# Cure Alzheimer's FUND
# 2017 Annual Report

Cure Alzheimer's FUND

**MISSION**

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

# Annual Report 2017


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# Dear Friends,

**Thank you for making 2017 another record-breaking year for Cure Alzheimer's Fund (CureAlz). We granted a record $15.7 million for 67 research projects, an increase of 16 percent over funds granted in 2016. Our cumulative committed research is nearing $70 million. In 2017, we raised $18.5 million in donations from 17,000 gifts, our 13th consecutive record fundraising year and an increase of 19 percent over funds raised from 2016. We are humbled by your continued generous support. We are committed to making sure that CureAlz research provides the "highest return on investment" for your donations dedicated to understanding this complex disease, and identifying and developing effective therapies to defeat it.**

## Maintaining and Accelerating Our Scientific Leadership Roles

In previous annual reports we have described what we believe to be the important leadership roles we have in the Alzheimer's research field. Some examples follow.

### LEADERSHIP IN THE GENETICS OF ALZHEIMER'S DISEASE

We are without question one of the world's leaders in the understanding of the genetics of Alzheimer's disease (AD). Right at the outset of our founding 14 years ago, we realized it was going to prove impossible to find a cure without finding the genes causing the disease, and then understanding the function of each of those genes. When we first began our genomic scans, there were only four known Alzheimer's genes. Now, largely as a result of our work, more than 100 AD genes have been identified. But more important, we now know hundreds of variants of these genes that are contributors to the disease.

We believe we have the largest database in the world of the genetics of Alzheimer's disease. This extensive database informs a whole new series of research projects designed to understand the exact chemistry of the key genetic variants and how to stop the deleterious impact of such variants. This effort is called the Genes to Therapies™ (G2T) program. It involves hundreds of researchers working on different variants to determine how the genetic information can lead to cures or preventatives. In the accompanying letter from Dr. Rudy Tanzi, he describes some of the more promising projects we are currently undertaking to do just that.

Our leadership in genetics has resulted in new discoveries and insights. We now know from the new field of epigenetics that one's life history ("nurture") actually influences the way our genes express themselves; we also know that the human biome (the millions of microbes in our gut) likewise impacts the expression of our genes in important ways. So both epigenetics and biome phenomena are potentially relevant to Alzheimer's disease. We have major projects under way to further understand such processes.

Our database also gives us the capacity to undertake specific analyses that would be impossible to do in any other way. For example, we recently funded a project to identify why women have a significantly higher rate of Alzheimer's than men. This investigation is comparing the DNA of men vs. women on a gene-by-gene basis and correlating that information with the incidence of Alzheimer's on a gene-by-gene basis. Surprisingly, there are important different genetic impacts, which we now are analyzing.

**LEADERSHIP IN THE DESIGN OF TOOLS FOR ALZHEIMER'S RESEARCH**

Our genetic database is one very important tool for research. CureAlz has been involved in the development of other tools critical to the successful investigation of Alzheimer's disease. Alzheimer's in a Dish, a groundbreaking tool developed several years ago through a CureAlz grant, has been greatly enhanced to now include microglia and the blood-brain barrier, in addition to the protein bundles, tau tangles and inflammation that are the hallmarks of Alzheimer's disease.

Transgenic mice, those bred with human DNA containing deleterious genes such as AD, are a major research tool for science because such mice succumb to the implanted human genes just as a human would, and therefore can be used for experiments and to test potential drugs. One of the paradoxes of Alzheimer's science is that the breed of transgenic mice originally used for the discovery of the first four AD genes still is used today in great preponderance for scientific experimentation, even though there now are more than 100 additional known AD genes. In other words, current science has virtually ignored the new genes in their use of the older mice models, even though these new genes are essential to thorough scientific investigations.

"Our database also gives us the capacity to undertake specific analyses that would be impossible to do in any other way. For example, we recently funded a project to identify why women have a significantly higher rate of Alzheimer's than men."

Jeffrey L. Morby (left) and Henry F. McCance

One of the important services we are providing our researchers is to develop new transgenic mouse models with the newer Alzheimer's genes. We plan to make these mice available to other scientists, not just those within our research collaboration.

Another very exciting new model for discovery is a rapid through-put process using Alzheimer's in a Dish technology that Drs. Rudy Tanzi and Stephen Wong have developed to rapidly screen drugs for their potential impact on AD. The reason this is so exciting is that in using this process, we are able to rapidly test virtually every drug in the world separately to see whether that drug might impact AD disease. If we are able to find known safe drugs that already have been

approved for another disease but could be repurposed to become AD drugs, we could greatly shorten the process of bringing such drugs to public use. We have now identified about 40 drugs in that category, which we are analyzing in detail.

