolph Tanzi, Ph.D., Chairman, Research Consortium

Approximately 35,000 genes provide the blueprints for the roughly 350,000 proteins made in the human body. Genes are chemically made of deoxyribose nucleic acid (DNA), first described by Jim Watson and Francis Crick in the late 1950s. DNA is packaged into 46 different chromosomes, such as the X-shaped one on page 7. Chromosomes are found in the nucleus at the center of the cell—in this case, a nerve cell. There are two pairs of 23 chromosomes, 1–22 and either X or Y. Each parent gives you a set, making a total of 46 per cell.

The structure of DNA resembles a double helix consisting of chemicals called nucleotides (bases). The bases are named by letters: A (red), T (green), C (blue) and G (yellow). A on one strand always binds to T on the other, and C always to G. These are called "base pairs." The human genome consists of 3 billion of these base pairs of DNA. Whole Genome Sequencing involves determining all 3 billion base pairs of DNA in a subject's human genome as they are laid out, in order, across the 46 chromosomes. This sequential determination of the base pairs is called "sequencing" of the DNA.

Just picture recording the order of 3 billion red, yellow, green and blue beads on a string to get an idea of the process. Roughly 4 percent of the DNA in humans is in genes. Most, but not all, genes provide the blueprint used by cells of the body to make a protein, which is itself composed of a chain of 20 different amino acids arranged in different combinations, which in a given protein may number in the thousands. To make proteins, DNA is used to create RNA. Proteins then are assembled in RNA-based factories called "ribosomes," which read the "genetic code" originally contained within the DNA for a particular gene in the nucleus of a cell. The RNA in the ribosome then guides the assembly of the protein from amino acids. The protein later is processed in various parts of the cell to achieve its final configuration. Some proteins serve as the building blocks of the body, while others carry out specific functions.

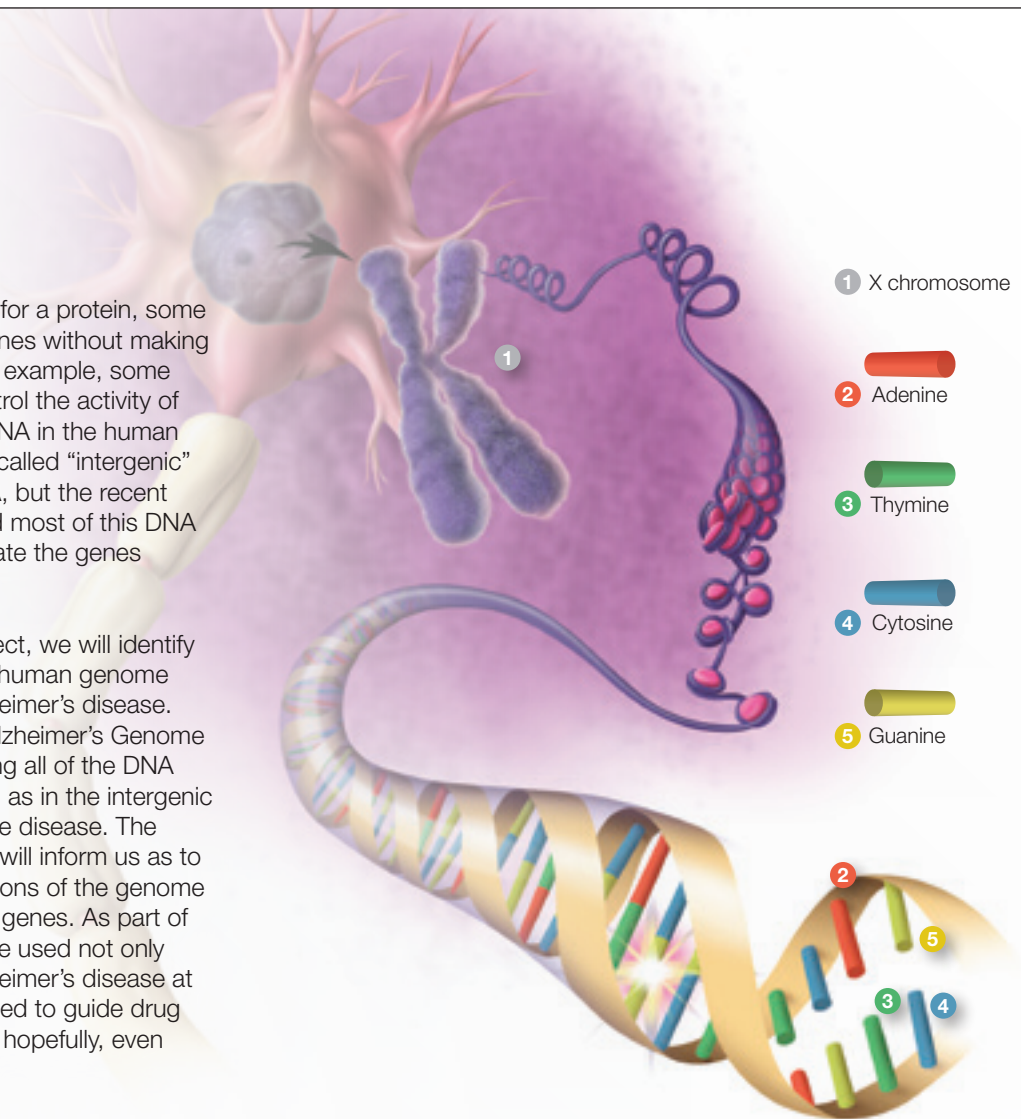
part of Alzheimer’s research), and attained their valuable advice and expertise on how to investigate this gene’s potential role in Alzheimer’s pathology. After four years of intensive study, culminating this past year, we found a functional variant in the CD33 gene that protects against Alzheimer’s disease. Based on what we have learned from this functional variant in CD33, we already have begun the process of translating these findings into a novel Alzheimer’s disease therapeutic program. We think a CD33-targeted drug could be a potential blockbuster for Alzheimer’s disease by preventing nerve cell death caused by inflammation in the brain as part of Alzheimer’s pathology.

3. Gamma-Secretase Modulators (GSM)

Several years ago, Cure Alzheimer’s Fund provided the initial seed funding to develop a novel class of drug (GSM) that would hopefully lower beta-amyloid levels safely, avoiding the adverse side effects of so-called gamma-secretase inhibitors (GSI). The funding was provided to Dr. Steve Wagner at the University of California, San Diego (UCSD) and the studies were carried out collaboratively with my laboratory, which had the initial drugs synthesized and tested.

While most genes provide the template for a protein, some serve to regulate the activity of other genes without making proteins, e.g., by only making RNA. For example, some genes make “microRNAs” that can control the activity of other genes. About 96 percent of the DNA in the human genome sits between the genes and is called “intergenic” DNA. This used to be called “junk” DNA, but the recent international “ENCODE” project showed most of this DNA is not junk at all, since it serves to regulate the genes themselves.

In our Whole Genome Sequencing project, we will identify functional DNA variants throughout the human genome that are inherited as risk factors for Alzheimer’s disease. This study constitutes Phase III of the Alzheimer’s Genome Project™, and will be aimed at identifying all of the DNA variants in the genome (in genes as well as in the intergenic regions) that directly influence risk for the disease. The Whole Genome Sequencing study also will inform us as to how DNA variants in the intergenic portions of the genome regulate the activities of the Alzheimer’s genes. As part of our road map, these findings then will be used not only to better understand the causes of Alzheimer’s disease at the genetic level, but also be implemented to guide drug discovery efforts to slow down, stop or, hopefully, even reverse Alzheimer’s disease pathology.



Message from the Research Consortium Chairman (continued)

As a result of that seed funding, we generated ample positive data, enabling Dr. Wagner to obtain a highly prestigious NIH Neurotherapeutics Blueprint grant to develop the GSMs and advance them toward clinical trials in Alzheimer's disease patients. This drug program is directed by an NIH Lead Development Team (LDT), on which Dr. Wagner and I serve. The LDT oversees the development of the drug with a host of NIH-supported consultants, who have a strong background in pharmaceutical drug development. The NIH provides funds for the drugs to be tested for toxicity, brain penetration, half-life, etc., all of which are needed to advance them to human clinical trials. To date, the NIH has provided millions of dollars to develop these drugs, a tremendous amount of leverage on the initial investment of Cure Alzheimer's Fund! After synthesizing and testing hundreds of drugs in this class, we recently have identified a subseries of the GSMs with very high potency and a safety profile that predicts we could have a clinical candidate nominated for human trials over the next year or so.

We envision using such a drug to both treat acute Alzheimer's and to protect against it—much like statins like Lipitor are now used to protect against heart disease. Our hope is to obtain NIH funding to test the best GSM in this class in Phase I and II clinical trials at Massachusetts General Hospital (MGH) and the University of California, San Diego (UCSD). If the trials are successful, a large pharmaceutical partner would be courted for larger Phase III clinical trials. In the meantime, in order to pave the way for FDA approval of Phase I trials, we also will need data regarding the precise molecular mechanism action by which these GSMs safely and effectively lower Abeta production. For this purpose, Cure Alzheimer's Fund continues to support such studies in the laboratory of Dr. Steve Wagner at UCSD, in close collaboration with our laboratory at MGH.

4. Other Alzheimer's Disease Therapies

Over the past year, Cure Alzheimer's Fund has supported a number of exciting projects testing a variety of promising therapies aimed at halting or reversing disease progress. There was much excitement about a drug called bexarotene based on a study from the Cleveland Clinic in an Alzheimer's mouse model. Members of our Research Consortium, including Drs. David Holtzman (Washington University, St. Louis), Sam Sisodia (University of Chicago) and Robert Vassar (Northwestern University), in collaboration with my laboratory, have attempted to replicate those studies. So far, our studies do not strongly support a role for bexarotene in treating Alzheimer's. However, our investigation is ongoing.

An important role for the Cure Alzheimer's Fund Research Consortium is to provide critical information such as this to the AD research community so that time, effort and funding are targeted only toward the most promising research endeavors.

Cure Alzheimer's Fund also has continued to support the development of cholesterol-targeted drugs for Alzheimer's in the laboratory of Dr. Dora Kovacs at MGH. Dr. Kovacs has been developing drugs known as "ACAT inhibitors," which have been shown to dramatically reduce Abeta levels in Alzheimer's animal models. Dr. Kovacs is now testing novel ACAT inhibitors being designed and synthesized with Cure Alzheimer's Fund support. Dr. Philip Haydon (Tufts University; UDP analogs) and Dr. Gal Bitan (University of California, Los Angeles; "molecular tweezers") also are developing compounds aimed at lowering Abeta accumulation in the brain. The UDP analogs (Haydon) are intended to promote clearance of beta-amyloid in the brain via microglial cells, while the "molecular tweezers" (Bitan) are targeted at preventing the aggregation of the Abeta protein into deposits of beta-amyloid in the brain.

Cure Alzheimer's Fund has continued to fund projects aimed at preventing tangle formation. Beta-amyloid deposits in the brain must induce tangle formation inside nerve cells to drive their dysfunction and death. Working with Research Consortium member Dr. Charles Glabe (University of California, Irvine), Dr. George Bloom (University of Virginia) discovered specific forms of aggregated Abeta (oligomers) that induce the formation of tangles. Over the last five years, it has become increasingly clear that tangles, made up of an aggregated form of the protein called "Tau," can "spread" from dying, tangle-ridden nerve cells to healthy ones, leading to serial nerve cell death in the brains of Alzheimer's patients. Thus, Cure Alzheimer's Fund also has been funding the development of therapies targeted at stopping the formation and spread of tangles as part of research being carried out in the laboratories of Drs. Dennis Selkoe and Dominic Walsh at Harvard Medical School, and Dr. Virginia Lee at the University of Pennsylvania.

5. Understanding Alzheimer's Pathology

Cure Alzheimer's Fund also continues to support state-of-the-art research aimed at furthering our understanding of the pathological process in Alzheimer's disease. Several years ago Dr. Robert Moir (MGH) was supported by Cure Alzheimer's Fund to follow up his groundbreaking studies showing Abeta may help protect the brain from infection in its capacity as an anti-microbial peptide. More recently, Dr. Moir has been

investigating (1) How Abeta neutralizes bacterial/fungal infections; and (2) Whether other amyloids, e.g., in diabetes and Parkinson's disease, carry out similar roles. These studies are testing the basic premise that diseases characterized by amyloids of various types may be initiated by certain microbial pathogens, which trigger the formation of amyloids as anti-microbial peptides. In 2012, Dr. Moir showed that Abeta counters bacterial and fungal (yeast) infections by forming a cage (nano-net) that traps the pathogen and suffocates it from obtaining nutrients. He also definitively showed that the amyloid of the pancreas in diabetes, amylin, is a potent anti-microbial peptide. The anti-microbial capabilities of both Alzheimer's-related beta-amyloid and diabetes-related amylin were shown in cell-based experiments and in *Drosophila* (fruit fly) disease models. Potentially protective roles of beta-amyloid also are being investigated in mice with brain infections, e.g., meningitis.

In collaboration with Scientific Advisory Board member Dr. Paul Greengard (Nobel Laureate, The Rockefeller University), we have shown that some of the key genes active in vulnerable vs. resistant nerve cell populations of the brain in Alzheimer's disease patients exhibit strong association with risk for Alzheimer's disease in the genomic studies of our AGP. These genes are being studied further in collaboration with Dr. Greengard's laboratory. In other studies addressing vulnerable vs. resistant brain regions in Alzheimer's disease, Dr. Lee Goldstein (Boston University) has carried out state-of-the-art imaging studies in Alzheimer's disease mouse models to determine the role of reactive metals such as copper and iron in driving Alzheimer's disease pathology. In yet other studies of vulnerable vs. resistant nerve cell populations of the brain in Alzheimer's disease, Dr. Sam Sisodia has been collaborating with our group to determine exactly which nerve cell and glial cell populations of the brain contribute to neurodegenerative processes in Alzheimer's disease.

In studies aimed at investigating the propagation of Alzheimer's disease pathology in the brain, Dr. Giuseppina Tesco (Tufts University) and Dr. Zhongcong Xie (MGH) have been funded by Cure Alzheimer's Fund to explore how traumatic brain injury and surgical wound-induced brain inflammation contribute to Alzheimer's pathology, respectively. Drs. Doo Yeon Kim (MGH), Sehoon Choi (MGH) and Marc Tessier-Lavigne (The Rockefeller University) were supported to study how the generation of new nerve cells in the brain (neurogenesis) and injection of neural stem cells into the brain can slow down or prevent Alzheimer's pathology. Skin cells also are being used to create neural stem cells from genetically defined Alzheimer's disease patients.

These are injected in the brains of mice to study the properties of these Alzheimer's disease patient-derived "neurons" in a natural environment in the brain.

Research Consortium member Dr. Bob Vassar has been funded to collaborate with Dr. Gopal Thinakaran (University of Chicago) to study the mechanism of Abeta production in synapses, focusing on the enzyme BACE1, which serves as the beta-secretase needed for the first step in Abeta generation. This study is centered on how beta-secretase is controlled by the EHD genes, which also have been shown to be associated with AD in the AGP. Finally, Cure Alzheimer's Fund has supported follow-up studies of two other novel AD candidate genes discovered in the AGP. Dr. Betza Zlokovic (University of Southern California) is studying how the novel AD gene PICALM affects the clearance of Abeta out of the brain into the blood, while Dr. Cindy Lemere (Harvard Medical School) is studying how the novel AD gene CR1 governs the onset of inflammation in Alzheimer's brain pathology. Both genes, PICALM and CR1, represent excellent drug targets for the treatment and prevention of Alzheimer's disease.

In conclusion, 2012 truly has been a banner year for research efforts supported by Cure Alzheimer's Fund, ranging from gene discovery to translation research fostering our understanding of Alzheimer's disease pathology to novel drug development. On behalf of the Research Consortium and all scientists being supported by Cure Alzheimer's Fund, we thank you for your very generous and continuous support of this cutting-edge research aimed at ending this devastating disease in our lifetimes.

Sincerely yours,

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
MassGeneral Institute for Neurodegenerative Disease
Massachusetts General Hospital

Our Research Roadmap



2012 Research Projects

In 2012 Cure Alzheimer's Fund distributed \$3,375,343 for research supporting 14 projects.

The Alzheimer's Genome Project™

FOUNDATIONAL GENETICS



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

Director, Genetics and
Aging Research Unit,
Massachusetts General Hospital

2005–2012

\$1,200,000

The goal of this project is to evaluate our new Alzheimer's disease gene candidates for effects on Alzheimer's pathology and related biological pathways, including APP processing, amyloid beta protein generation, tangle formation and cell death. These studies are being carried out as part of Phase II of the Alzheimer's Genome Project (AGP) and entail functional analyses of the Alzheimer's gene candidates identified in Phase I of the AGP. We have focused the Phase II studies on the novel Alzheimer's genes known as ADAM10, ATXN1 and CD33, all identified in 2008 as part of Phase I of the AGP.

The functional studies, aimed at how these genes influence risk for Alzheimer's, are carried out in both cell-based and animal models. We also have performed genetic follow-up and functional studies for AD-associated aberrations in the human genome, known as copy number variants (CNV). This has led to the identification of several CNVs in novel Alzheimer's genes underlying the inheritance of cases of familial early-onset Alzheimer's that were not explained by the known early-onset Alzheimer's genes co-discovered by our lab in the 1980s and '90s (amyloid precursor protein, presenilin 1 and presenilin 2).

The knowledge gained from how the newly identified Alzheimer's genes (from Phase I) biologically increase or decrease risk for Alzheimer's disease is being implemented to design new drug discovery efforts, also as part of Phase II of the AGP. Phase III of the AGP is being carried out parallel to Phase II and includes Whole Genome Sequencing of the human genomes of subjects from both early-onset and late-onset Alzheimer's families. The goal of Phase III of the AGP is to identify all of the biologically relevant functional gene variants that influence risk for Alzheimer's disease. Once identified, these gene variants will be analyzed using similar methods to those described here in Phase II of the AGP. A detailed description of Phase III of the AGP can be found next in this section under "Whole Genome Sequencing of Alzheimer's Disease Families."

Whole Genome Sequencing of Alzheimer's Disease Families



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

Director, Genetics and
Aging Research Unit,
Massachusetts General Hospital

2012
\$750,000

We will carry out Whole Genome Sequencing (WGS) of all subjects in the National Institute of Mental Health (NIMH) Alzheimer's disease family sample (1,510 subjects; 437 AD families). We will identify functional DNA variants throughout the human genome that are inherited as risk factors for Alzheimer's disease. We also will analyze DNA from brain samples of subjects who exhibited significant Alzheimer's pathology at autopsy, but never suffered from dementia; this will allow us to identify protective gene variants as well.

This study constitutes Phase III of the Alzheimer's Genome Project™. While Phase I and II informed regarding which genes are implicated in risk for Alzheimer's disease, this study will allow us to assess the entire human genome, including the 96 percent that is not made up of "genes," per se, but instead includes the DNA that regulates the activity of the genes. While the goal of Phases I and II was to identify all of the genes involved in Alzheimer's disease susceptibility, in Phase III, we will (1) determine all of the DNA variants in the Alzheimer's genes that directly influence risk for the disease; and (2) determine all of the DNA variants in the rest—the (intergenic) portions of the genome that regulate the activities of the Alzheimer's genes.

As in the past, we will use this information to determine exactly how each Alzheimer's gene (emerging from Phase I and II), functionally affects risk for the disease at the biological level. These findings then will be used not only to better understand the causes of Alzheimer's disease, but also to guide drug discovery efforts to slow down, stop or, perhaps, even reverse the disease process.

While the first phase of the Alzheimer's Genome Project determined which genes influence Alzheimer's, this new phase will determine how these genes confer increased risk of—or in some cases, protection against—the disease. The data from the WGS initiative will drive much faster development of therapies, both to prevent the disease and arrest its progress. This approach is highly efficient. While the dollar commitment is significant, the cost per discovery will be quite low.