**LEADERSHIP IN CONCEPTUALIZING NEW FORMS OF SCIENTIFIC UNDERSTANDING**

One of the most paradigm-changing research breakthroughs is the finding, led by Drs. Rob Moir and Rudy Tanzi, that amyloid is actually a component of the innate immunity system. It is an "antimicrobial" substance that attacks pathogens entering the brain. Often this role is immensely important and positive, but occasionally, as a result of the wrong genes or conditions, amyloid can become toxic and become the trigger that starts the long series of reactions ultimately leading to AD. This insight, recently described in the journal *Nature*, already is changing the way scientists are dealing with the development of AD drugs—it will have a huge impact on the field.

APOE4, one of the leading AD genes, is thought to have its main impact in the clearing of amyloid from the brain. But more recently, Dr. David Holtzman and members of our APOE consortium discovered that APOE also has important roles relative to tau and different cell types—totally new insights.

The above and many other insights now have led us to the pathways of potential drug development. Rudy's letter describes some of the most promising of these.

**LEADERSHIP IN VENTURE PHILANTHROPY AND COLLABORATIVE SCIENTIFIC RESEARCH**

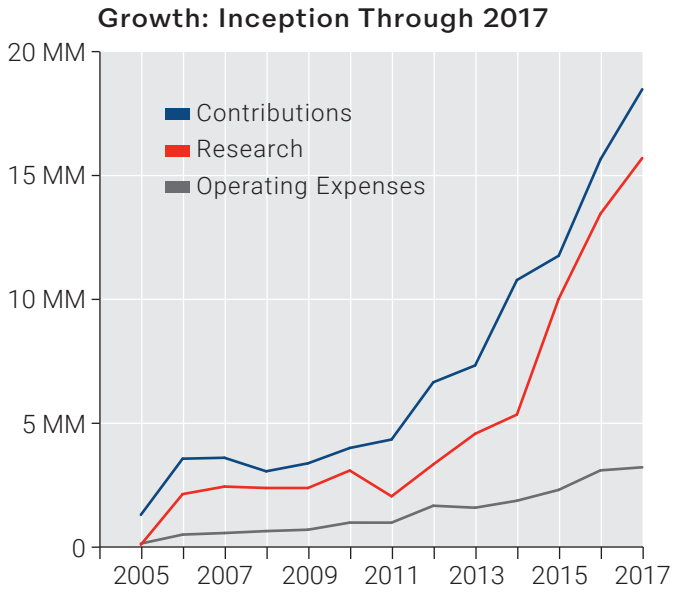
Our model of venture philanthropy is now familiar. We proactively identify and recruit the best Alzheimer's researchers around the world to receive our funding. We encourage them to submit "high-risk/high-reward" projects they can't get funded from traditional sources. We usually fund those requests promptly and with a minimum of bureaucratic forms. Most importantly, we require our "dream team" of researchers to collaborate with each other by sharing unpublished data, by constructively critiquing each other's research and by partnering in mini-consortia projects.

As we grow, we also recognize the need to refine and improve our strategy. As Rudy's letter explains, in 2017 we implemented a key recommendation of our 2016 strategic review by combining our Research Consortium and our Scientific Advisory Board into a new Research Leadership Group (RLG). In 2018, we are implementing a second key recommendation from our strategic plan by establishing and recruiting the Research Strategy Council (RSC). The RSC is a new independent group consisting of distinguished researchers and industry practitioners who are experienced in drug discovery, clinical trial design and successful introduction of new therapies. The RSC will meet annually to review the CureAlz research portfolio and strategy, and make recommendations to our Research Leadership Group and our Board on how to make our research funding even more effective. Their focus will be to ensure that CureAlz is funding optimal areas of AD research in ways that will enable potential therapeutic leads to accelerate their trajectory toward clinical trials and patients.

We hope you will be as inspired as we are by the research described in Rudy Tanzi's accompanying letter and in this entire annual report. We are confident CureAlz can continue to grow its leadership roles in the years to come to defeat this dreadful disease.

## Our Growth

The chart on the next page summarizes our historical growth. Since 2011, our revenues from donations have grown at a compound rate of 26 percent. Our research funding has grown at a 41 percent compound rate over the same period. These growth rates are extraordinary for any nonprofit. They are testimony to the importance of our mission, the excellence of our researchers, the validity of our strategy and the depth of the commitment we share with you. As we get larger, of course, our growth will inevitably moderate, but we are determined to continue to scale our organization as fast as we can to maximize our impact.