—Jeff Morby, Cure Alzheimer's Fund chairman



Samuel Gandy, M.D., Ph.D.
Mount Sinai School of Medicine

2010–2012
no-cost extension

This is an extension of an earlier grant. SorCS1 and SorL1/SorLA/LR11 belong to the sortilin family of vacuolar protein sorting-10 (Vps10) domain-containing proteins. Both are genetically associated with Alzheimer's disease (AD), and SORL1 expression is decreased in the brains of patients suffering from AD. SorCS1 also is associated genetically with Types 1 and 2 diabetes mellitus (T1DM, T2DM). We have undertaken a study of the possible role(s) for SorCS1 in metabolism of the Alzheimer's amyloid-beta peptide (A β) and the A β precursor protein (APP), to test the hypothesis that SorCS1 deficiency might be a common genetic risk factor underlying the predisposition to AD that is associated with T2DM. Overexpression of SorCS1c-myc in cultured cells caused a reduction ($p < 0.002$) in A β generation. Conversely, endogenous murine A β_{40} and A β_{42} levels were increased (A β_{40} , $p < 0.044$; A β_{42} , $p < 0.007$) in the brains of female SorCS1 hypomorphic mice, possibly paralleling the sexual dimorphism that is characteristic of the genetic associations of SorCS1 with AD and DM. Since SorL1 directly interacts with Vps35 to modulate APP metabolism, we investigated the possibility that SorCS1c-myc interacts with APP, SorL1 and/or Vps35. We readily recovered SorCS1:APP, SorCS1:SORL1 and SorCS1:Vps35 complexes from the nontransgenic mouse brain. Notably, total Vps35 protein levels were decreased by 49 percent ($p < 0.009$) and total SorL1 protein levels were decreased by 29 percent ($p < 0.003$) in the brains of female SorCS1 hypomorphic mice. From these data, we propose that dysfunction of SorCS1 may contribute to both the APP/A β disturbance underlying AD and the insulin/glucose disturbance underlying DM.

Dr. Alan Attie linked SorCS1 to diabetes, and the similarity of SorCS1 to SORL1 led Dr. Gandy to guess that SorCS1 would link diabetes to Alzheimer's. "CAF was willing to take a chance on this hunch and with their 2010 support our lab first discovered the molecular pathogenesis of the two diseases. SorCS1 was established as the first gene to cause a coordinated increase in the risk for both diseases. We were able to leverage the \$100,000 pilot funding from CAF into an NINDS R01 and an American Diabetes Association research grant totaling \$1.5 million. Now the challenge: Why is SorCS1 the linchpin of TWO major human diseases? We believe this has to do with protein sorting and amyloid generation.

"In the future, we plan to induce neurons and islets from the pluripotent stem cells of diabetics with Alzheimer's, enabling us to study the cell biology of the link. This, too, is supported in part by the newly formed CAF Stem Cell Consortium. My sense is that if you are looking for what is newly emerging and important in Alzheimer's, CAF is the first place to look!"

—Samuel Gandy, M.D., Ph.D.

The AlzGene Database

FOUNDATIONAL GENETICS



Lars Bertram, M.D.
Max-Planck Institute
for Molecular Genetics

2006–2012
no-cost extension

**Thanks, Cure
Alzheimer's Fund!
You made a whole lot
of stuff possible!**

—Lars Bertram, M.D.

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 previous decades, hundreds of reports have been published claiming or refuting genetic association between AD genes and disease risk. Presently, nearly a dozen AD association studies are being published monthly from research groups worldwide. The pace of genetics research was substantially stepped up by the advent of genomewide association studies (GWAS), of which more than a dozen already have been published on AD. An even steeper increase can be expected to result from a widespread application of so-called "next-generation sequencing" technologies. For the AD genetics research community, this wealth of information is becoming increasingly difficult to follow, evaluate and interpret. The AlzGene database has been developed to manage this huge amount of information and to allow it to be used productively. AlzGene is undergoing a major software upgrade in order to efficiently handle data emerging from large-scale genetics studies. To access the database, visit www.alzgene.org. (AlzGene is embedded into the Alzheimer Research Forum [www.alzforum.org].)

The Amylin Protein of Diabetes Mellitus is an Antimicrobial Peptide

TRANSLATIONAL RESEARCH



Robert Moir,
Ph.D.



Rudolph Tanzi,
Ph.D.

Harvard Medical School/
Massachusetts General Hospital

2010–2012
\$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 share 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. >

(Continued)

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 nonpathological 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.

Abeta Oligomers and Tau Aggregation

TRANSLATIONAL RESEARCH



(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

2012

\$125,000

**Cure Alzheimer's is
the springboard, and
we are very grateful.**

—Dominic M. Walsh, Ph.D.

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's brain clumps of Abeta, known as amyloid plaques, are found in the spaces between nerve cells, and clumps of Tau, known as neurofibrillary tangles, are found within nerve cells. Until recently it was assumed Abeta had to form plaques to be toxic; however, it now is clear that smaller, mobile clumps of Abeta (referred to as oligomers) also are 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.

This understanding how Tau pathology is "transmitted," and a determination 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.

BACE1 Transcytosis in Alzheimer's Disease Pathogenesis

TRANSLATIONAL RESEARCH



Gopal Thinakaran, Ph.D.
University of Chicago

2012

\$100,000

Many lines of evidence suggest that beta-amyloid peptides cause neuronal damage and affect fundamental memory processes early in the course of Alzheimer's disease (AD). Two membrane-associated enzymes, betasecretase (BACE1) and gamma-secretase, are responsible for beta-amyloid production. Understanding the details regarding the cellular and molecular mechanisms involved in beta-amyloid production in neurons is a topic of central importance in molecular AD research.

Many investigators have studied the membrane transport of amyloid precursor protein in cultured cell lines and neurons to ascertain where in neurons this protein is processed by BACE1 and gamma-secretase. There is a general agreement in the field that amyloid precursor protein is transported along the nerve fibers (called axons) and is proteolytically converted into beta-amyloid near axon terminals, termed presynaptic sites. BACE1 has been found in neuronal dendrites and axons (the two types of neuronal projections). How BACE1 is transported in axons is not clearly understood. Recent findings from our lab suggest BACE1 is transported in membrane organelles called recycling endosomes in neurons cultured from embryonic mouse hippocampus. Moreover, we found evidence for a highly polarized transport of BACE1 from the cell surface of dendrites toward axons (a process termed transcytosis).

The goal of this proposal is to characterize the functional significance of polarized BACE1 transport in neurons. Specifically, we propose to interfere with BACE1 transcytosis in cultured hippocampal neurons and in brains of transgenic mice to test our hypothesis that this process contributes to neuronal beta-amyloid production and deposition. Our proposal is timely, unique and highly innovative because BACE1 transcytosis in recycling endosomes has never been described. Our proposal also is highly significant because we employ both *in vitro* and *in vivo* models to investigate the molecular and cellular mechanisms involved in neuronal BACE1 trafficking that is functionally important for A β production. This is a novel and exciting area of research, and we think our investigation will uncover significant insights on cellular and molecular mechanisms that are relevant to AD pathogenesis.

General Anesthetics and Alzheimer's Disease

TRANSLATIONAL RESEARCH



Zhongcong Xie, M.D., Ph.D.
Associate Professor of Anesthesia
Harvard Medical School

Director, Geriatric
Anesthesia Research Unit
Massachusetts General Hospital

2012

\$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 set out to identify anesthetics that 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 No. 1) and in real human AD patients (Aim No. 3). In addition, they will study the upstream mechanism of the anesthetics-induced cell death and increases in Abeta levels (Aim No. 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 finally will help them find safer anesthetics that may not worsen the AD symptoms (e.g., learning/memory impairment). These efforts are consistent with the goals of the 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.

iPS-derived and Trans-differentiated Human Neurons as Models to Study Alzheimer's Disease

TRANSLATIONAL RESEARCH



Marc Tessier-Lavigne, Ph.D.
The Rockefeller University

2012

\$100,000

Recent groundbreaking work in stem cell biology has made it possible to reprogram non-neuronal cells obtained from Alzheimer's-diseased patients into neurons. For the first time, the research community has the means to study diseased human neurons from Alzheimer's patients. These models already have yielded novel insights into the disease. However, different reprogramming techniques and various sources of cell material have been used to generate these models, and it is currently unclear whether one approach provides an advantage over the other (in terms of phenotype robustness and disease relevance). Here, we propose to derive PSEN1-mutant neurons in two distinct ways, i.e., from induced pluripotent stem cells (iPSCs) or directly from fibroblasts by trans-differentiation. We then will characterize the epigenetic signatures of these neurons and determine whether the two reprogramming techniques yield phenotypically similar neurons or if one set more closely resembles adult, aged neurons from diseased patients.

Alzheimer's is a terrible affliction, and the progress may appear to have been slow over the past few years. But I really believe progress is accelerating because of the very powerful tools that have been developed and the huge discoveries that have been made over the past two decades in biological science. Our knowledge is accelerating dramatically, and I think we can be guardedly optimistic that we're really at the dawn of an age in which our knowledge of Alzheimer's is going to explode and we're going to be able to really build on that to make a big difference for the disease.

—Marc Tessier-Lavigne, Ph.D.

Amyloid Beta Clearance and Alzheimer's Disease Pathogenesis

TRANSLATIONAL RESEARCH



Cynthia Lemere, Ph.D.
Brigham & Women's Hospital

2012

\$100,000

The immune system uses complement proteins and receptors to "coat and clear" pathogens and proteins from the body. Complement Receptor 1 (CR1/CD35) is found on the surface of red blood cells in humans and helps shuttle cellular debris to the liver for degradation. Recently, specific genetic variations, called polymorphisms, in the CR1 gene were found to be associated with an increased risk of late-onset Alzheimer's disease. We hypothesize that people with AD-risk CR1 polymorphisms have low levels of CR1 protein on their red blood cells and, therefore, are less efficient at clearing amyloid- β protein (A β) throughout life, gradually leading to A β aggregation and deposition in the brain. To test this hypothesis, we will examine A β and CR1 in archived human brain and measure the amount of CR1 molecules in red blood cells in individuals with and without AD-risk CR1 polymorphisms.