To grow effectively, we need to grow our Board. We are delighted to announce that in the last three months, we have recruited two outstanding new board members. Jay Jester is a Managing Director of Audax Private Equity, a middle-market private equity firm headquartered in Boston. Jay lost his father to Alzheimer's disease in 2017. Bill Benter is a businessman and philanthropist in Hong Kong and Pittsburgh. He is Chairman of Acusis, LLC and the Benter Foundation. Both Jay and Bill will bring new energy, new contacts and new insights to CureAlz, and we are excited and grateful about their new commitments.

We also thank Matthew Szulik for his years of service as a Director and wish him success on his two new startup ventures. We appreciate his commitment to continue to support us financially and with advice.

One of the key practices of CureAlz is having the Founders and Board pay for all operating expenses so that donors like you know that all their funds go directly to research. To date, Founders and Board members have donated $31.5 million, and this has more than covered the $18.3 million of overhead expenses since inception. Continuing to recruit outstanding new directors will help CureAlz to continue this important practice for years to come.

## Outside Recognition

In 2017, we were pleased to be recognized and supported by a number of new organizations and initiatives. Our first public service announcement (PSA) was produced and is designed to educate the public about Alzheimer's disease. The 60-second television spot features Rudy Tanzi and businessman Dan Gasby talking about Alzheimer's and its impact on patients and their families. The PSA is being shown on TV and social media. Advertising industry leader BBDO created a *pro bono* two-minute social media film in cooperation with CureAlz. Being shown in movie theaters and on social media outlets, the film won the Silver Hugo Award at the Chicago International Film Festival.

In addition, mall operator Simon Malls offered to display *pro bono* advertising for CureAlz in several of its locations throughout the 2017 holiday season. The ads were designed for their malls' new interactive kiosks, and included videos with touch screens to educate customers about the disease and CureAlz. In the first quarter of 2018, Northern Trust hosted well-attended seminars in Naples and Boca Raton, Florida, for their clients, featuring presentations by Rudy Tanzi on the latest state of the art in Alzheimer's research.

In November, Good Housekeeping recognized CureAlz as one of 10 "Best Charities to Give to Right Now." Once again, and for the seventh consecutive year, Charity Navigator awarded CureAlz a four-star designation. We continue to be the only Alzheimer's philanthropy with both a four-star rating on Charity Navigator and a Platinum rating on GuideStar. In January, the Boston Red Sox notified us they are declaring June 5th "Cure Alzheimer's Fund Day" in recognition of our contributions to the field of Alzheimer's research. Rudy Tanzi and members of the Research Leadership Group will be honored in pre-game ceremonies at Fenway Park. We also expect to be interviewed on radio and TV Red Sox broadcasts and to share our message broadly to "Red Sox Nation."

We are both enormously appreciative and proud of these endorsements. Collectively these and other recognitions

in the popular press, together with our new website, are building our brand. Immodestly, we are becoming a "go to" organization for those interested in breakthrough Alzheimer's research and this, in turn, has helped fuel our extraordinary growth.

On a broader front, noted billionaire philanthropist Bill Gates announced in November that he would invest $100 million of his own money in Alzheimer's disease. This is the first time ever that Gates or the Gates Foundation has invested in research for a noncommunicable disease. In an article on Gates' announcement, *Forbes* magazine interviewed CureAlz President and CEO Tim Armour. "Funding of research for Alzheimer's disease lags far behind the other top 10 illnesses," Armour said. "Bill Gates and his contributions to research of Alzheimer's disease…will not only elevate awareness of the disease, it will make a true difference." Gates invested $50 million in a private venture fund, and he plans to invest an additional $50 million in start-up efforts over time. "We are optimistic that Gates' sizeable commitment to the eradication of Alzheimer's disease will act as a catalyst for further sizeable investments by others, and we intend to encourage that and create the vehicles for doing so," added Armour.

## Importance of the Mission

In spite of all the progress that CureAlz and the Alzheimer's research community have made, finding a cure is as important, or even more important, as it was when we started 14 years ago. Alzheimer's is a 21st century global health care crisis:

- 6 million Americans are living with Alzheimer's now. Our aging population means this will grow to 15 million by 2050 if no cure is found.
- Two-thirds of patients and caregivers are women.
- Alzheimer's is the sixth leading cause of death in the United States, and the only fatal disease, of the top six, where mortality rates are increasing.
- There are 15+ million unpaid caregivers. This disease broadly impacts families.
- 1 in every 5 Medicare dollars is spent on caregiving for someone with the disease, and this share is growing.