We are very grateful to Cure Alzheimer's Fund for its support. This new pilot project will allow us, for the first time, to investigate how genetic variations in an immune system molecule, Complement Receptor 1, increase the risk of developing Alzheimer's disease in humans. The project is highly collaborative, bringing together clinicians and infectious disease experts as well as basic scientists. The data obtained from this study will contribute to a better understanding of the role of the immune system in Alzheimer's disease and may identify new therapeutic targets to be tested in future studies.

—Cynthia Lemere, Ph.D.

The Role of PICALM in Vascular Clearance of Amyloid- β

TRANSLATIONAL RESEARCH



Berislav Zlokovic, M.D., Ph.D.
University of Southern
California

2012

\$100,000

PICALM, the gene encoding phosphatidylinositol binding clathrin assembly (picalm) protein, plays a key role in endocytosis, a process that regulates the function of cell receptors and synaptic transmission. PICALM is one of the most highly validated Alzheimer's disease (AD) risk factors. Its role in AD, however, is unknown. A recent genomewide screen for modifiers of amyloid- β peptide (A β) toxicity in yeast has identified the key role of the yeast homologue of PICALM.

This study has shown that PICALM efficiently controls A β toxicity in yeast, nematode models and mammalian neurons by regulating endocytosis-dependent cell vulnerability to A β . Our preliminary data in human and mouse brain show that picalm protein is most abundantly expressed in blood vessels that have been shown to provide a major pathway for A β removal from the brain into the bloodstream. Therefore, picalm in brain endothelium is ideally situated to participate in A β clearance from brain. Interestingly, our pilot data also show significantly reduced picalm expression in brain vessels in AD. Previous findings have established that low-density lipoprotein receptor (LRP) in the brain endothelium mediates vascular clearance of A β from the brain via transport across the brain capillary endothelium, a site of the blood-brain barrier (BBB) *in vivo*. Our preliminary data using human brain endothelial cells show that PICALM is required for rapid endothelial internalization of A β after its initial binding to LRP.

The current proposal will determine the role of PICALM in regulating internalization and transcellular transport (transcytosis) of LRP-bound A β across the endothelial cell wall of the BBB *in vitro* and *in vivo*. To test our hypotheses, we will use a human model of the BBB and a mouse model of A β clearance, both developed in our laboratory. In collaboration with Dr. Tanzi, we will study the effects of novel PICALM mutations on amyloid- β vascular clearance once the sequence of these functional variants/mutations becomes available. The proposed studies will represent a novel advance in our understanding of the molecular regulation of CNS A β homeostasis and will demonstrate a pivotal role of PICALM in controlling brain A β .

Antibody Signature of Alzheimer's Disease: Promise of an Early Screening Test

TRANSLATIONAL RESEARCH




Lucas Restrepo, M.D., Ph.D.
University of California,
Los Angeles

2012

\$100,000

A physician can't cure what he can't diagnose. The diagnosis of Alzheimer's disease is based on the exclusion of several neurological syndromes, rather than directly testing for the disease of interest. This can be an inaccurate exercise in up to 20 percent of the cases. Promising biomarkers are being developed, such as the cerebrospinal fluid profile of beta amyloid and Tau proteins, as well as amyloid imaging with positron-emission tomography. However, these tests are not universally available and have some disadvantages, including the need for a spinal tap or the injection of radioactive material. A plasma biomarker capable of identifying asymptomatic individuals developing Alzheimer's-type pathology is needed, as they are ideal targets for intervention (i.e., amyloid-binding therapies) to prevent dementia or delay its onset.

PSEN-1 mutations cause a predictable onset of mild cognitive dysfunction by age 40, followed by frank dementia a few years later. If characteristic biomarkers accompany different disease stages, these patterns could guide clinicians in the future to decide when to pursue more elaborate tests such as a spinal tap and PET scans. Immunosignaturing, a technology that employs antibody binding to a random-peptide microarray, is capable of generating profiles that distinguish transgenic mice engineered with familial Alzheimer's disease mutations (APP^{swe} and PSEN1-dE9) from nontransgenic littermates. The signature is distinguishable in transgenic mice as early as 2 months of age and intensifies as animals grow older. Immunosignatures also can distinguish individuals with nongenetic Alzheimer's disease from nondemented elderly controls. In this project, we will evaluate whether late-stage Alzheimer's disease patients with presenilin-1 (PSEN-1) mutations have a different signature as compared with young nondemented PSEN-1 carriers. In addition, we will assess the differences between the signature of demented patients with PSEN-1 mutations and elderly Alzheimer's disease patients without PSEN-1 mutations. We also will investigate whether age-matched individuals without the mutation can be distinguished from asymptomatic carriers. Finally, we will determine whether patients with different PSEN-1 mutations born and raised on different continents (North America and South America) have similar signatures. This will be a collaborative project between four institutions: Arizona State University (Tempe), Banner Alzheimer's Institute (Phoenix), Universidad de Antioquia (Medellin, Colombia) and UCLA Medical Center.

A photograph of two men in white lab coats. The man on the left is younger with dark hair, looking down at a document. The man on the right is older with glasses and a goatee, also looking at the document and smiling slightly. They are in a laboratory or office setting with a clock on the wall in the background.

What really impresses me about Cure Alzheimer's Fund is that 100 percent of the donations go to research. That is unprecedented in the field and I don't know any other foundation that does that. Without them, research such as my work would probably not be done. The more we know about this disease on the scientific level as well as the applied level, the closer we get to curing this disease and CAF is right at the forefront of this.

Today we're pessimistic that there will be government funding for the research that my colleagues and I do. The NIH is looking at a pay cut, and as resources go down the funding from other sources like CAF becomes more important than ever. Without CAF our research efforts would dwindle, and I am thankful for them stepping up to the plate. I just hope that lawmakers in Congress understand that Alzheimer's is a threat to our country, health and economy. With the money that I get from CAF I can fund my research, my experiments, and pay the people who are conducting these experiments. Without that support I would have to shut down parts of my lab and that research would never get done. CAF has stepped up and saved research in my lab and other labs. They are really very important to the continued success of finding a cure to Alzheimer's disease.

—Robert Vassar, Ph.D.

The Roles of Eps Homology Domain (EHD) Proteins and Synaptic Activity in Axon Transport of the Alzheimer's β -secretase BACE1 in the Brain

TRANSLATIONAL RESEARCH



Robert Vassar, Ph.D.
Northwestern University

2012

\$100,000

The membrane-bound aspartic protease 13-site amyloid precursor protein (APP) cleaving enzyme 1 (BACE1) is the 13-secretase enzyme that generates the first cleavage in the formation of the 13-amyloid (A β 3) peptide from APP. Thus, BACE1 is a prime therapeutic target for Alzheimer's disease (AD). However, BACE1 inhibitors with drug-like properties that cross the blood-brain barrier (BBB) have proven difficult to develop. Although the first BBB-penetrant BACE1 inhibitors currently are entering clinical trials in humans, we still are years away from knowing whether any will be successful in treating or preventing AD. Meanwhile, it is of paramount importance to study the cell biology of BACE1 to fully elucidate its mechanism of action in A β 3 generation, for deep understanding of factors that regulate BACE1 trafficking and access to APP substrate in neurons of the brain may uncover novel, effective and practical AD therapeutic targets.

The current proposal aims to elucidate the roles of Eps homology domain (EHD) proteins and synaptic activity in BACE1 axon transport in the brain and is linked to the application of our collaborator Dr. Gopal Thinakaran (University of Chicago) to determine the function of EHD proteins in A β 3 production and amyloid deposition *in vivo*. EHD proteins regulate dynamic BACE1 axon transport in primary hippocampal neurons *in vitro* (manuscript in preparation). In addition, synaptic activity controls A β 3 generation *in vivo*. Here, we will investigate the dependence of BACE1 axon transport on EHD function and synaptic activity in the hippocampus, a brain region critical for memory formation that is severely affected in AD. We hypothesize that inhibition or stimulation of EHD protein function or synaptic activity will decrease or increase hippocampal BACE1 axon transport, respectively. Our specific aims are: (1) Determine whether EHD proteins regulate dynamic BACE1 axon transport in *ex vivo* hippocampal slice cultures; and (2) Determine whether synaptic activity regulates dynamic BACE1 axon transport in *ex vivo* hippocampal slice cultures in an EHD-dependent manner. Our studies together with those of Dr. Thinakaran's proposal will increase our understanding of A β 3 production in the brain and may reveal new therapeutic strategies for AD.

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

DRUG DISCOVERY



Steven Wagner, Ph.D.
Principal Investigator/
Project Scientist

University of California,
San Diego, Neurosciences

2012

\$150,000

The goal of this project is to identify a series of highly potent gamma-secretase modulators able to lower Abeta₄₂ and Abeta₄₀ production while concomitantly increasing the less toxic production of Abeta₃₈ 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), small molecules that bind directly to gamma-secretase, decrease Abeta₄₂ and Abeta₄₀ levels while concomitantly increasing Abeta₃₈ and Abeta₃₇ levels without affecting gamma-secretase-mediated enzymatic processing of other known substrates, such as Notch-1.

AGSMs were shown to be efficacious *in vivo* for lowering the levels of Abeta₄₂ and Abeta₄₀ 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 with 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 Abeta₄₂ and Abeta₄₀ production while concomitantly increasing Abeta₃₈ production without measurably affecting gamma-secretase-mediated processing of another known gamma-secretase substrate, namely, the Notch 1 receptor.

Wagner received two previous grants from Cure Alzheimer's Fund to provide "proof of concept" for the innovative GSMs that he and colleagues developed. The findings were leveraged into a blockbuster NIH premier "Blueprint" grant award. They believe that the work Steve's lab is doing has the best chance of becoming an effective Alzheimer's drug of all the research being done today.

—Tim Armour, president and CEO, Cure Alzheimer's Fund

Development of UDP Analogs

DRUG DISCOVERY



Philip G. Haydon, Ph.D.
Tufts College

2012

\$100,000

The brain is composed of two classes of cells—electrically active neurons and electrically silent glia. Over the last 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.

Investigations of the Mechanism of Action of TargretinR/Bexarotene on Amyloid Clearance in Transgenic Mouse Models

DRUG DEVELOPMENT



Sangram S. Sisodia, Ph.D.



Robert Vassar, Ph.D.

University of Chicago/
Northwestern University

2012

\$50,343

Recent studies from the laboratory of Dr. Gary Landreth (Cramer P. et. al (2012) Science 335) have demonstrated that Bexarotene (Targretin), a highly selective, blood-brain barrier-permeant, FDA-approved, RXR agonist for the treatment of cutaneous T-cell lymphoma, can rapidly reduce amyloid plaque burden and rescue behavioral deficits in transgenic mouse models of AD. The proposed mechanism of action is via transcriptional activation of PPAR γ :RXR- and LXR:RXR-regulated genes, including ApoE, ABCA1 and ABCG1 expression, that facilitates A β clearance and promotes microglial phagocytosis. In support of this proposal, the authors reported that treatment of primary microglia or astrocytes with Bexarotene stimulated the expression of ApoE, ABCA1 and ABCG1 and secretion of highly lipidated HDL particles, leading to degradation of soluble A β ₄₂ in a PPAR γ -, LXR- and ApoE-dependent manner.

Most notably, Landreth and colleagues observed the rapid removal of both diffuse and compact A β plaques in the cortex and hippocampus of APP^{swe}/PS1^{DE9} transgenic mice (APP/PS1 mice) after acute treatment with Bexarotene. Targretin or vehicle (H₂O) was orally administered in 6-month-old APP/PS1 mice daily for three, seven or 14 days. The authors observed the progressively enhanced expression of ApoE, ABCA1 and ABCG1 and elevated HDL levels in both the hippocampus and cortex of Targretin-treated mice, accompanied by a sustained 30 percent reduction in soluble A β levels throughout the 14-day treatment period. Insoluble A β levels were reduced by 40 percent after 72 hours and progressively decreased over the subsequent 14 days. Total and thioflavin-S+ A β plaques were reduced by ~75 percent after seven and 14 days of Bexarotene treatment. >



Cure Alzheimer's Fund is manna from heaven as our budgets are constantly shrinking. We are seeing that it's getting harder and harder to do the research that we do and NIH isn't going to support us. CAF allows us to take risks, and if it doesn't work—it's a chance taken.

—Sam Sisodia, Ph.D.

Photo by Asaf Selinger

Furthermore, abundant A β -laden microglia were observed after three days of Bexarotene treatment, suggesting their involvement in the phagocytic removal of A β deposits. To assess whether Targretin could decrease A β burden in older animals with greater plaque deposition, 11-month-old APP/PS1 mice were treated with Targretin for seven days and again, there was found significantly reduced levels of soluble and insoluble A β_{40} and A β_{42} , a 50 percent reduction in plaque number, and a concurrent increase in expression of ApoE, the cholesterol transporters and HDL levels. Thus, the authors concluded that acute Targretin treatment is efficacious at both early and later stages of pathogenesis in this mouse model.

In view of the significant implications of these landmark findings for the development of novel AD therapeutics, we performed a small pilot study (N=3 each for vehicle and drug) using 8-month-old male APP/PS1 mice that were treated orally with a commercial source of Bexarotene for seven days. We failed to observe any differences in hippocampal or cortical amyloid plaque area or plaque counts between vehicle and Bexarotene-treated animals. We confirmed the levels of ABCA1 were elevated in the brains of Bexarotene-treated animals, indicating access of the compound into the CNS. We now propose to extend our preliminary findings by assessing the impact of Targretin on Abeta levels and amyloid pathology in larger cohorts of APP/PS1 and "5X FAD" transgenic mouse models..

Our Research Influence



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 funders. This “pump priming” is proving increasingly successful, as more of our early-stage grants are leveraged into more substantial and longer-term funding. Another indicator of success are the number of peer-reviewed papers that Cure Alzheimer's Fund researchers have published, and the number of times those papers have been cited by other investigators.

Our researchers
have published

111 papers,

which have been
cited almost

5,000

times.

Since we
began in
2004

our more than
\$18,000,000
investment

resulted in
more than
\$23,000,000
in NIH grants

for a total of more than
\$41,000,000
going to Alzheimer's
disease research.

Our approach works.

2012 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 and renewal
- David Holtzman, M.D., Regional, Synaptic, Cellular Modulation of Abeta Metabolism Project, received HIH-NINDS grant
- David Holtzman, M.D., Sleep, Aging and Alzheimer's Disease Project, received Senior Scholar Award, Ellison Medical Foundation
- Giuseppina Tesco, M.D., Ph.D., TBI and Stroke Relationship to AD, received 2 RO1 grants
- Samuel Gandy, M.D., Ph.D., SorCS1 Study, received NINDS RO1 grant

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

NOTE: For a full listing of published papers supported by Cure Alzheimer's Fund, see www.curealz.org.



About Cure Alzheimer's Fund

Cure Alzheimer's Fund is a 501(c)(3) nonprofit organization founded in 2004 by three families frustrated by the slow pace of Alzheimer's research and by the cumbersome, risk-averse bureaucracies hindering our best scientists. Leveraging their experience in venture capital and corporate start-ups, Henry McCance, Phyllis Rappaport and Jacqui and Jeff Morby came together to build a new venture-based Alzheimer's research fund designed to dramatically accelerate research, make bold bets and focus deeply on finding a cure. They recruited renowned Alzheimer's geneticist Rudy Tanzi and asked him to put together a "dream team" of the world's best Alzheimer's scientists, and to help them fund the biggest and boldest ideas without bureaucratic hesitation or deference to politics.

Since its founding, Cure Alzheimer's Fund has raised more than \$20 million for research, and its funded initiatives have been responsible for several key breakthroughs—including a potential treatment recently selected by the NIH for its elite "Blueprint" drug discovery program. Tanzi's Alzheimer's Genome Project™ was recognized as one of the "Top 10 Medical Breakthroughs" in 2008 by *Time* and CNN.

Fully 100 percent of funds raised by Cure Alzheimer's Fund go directly to research—the founders cover all overhead expenses. It is audited annually and meets all 20 Standards for Charity Accountability. Cure Alzheimer's Fund focuses the best scientific minds in the field of

Alzheimer's research, and does so scrupulously and without any financial gain for its founders, donors or researchers.

The goal of Cure Alzheimer's Fund is to stop the disease before it even strikes, with early prediction and prevention. Please join us in our quest for a cure.

About Alzheimer's Disease

Alzheimer's, a progressive, fatal neurological disorder, is the sixth-leading cause of death in the United States. The risks of getting the disease increase dramatically with age. About 10 percent of 75-year-olds have Alzheimer's; 20 percent of 85-year-olds; and about half of everyone older than 85. No one is immune, though certain genetic factors can reduce the risk in some and increase it in others. There is currently no cure or effective treatment. As of 2012, an estimated 5.4 million Americans had Alzheimer's disease; this includes 5.2 million people ages 65 and older and some 200,000 younger than 65 who have early-onset Alzheimer's. Payments for care in 2012 were estimated to be \$200 billion—and more than 15 million Americans provided unpaid care for persons with Alzheimer's. Without a cure, these figures will nearly triple by the year 2050.

The emotional and physical cost always has been devastating to every family dealing with Alzheimer's. Now, with aging populations, the disease also threatens to engulf the health care system of every industrialized nation.

Left to right: Jacqueline C. Morby, Jeffrey L. Morby, Sally Rosenfield, Tim Armour, Rudy Tanzi, Phyllis Rappaport, Michael Curren and Henry F. McCance



Letter from the President

Dear Friends,

Thank you. 2012 has been our best year yet—financially, scientifically and in meaningful commitment to our cause. We are determined to build on this momentum.

In the realm of fundraising, it was a banner year. Our founders and board members continue to cover the foundation's overhead costs as well as contribute substantially to research. We also are blessed with a solid core of longtime supporters who have provided sustaining support since our inception. In addition to these two bulwark groups, we added a large number of new donors in 2012 through referrals and intensive media outreach.

The accompanying charts tell this story vividly. We welcomed more than 2,000 new donors in 2012 and raised more than \$6.5 million, a substantial increase from last year's \$4.3 million. This impressive growth came from a wide variety of sources, including individuals giving small gifts, corporations matching employee donations and one generous new donor who gave \$1 million. Alzheimer's cannot be defeated without a broad base of support; ours is expanding month by month.

Driving this growth, we believe, is a mounting awareness of our stellar research program. While we continue to focus on rooting out the fundamental causes of Alzheimer's, we also are much closer now to true drug development. (Please read the letters from our chairman and Research Consortium chair for the impressive specifics.) To make the public even more aware of our progress, we have employed new ways to reach out, including our annual fall symposium in Boston (streamed online); webinar interviews with our groundbreaking researchers; social media activity using Facebook, Twitter and our website; videos on YouTube; and speaking opportunities at events around the country.

In addition to our new funders, we are honored to have a number of volunteer efforts from "local heroes" who take it upon themselves to climb mountains, swim oceans, complete the Appalachian Trail and host runs and walks to raise money for Cure Alzheimer's Fund. We salute the courage and tenacity of these champions. They inspire us all to work harder for the cause.

No one is more grateful for your support than our scientists. While other funding sources around the country are decreasing, Cure Alzheimer's Fund is able to step into the breach to provide fast and flexible funding for the best ideas. Looking forward, we're hopeful we can make 2013 our most impressive funding year yet. Because much of our new support arrived near the end of the year, we expect to see a very significant increase in our research funding in the first quarter of 2013.

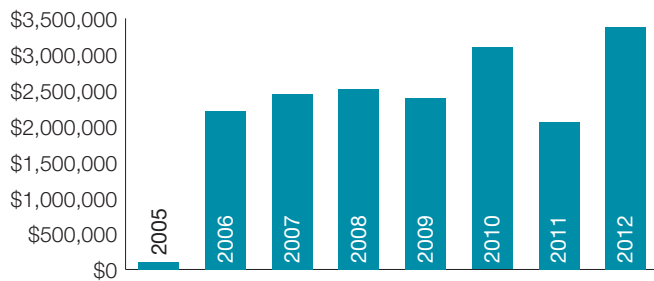
We are grateful beyond words to all who have made this success possible. If you have not yet joined this winning team, please consider doing so now. We need you.