Alzheimer's is a particularly challenging disease:

- For 95 percent of patients, many different genes contribute to an individual's risk.
- The pathological hallmarks (plaques, tangles, inflammation) are well known, but what triggers them to develop and what causes neurodegeneration are not.
- This pathology is present long before cognitive decline, but does not guarantee clinical symptoms of dementia will occur.
- A 2013 economic analysis estimated the capitalized cost of developing a disease-modifying therapy, including failed attempts, to be $5.7 billion.

These facts, as well as countless personal stories from Alzheimer's patients and their families, remind us of the importance of our mission and our strategy. Through venture-based philanthropy, CureAlz catalyzes breakthrough research with the highest probability of slowing, preventing or reversing Alzheimer's disease.

## Many, Many Thanks

There have been announcements from the pharmaceutical industry in the last 12 months, such as failed trials by Lilly and Merck, that remind us what a complex disease Alzheimer's is. However, when you read Rudy's letter and read about the cutting-edge projects in this report, you can't help but be excited and optimistic. All of the success and momentum of our researchers has been made possible by your generous and continuous support. We are forever grateful to each and every donor. Thank you also to our wonderful, world-class researchers and to our dedicated staff. We will not rest until a successful set of therapies is developed to help patients and families be free from this dreaded disease. We are making significant progress toward this worthy goal. Together, we will succeed.

Very best wishes,

Jeffrey L. Morby
Henry F. McCance
Co-Chairmen and Co-Founders

# Cure Alzheimer's Fund Friends,

**Thank you for making possible another powerful and groundbreaking year of Alzheimer's disease research. Speaking on behalf of the many scientists whose 2017 Cure Alzheimer's Fund (CureAlz) grants have enabled them to deepen our understanding of this disease and pursue novel therapies for treatment and prevention, we are all immensely grateful for your unwavering commitment to and generous support of our goal to end this horrendous disease.**

As you will see from the list of our funded grants included in this report, 2017 was a year of exceptional growth for Cure Alzheimer's Fund. The breadth and depth of CureAlz research has never been greater. And our impact on elucidating the underpinnings of this disease and how to implement them to create novel treatments continues to grow with every year—all thanks to your support and generosity.

We once again have provided funding to more researchers and projects than in any previous year; we also have added such scientists with proven track records of achievement as Dr. Paula Grammas and Dr. Hermann Steller; and our global reach has increased as we funded for the first time research in Canada, with Dr. Cheryl Wellington, and Korea, with Dr. Won-Suk Chung. The impact of Alzheimer's is felt worldwide, and it is fitting that we continue to harness the efforts of the best scientists globally to fight this terrible disease.

In 2017, we implemented one of the key recommendations of our 2016 strategic plan by merging our Research Consortium and Scientific Advisory Board into a new Research Leadership Group (RLG) (see page 12). We continued to add breadth and depth to the expertise of this group by welcoming three new extraordinary colleagues: neuroimmune expert Dr. Marco Colonna; renowned leader in the study of microglia Dr. Beth Stevens; and acclaimed neuroscientist and biomedical engineer Dr. Steve Wong. Their addition provides us with important new perspectives and guidance in each of their respective specialties, and we already are benefiting greatly from their involvement.

Rudolph Tanzi, Ph.D.

The researchers funded by CureAlz want nothing more than to advance our understanding of this highly complex disease and translate that information into effective strategies for prevention and treatment, and the work that was performed this year made great progress toward achieving our goals.

First, our Alzheimer's Genome Project™ (AGP) providing detailed genetic data on more than three dozen risk genes for the disease now can be employed to begin developing screens that can more accurately predict who is at risk before pathology begins. Second, our support of biomarker and brain imaging programs will facilitate the early detection of Alzheimer's, when pathology first begins pre-symptomatically and is best addressed therapeutically. Third, we already are funding a large number of projects aimed

"If we can someday identify the main microbes driving amyloid formation in the brain, we may be able to specifically target them with antimicrobial drugs or even vaccination as a form of primary prevention of Alzheimer's disease. I will be eager to share more with you as 2018 progresses."

at intervening with the development of the initial plaque and tangle pathology that triggers the disease.