Sincerely yours,

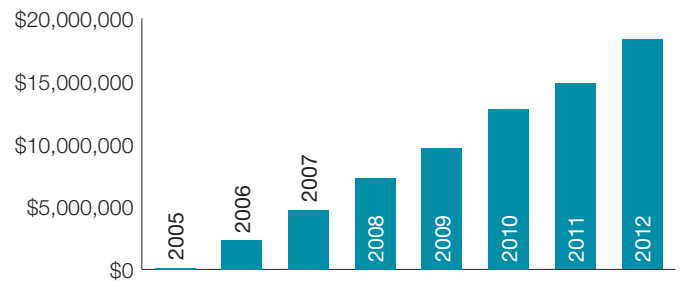
Timothy W. Armour
President and CEO, Cure Alzheimer's Fund

“your year yet” “groundbreaking researchers” “very significant”

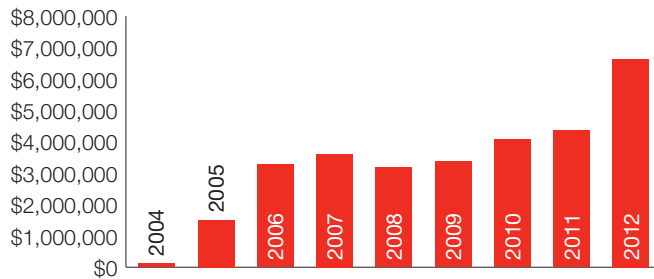
Annual Research Grants



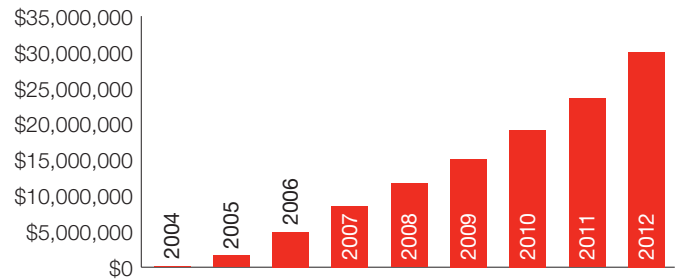
Cumulative Grant Totals



Annual Donation Trends



Cumulative Donation Totals



Funding Our Vital Research

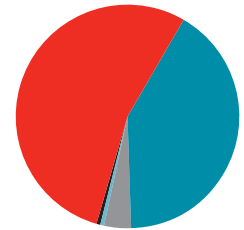
- Founders pay for all Cure Alzheimer's Fund (CAF) expenses as well as contribute to research.
- 100 percent of non-founder contributions go to research.
- CAF does not support overhead or indirect costs at recipient institutions.
- CAF has no endowment and passes all funds raised directly to researchers.
- 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 of "clean" audits.
- For the second consecutive year, Cure Alzheimer's Fund has been awarded the highest rating for sound fiscal management and commitment to accountability and transparency by Charity Navigator, the country's largest evaluator of charities.

2012 Fundraising

In 2012, Cure Alzheimer's Fund (CAF) received financial support from individuals, corporations and foundations in the amount of \$6,632,710 from 2,985 donors in cash and in-kind revenues.

Source of Funds

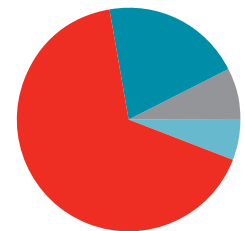
	\$	%
● Non-Founders	3,573,759	53.8%
● Founders/Board	2,726,580	41.1%
● Foundations/Trusts/Bequests	266,549	4.0%
● Corporations	35,103	0.5%
● Donated Goods and Services	30,719	0.4%
○ Government	—	0%
Total	\$6,632,710	100%



Source of Funds

Use of Funds

	\$	%
● Distribution to Research (grants)	3,341,898	66.6%
● Grant Support/Programs	1,009,803	20.1%
● Management and General	384,877	7.7%
● Fundraising	278,543	5.6%
Total Expenses	\$5,015,121	100%



Use of Funds

Source: IRS Form 2012 990, now posted on www.curealfund.org.

Financials

(Year ended Dec. 31, 2012, rounded to the nearest \$1,000)

Statement of Financial Position

ASSETS	
Cash and cash equivalents	\$6,011,041
Restricted cash, documentary project funds (temporarily restricted)	191,863
Contributions receivable and undeposited funds	99,630
Pledges receivable (temporarily restricted)	2,460,204
Grants receivable (temporarily restricted)	66,666
Deposits – donor-advised funds	22,120
Fixed assets, net	16,009
Other assets	3,548
TOTAL ASSETS	<u>\$8,871,081</u>
LIABILITIES AND NET ASSETS	
Liabilities	
Accounts payable and accrued expenses	\$76,842
Unexpended authorizations	100,000
Total liabilities	176,842
Net assets	
Unrestricted	5,975,506
Temporarily restricted	
Pledges receivable	2,460,204
Grants receivable	66,666
Documentary project	191,863
Total temporarily restricted	<u>2,718,733</u>
TOTAL NET ASSETS	<u>8,694,239</u>
TOTAL LIABILITIES AND NET ASSETS	<u>\$8,871,081</u>

Statement of Activities

REVENUE AND OTHER SUPPORT	
Contributions	\$6,550,453
Donated services	30,719
Investment income	1,598
Realized gain (loss) on sale of stocks	9,568
Unrealized gain (loss) on donor-advised funds	107
Other income	13,447
Net assets released from restrictions, pledges collected	167,814
TOTAL REVENUE AND OTHER SUPPORT	<u>6,773,706</u>
EXPENDITURES	
Program expenses	
Grants distributed	\$3,341,898*
Documentary program expenses	167,814
Other program expenses	841,989
Total program expenses	4,351,701
Management and general	384,877
Fundraising	278,543
TOTAL EXPENDITURES	<u>5,015,121</u>
INCREASE IN UNRESTRICTED NET ASSETS	<u>1,758,585</u>
TEMPORARILY RESTRICTED NET ASSETS	
Pledge contributions	2,500,000
Documentary project contributions	53,000
Net assets released from restrictions	(167,814)
INCREASE IN TEMPORARILY RESTRICTED NET ASSETS	<u>2,385,186</u>
CHANGES IN NET ASSETS	<u>4,143,771</u>
NET ASSETS, beginning of year	<u>4,550,468</u>
NET ASSETS, end of year	<u>\$8,694,239</u>

Adapted from the 2012 audited statements which, along with IRS Form 990, is available online at www.curealz.org.

*This number reflects a \$33,445 refunded portion of a previous grant.



2012

Special Events

A quick thank you for your time and for the work you are doing to find answers to eliminate the Alzheimer's nightmare. Every step forward gets us closer to the answer. Since I have it, I am one of many that have to deal with Alzheimer's on a daily basis. Some days are wonderful, others not so. However, all days are ones we look at for learning and for extended hope.

The webinars Cure Alzheimer's does keep us aware, keep us involved and get us to do our damndest to stay positive.

Thank you for bringing energy for one curmudgeon ... me.

Keep it coming!!

—Robert (Skip) Savoia

7 Summits – 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.”

Cure Alzheimer's Fund continues to receive money from Arnette's climb, and we continue to salute his phenomenal achievement on our behalf. In total, Arnette has raised almost \$43,500 for us.

Arnette had to remember to drive on the left and look out for 'roos!



Arnette preparing to cross a 50-foot gap 16,000 feet high on Carstensz Pyramid.



Arnette with local kids at the remote Papua village of Bilogia.



Two Sides of Abeta for the Layperson

Shenk • Tanzi • Moir

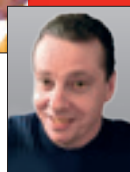
**1-25-2012
1 p.m. EST**



David Shenk



Dr. Rudy Tanzi



Dr. Rob Moir

WEBINAR

‘Two Sides of Abeta for the Layperson’

Cure Alzheimer's Fund presented a webinar, “Two Sides of Abeta for the Layperson,” on Wednesday, Jan. 25, 2012. The presentation, moderated by David Shenk, author of the national bestseller *The Forgetting, Alzheimer's: Portrait of an Epidemic*, featured Dr. Rudy Tanzi and Dr. Rob Moir.

These Alzheimer's experts looked at Abeta and its implications in the work toward a cure for Alzheimer's disease. For the last 27 years, Abeta, a fatty protein that is created in the brain, has been identified as “residual junk” and the leading cause of Alzheimer's disease. As a result, the majority of research efforts into the cause of Alzheimer's have targeted Abeta as the enemy. But recent studies financed by Cure Alzheimer's Fund have indicated that simply wiping out Abeta in the brain is not the solution.

Reaching New Heights in the Fight Against Alzheimer's

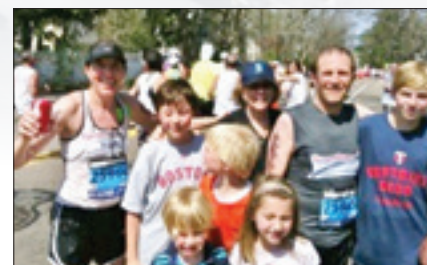
At age 28, Maria Pugliese may not be able to move mountains, but she certainly made an impact when she ran 60 miles across the Andes Mountains and raised more than \$3,000 for Cure Alzheimer's Fund.

On Feb. 3, Pugliese woke up at the site of the starting line in Chile, where she and her running partner, Laura Milsom, set out on a three-day adventure through the Andes to the finish line in Argentina. While Pugliese ran with 1,500 others in the *El Cruce de los Andes* race, her journey was a personal one.

On the first day she ran almost a full marathon up a dormant volcano (Mocho-Choshuenco). On her last day the terrain was mostly flat and it was a shorter run. It was also the day they got to cross the border. With passport in hand, Pugliese ran into Argentina and finished her long journey in the scenic Lanín National Park, where she received a stone medal that was handmade by local Chileans. "The entire race was an amazing experience," Pugliese reports. Read the full story at www.curealz.org.



Pugliese and Milsom crossing the finish line.



Ann and Peter Bulson and their family on marathon day.



Beating the Heat

On one of the hottest marathon days on record, three committed individuals ran 26.2 miles for Cure Alzheimer's Fund—Peter and Ann Bulson of Wellesley, Mass., and Anna Shepard of Cape Cod, Mass. While they all had trained hard, nothing could prepare them for the blistering temperatures on Patriot's Day 2012.

Still, these avid runners persevered, sticking together throughout the race in Boston and finishing within eight minutes of each other. "Basically, the only reason I finished," says Peter Bulson, "was because I was running for Cure Alzheimer's Fund. I couldn't let them down."

Together—along with the support of Pam Girouard of the Boston area, who assisted in coordinating the group—they raised almost \$13,400 toward finding a cure. "We are so appreciative of their commitment and passion to make a difference," says Tim Armour, president and CEO, Cure Alzheimer's Fund.

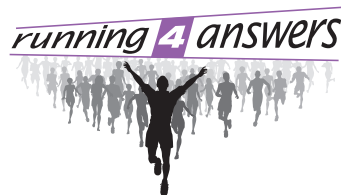
Running 4 Answers

On Saturday, April 28, co-founders Carolyn Mastrangelo and Barbara Geiger held the third annual Running 4 Answers fundraiser in Roseland, N.J. — their most successful race to date. Each year, this fun run/walk not only brings people together to honor the memories of loved ones who have been stricken with Alzheimer's disease, but it also raises money toward finding a cure.

This year, Cure Alzheimer's senior vice president, Mike Curren, attended the event along with 145 registered runners and 125 walkers. Together, they raised \$40,000 for Cure Alzheimer's Fund, bringing Running 4 Answers' three-year total to \$93,000.

"We are so appreciative of Mastrangelo and Geiger's commitment to our cause," says Curren. "Each year they continue to raise more and more money and reach more and more people. It's amazing what they've been able to accomplish."

For a list of winners and photos from last year's event, or to sign up for the 2013 run/walk, visit www.running4answers.org/.



Left to right:
Carolyn Mastrangelo
and Barbara Geiger,
founders of Running
4 Answers.



Friends and supporters on race day.

Hay Harbor Tennis Tournament

"I felt like we should have some sort of a charity tournament where we give to others," says Diana 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 Cure Alzheimer's Fund through Alison's husband, Henry McCance, co-founder of CAF, which sends every dollar raised directly to research.

So five years ago Fiske rallied a group of women at the New York club 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. To date, the tournament has raised \$21,400 for Cure Alzheimer's Fund, and we thank Diana for her tireless efforts on our behalf.



If Music Be the Food of Love, Play On

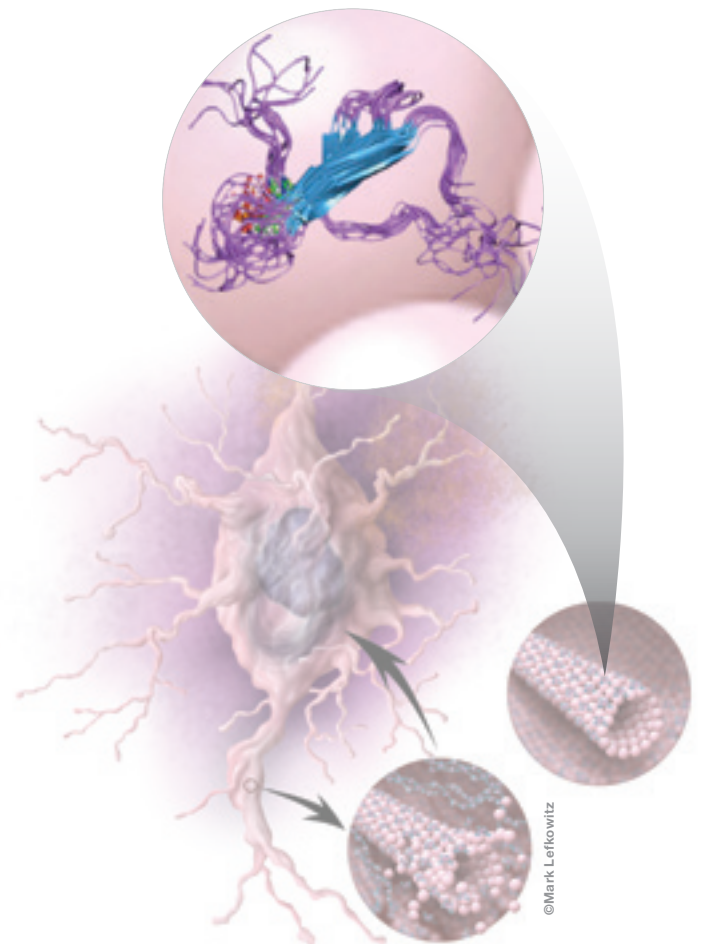
On June 16, 2011, patrons of the Don't Tell Mama Piano Bar and Cabaret in New York City enjoyed an evening of cabaret as talented musicians and vocalists in the greater metro area joined together to raise money for Alzheimer's and cancer research. Proceeds from this event were split between two organizations—with Cure Alzheimer's Fund receiving more than \$2,000 from the evening.

WEBINAR

Untangling Tau

Special guest Cure Alzheimer's Fund researcher Dominic Walsh, Ph.D., and David Shenk, author of the national bestseller *The Forgetting*, held a free webinar about the role of Tau in Alzheimer's on June 21, 2012.

Alzheimer's research has for many years been dominated by a focus on Abeta plaques and largely has overlooked the other infamous hallmark of the disease—the Tau-based neurofibrillary tangles. Dr. Walsh explained his research project and its special significance to the field of Alzheimer's research.



A Fight to the Finish

On March 8, Bobby Zerwick, 22, set out to hike the entire Appalachian Trail (AT). His goal? To raise \$5,000 to help in the fight against Alzheimer's—the disease his grandmother and his girlfriend's grandmother suffered from before they passed away.

The Kutztown University graduate had considered a number of nonprofits to walk for before he chose to support Cure Alzheimer's Fund. He selected it because he knew all the money he raised would go directly toward finding a cure for Alzheimer's disease.

Zerwick covered the 2,187 miles through 14 states—from Springer Mountain, Ga., to Mount Katahdin in Maine—despite tremendous foot pain, looming summits (Mount Washington, 6,200 feet, and Mount Lafayette, 5,200 feet, among them) and challenging weather elements. His journey included plummeting temperatures at night, deer flies and steep drop-offs that required him to “scramble” on all fours.

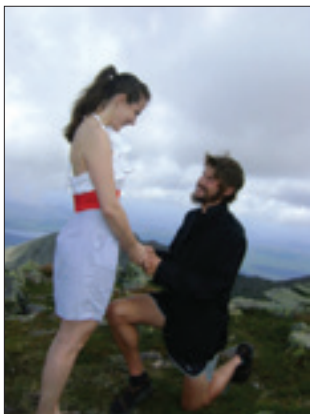
He averaged about 15 miles per day over a 10- to 12-hour span carrying a 20-pound pack on his back with only the essentials: a tent, sleeping bag, change of clothes, food and water, flashlight, toothbrush and cell phone, which he only used when he had to. He also carried two walking sticks that he says were “essential for hiking downhill.” He only stopped when downpours made the trail like a river. He lost 15 pounds, got into the best shape of his life, and still was always hungry. He survived on Pop-Tarts®, GORP (a mixture of granola, oats, raisins and peanuts) and other high-energy foods.



Mike Curren and Bobby Zerwick at Bascom Lodge on top of Mount Greylock, Mass.

After more than five months in the wilderness, Zerwick finished the AT on Aug. 17—with something else to celebrate as well. After hiking more than 2,000 miles, his girlfriend Ashley Bragner joined him for the very last part of his trek—5,200 feet up Mount Katahdin in Maine. And there on the summit he proposed to her.

Zerwick not only finished the AT at a very respectable pace, he exceeded his fundraising goal, raising approximately \$5,200 for Cure Alzheimer's Fund. “We are grateful for his commitment to our cause,” says Tim Armour, chairman and CEO of Cure Alzheimer's Fund. “I'm really proud of what I've accomplished,” says Zerwick. “It's rewarding to know that I did something to help other people.”



Zerwick proposes to Bragner at the peak of Mount Katahdin.



Art for Alzheimer's

After reading Barbara Kingsolver's *Animal Dreams* in Honors English at Scituate High School, Lexie Fidas, 15, was given another class assignment—to create a difference in society, much the way the characters in the book did.

Fidas came up with an idea that not only would change the lives of others, but her own as well. Since one of the characters in *Animal Dreams* has Alzheimer's disease, Fidas decided to help local Alzheimer's patients create their own artwork at Riverview Nursing Home, near Fidas' hometown of Hope, R.I. "I thought using art would be a great way to connect with Alzheimer's patients," she says. Although her grandmother had suffered from dementia, Fidas hadn't had any experience with the disease prior to beginning her project.

"I included anyone who wanted to participate," explains Fidas. She and her mother set up a drawing section with crayons, colored pencils and pastels, and a painting section with brushes and sponges. "Even though some of the patients didn't know what they were painting,



Lexie Fidas creates art with Alzheimer's patients.

or didn't remember how, they did it," says Fidas. Afterward, she and her mom framed each piece and Fidas auctioned them off at her school. "We raised \$80!" adds Fidas proudly.

"I decided to give the money to Cure Alzheimer's Fund, because all their donations go directly to research," she explains. "This project was one of the most life-changing things I have ever done. Even though the people at Riverview may not remember me, I will always remember them."



Greg Johnson, Susan and David's son, and head of the Johnson Foundation, with Jackie Carson, executive director of Sanborn Place.



Participants in the DKJ Foundation golf tournament.

David K. Johnson Foundation

The David K. Johnson (DKJ) Foundation was created in 2000 in honor and memory of David and Susan Johnson of Reading, Mass., to promote awareness of and provide support for individuals and families affected by Alzheimer's disease. David Johnson was diagnosed with progressive dementia at the age of 59 and he passed away in 2004. David's wife Susan had passed away suddenly in 1999 while caring for her husband. This is an all-too-common occurrence for families living with the challenges of Alzheimer's disease.

David and Susan's children created the DKJ Foundation as a way to give back and help others dealing with this terrible disease. The foundation's 12th annual golf tournament, held in August 2012 at the Black Swan Country Club in Georgetown Mass., raised \$5,000 for Cure Alzheimer's Fund among other charitable recipients.

In addition to the tournament, other DKJ fundraising events last year included a "cut-a-thon" at Lumina Salon at the Reading Street Faire, with proceeds earmarked for Cure Alzheimer's Fund through the DKJ.

A Test of Endurance

On Sept. 6, 2012, 30-year-old Brett Reynolds flew to London to swim the English Channel. Reynolds took on this challenge to honor his grandmother, who suffered from Alzheimer's disease before passing away. "I wanted to raise money to help stop the disease and to honor her memory," says Reynolds.

His goal was to raise \$5,000 for Cure Alzheimer's Fund—which he well surpassed, raising more than \$8,000. "I wanted to support an organization focused on finding a cure," says Reynolds. "I was impressed with their vision and believe in their entrepreneurial approach."

Native Southern Californian Reynolds is no stranger to water, having grown up playing water polo, eventually winning an NCAA championship at USC and playing for the U.S. men's team in the World University Games. Still, this task posed unique challenges.

Only 10 percent of people who set out to swim the channel actually succeed. Stretching 21 miles from Dover, England, to Calais, France, it can take anywhere from seven to 18 hours to swim across. But it's not the distance that makes the swim so difficult.

The channel is the world's busiest seaway, with more than 700 commercial ships and ferries running through it daily. With water temperatures between 59 and 63 degrees and no wetsuits permitted (to make the swim "official"), hypothermia and cramping are severe risks. Still, the biggest threat is the currents, because every six hours or so they change direction. If swimmers get the timing

wrong, even if they're in sight of the coast, they might as well give up, because they'll only be swimming backward.

To make the crossing official, swimmers cannot touch their guide boat (necessary to provide food, water, light and encouragement) or another person at any time during their swim, and they must present a passport when arriving in France. Despite all these challenges, seasickness was Reynolds' biggest concern.

Reynolds began his journey at 3:30 a.m. on Sept. 7 in darkness, with his mom cheering him on from a chartered boat. "She is the only one of my family and friends who doesn't succumb to seasickness," says Reynolds.

Three hours into his swim, Reynolds experienced pain in his right shoulder, which unfortunately stayed with him throughout the race. Toward the end, he began to show signs of hypothermia, but seasickness wasn't an issue. "Swimming the channel was a humbling experience," he says. "I never would have made it without the support I received from so many friends and family on (and off) the boat." Reynolds completed his swim in just 12 hours and 5 minutes. We are thrilled with Brett's accomplishment and incredibly appreciative of his fundraising efforts.



Brett Reynolds before his channel swim.



Fall Symposium: Taking Control of Alzheimer's Through Research: The Road Map to Therapies

On Oct. 10, leading researchers from the Cure Alzheimer's Fund Research Consortium, including Steve Wagner, Ph.D., Sangram S. Sisodia, Ph.D., and Chairman Rudy Tanzi, Ph.D., gathered in Boston to discuss the road map to therapies.

David Shenk, author of the national bestseller *The Forgetting, Alzheimer's: Portrait of an Epidemic*, moderated the event and questions were encouraged from the audience. Those questions covered various health and lifestyle issues, as well as the current state of research and the direction in which it is headed, and the facts about Cure Alzheimer's Fund.

“As a physician who treats many patients with Alzheimer's disease in my medical practice, it was exciting to attend the Cure Alzheimer's Fund annual symposium to hear about the latest advances in research from the doctors and scientists who are leading the way in finding a cure for this condition in our lifetime. I am most encouraged to know that such highly committed individuals, with the support and involvement of the Fund, are accelerating the pace of innovation and discovery in order to cure this disease that profoundly affects millions of families.”

—Robert P. Fields, M.D., Fellow of the American College of Physicians, Olney, Md.



Above: Sam Sisodia, left, and Rudy Tanzi



David Shenk, moderator



Tim Armour, president and CEO
Symposium photos by Nir Landau



Steven L. Wagner, Ph.D., panelist

Join us for a discussion on research progress:

Broadcasting Live from The Society for Neurosciences Meetings

Oct. 15, 2:30 p.m. EDT

SPEAKERS:
David Shenk
Rudy Tanzi, Ph.D.
David Holtzman, M.D.
Caleb Finch, Ph.D.

[Click for Details](#)

WEBINAR

Live from The Society for Neurosciences, New Orleans

Broadcasting live from The Society for Neurosciences in New Orleans in mid-October, we hosted an interactive discussion on research progress from a gathering of world-class scientists. The advances were explained and discussed by webinar moderator David Shenk, author of *The Forgetting*, with Research Consortium Chair Rudy Tanzi, Ph.D.; David Holtzman, M.D., and Scientific Advisory Board member Caleb Finch, Ph.D. We heard their up-to-the minute impressions of research being presented at The Society for Neuroscience, and heard their discussions about it.

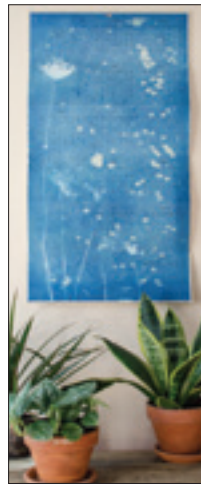
Calendars for a Cause

When Maggie Campbell's mother-in-law, Nancy Drapeau, was diagnosed with early-onset Alzheimer's disease last summer at age 59, Campbell decided she wanted to do something to help. Originally from Omaha, Neb., Campbell is a bookbinder and letterpress printer in Brooklyn, N.Y.

Inspired by her mother-in-law's garden in Dubuque, Iowa, Campbell designed and created a set of limited edition, handmade 2013 calendars and perpetual calendar books to raise money to fight Alzheimer's disease. The calendars are hand-printed and bound into an accordion-fold book designed for wall hanging.

Campbell used Charity Navigator to find the right place to donate. "I was so happy to come across Cure Alzheimer's Fund. I wanted to support an organization that was doing groundbreaking work and where the focus was so clear," says Campbell. "This whole project is an attempt to do something to mark a new path in all of our lives, and to give back in a way that is meaningful and lasting. It has been a labor of love."

To date Campbell has raised \$445. You can see the calendars at <http://shop.brooklynbookbinder.com/collections/2011-calendars>. Fifteen dollars from each calendar and \$5 from each book of days is earmarked for Cure Alzheimer's Fund to support continued efforts to research, prevent and cure Alzheimer's disease.



Campbell's special-edition calendars.



Nancy Drapeau and Charlotte (Maggie's daughter) in Dubuque, summer 2012.



Maggie Campbell (third from right) in Iowa with her in-laws and daughter.



Nogelo at her friend's home in Florida.

A Birthday Letter

When Gerry Nogelo of Vero Beach, Fla., turned 70 on Nov. 8, 2012, she only had one wish—to find a cure for Alzheimer's disease. So she mailed more than 40 letters to her friends and family asking them to make a donation to Cure Alzheimer's Fund in honor of her birthday. She wrote:

"I am asking you to consider sending a donation to Cure Alzheimer's Fund in honor of my 70th birthday. It would be the most important and blessed gift you could give to me. Every little bit will help find a cure."

Nogelo lost her mother, aunt and uncle to the disease. "They all started showing signs of the illness around age 75," explains Nogelo. "I took care of my mother for eight years and my aunt for 11 before they both passed away." Nogelo found out about Cure Alzheimer's Fund through her friend, Phyllis Rappaport, co-founder of the organization. Nogelo's family and friends have donated a total of more than \$1,400 in her honor.



In Honor and In Memory

Cure Alzheimer's Fund received gifts in honor or in memory of the following in 2012:

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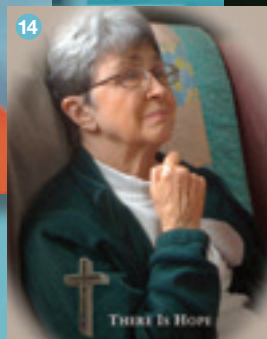
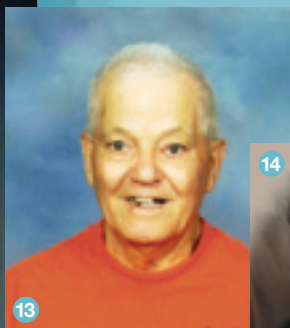
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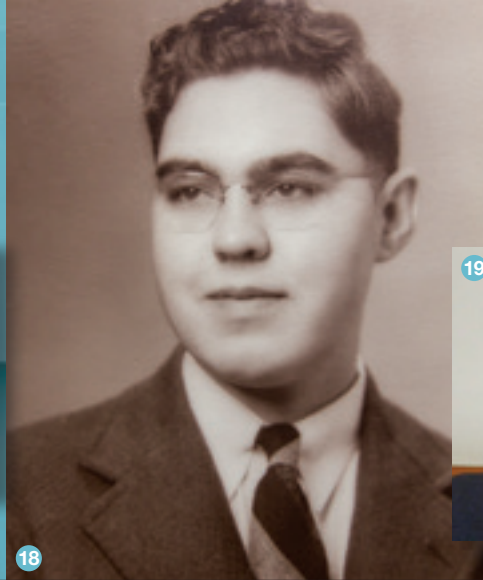
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If you would like to designate memorial gifts to come to Cure Alzheimer's Fund, please let us know whom to notify when we receive donations.

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.
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If you have any questions about our In Memory program, please contact Laurel Lyle, director of 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.

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

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



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.





34 Washington St., Suite 200
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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

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Research Consortium

Rudolph E. Tanzi, Ph.D., Chairman, Research Consortium;
Harvard Medical School/Massachusetts General Hospital
Sam Gandy, M.D., Ph.D., Mount Sinai School of Medicine
Charles Glabe, Ph.D., University of California, Irvine
David Michael Holtzman, M.D., Washington University, St. Louis
Virginia M.-Y. Lee, Ph.D., MBA, University of Pennsylvania
Robert C. Malenka, M.D., Ph.D., Stanford University
Roberto Malinow, M.D., Ph.D., University of California, San Diego
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