Along these lines, with CureAlz support, RLG members Drs. Steve Wagner and Bill Mobley of the University of California, San Diego, have been collaborating with my laboratory at Massachusetts General Hospital to develop gamma secretase modulators aimed at safely reducing amyloid levels in the brain. These are expected to be in clinical trials for Alzheimer's in 2019. CureAlz RLG member Dr. Bob Vassar of Northwestern University was among the first to discover the enzyme called BACE1, which is needed to produce amyloid beta, and his research is guiding the development of safe BACE1 inhibitors to lower amyloid levels. Our Genes to Therapies™ (G2T) program also is bearing fruit. CureAlz started G2T to translate the genetic findings of the Alzheimer's Genome Project into actionable biological information. As the Alzheimer's Genome Project continues to grow with the integration of new genomic datasets and technologies, we are identifying hundreds of genetic variants that directly impact risk for Alzheimer's disease. The G2T program then assigns these variants to expert researchers who investigate their role in Alzheimer's pathology. We then can identify ways to therapeutically intervene. In most cases, studies of these new gene variants have been lacking because the tools to investigate them did not exist. Thus, CureAlz commissioned specific mouse models for our funded investigators—and eventually the entire field—to use. The new CureAlz APOE mouse models already are being provided to the field (beyond our funded investigators), offering a powerful example of how our G2T program is accelerating the field's understanding of the vital biology of Alzheimer's.

We have seen exciting progress at all points in the G2T program. Our many G2T projects are at different points in their trajectories, but are yielding important possibilities. Dr. Jaehong Suh and I are pursuing an investigation of the Alzheimer-associated ATXN1 gene focusing on its regulation of BACE1. Inhibiting BACE1 activity has been the goal of a number of high-profile clinical trials, but off-target affects and the need for high doses of direct BACE1 therapeutics have challenged these efforts; intervening with ATXN1 may provide an alternative way to achieve the same outcome with lower risks. Dr. Tae-Wan Kim is investigating other new ways to modulate BACE1's activity as well. Dr. Robert Vassar is investigating a variant in the enzyme ACE, the protein that helps control blood pressure, to test how it impacts Alzheimer's risk. Given the epidemiological evidence for a strong link between cardiovascular health and dementia risk, pursuing better understanding of drivers for this link is a high priority. And finally, Dr. Sam Sisodia has shown that altering the composition of the gut microbiome (the thousands of different species of bacteria that live in your gut) has dramatic effects on the number of plaques in Alzheimer's mouse models. This suggests that diet and probiotics may profoundly affect amyloid plaque deposition.

In another G2T project, Dr. Berislav Zlokovic has discovered important functions for PICALM in removing amyloid from the brain by exporting it out into the bloodstream. In testing known drugs for their ability to affect PICALM pathways, Dr. Zlokovic recently identified one drug that my lab and that of Dr. Steve Wong—as part of the CureAlz 3-D Drug Screening (3DDS) Consortium—had simultaneously identified for

its ability to reduce amyloid beta and tau pathology in the CureAlz Alzheimer's in a Dish model. The fact that we recognized this mutual discovery on a Research Leadership Group call is truly a testament to the power of the collaboration model CureAlz has established. Summaries of our many other G2T projects are included in this report.

We've known for a long time that the APOE4 gene variant is the most common genetic risk factor for late-onset Alzheimer's disease, but our understanding of how this variant leads to the disease has remained largely a mystery, beyond obvious effects on clearance of amyloid from the brain. Apoliprotein E (the protein encoded by the APOE gene) is found throughout the body and is important for its role in cholesterol metabolism. In the brain, the majority of APOE is produced by astrocytes and is secreted in high-density-like lipoproteins; among other activities, it transports cholesterol to neurons. Although significant evidence has shown that APOE expression affects both amyloid beta aggregation and accumulation in the brain, more recent investigations also have shown important interactions with tau and cerebrovasculature. Our new APOE consortium, composed of five world-leading labs, is examining APOE in different cell types in the brain as well as outside the brain in the body's periphery. Drs. David Holtzman, Paul Greengard, Cheryl Wellington, Randy Bateman, Guojun Bu and Oleg Butovsky each are working individually and also in collaboration. Each project will include in its analysis data from animal models of both sexes, a high priority given the known but as-of-yet-unexplained difference in impact of the different APOE variants for men and women. We are eager to hear what this consortium learns over the next two years.

"The tremendous developments of this past year remind us that science is not a straight-line process, and that Alzheimer's is an extremely complex disease."

Our Alzheimer's Genome Project as well as findings from throughout the field have identified dozens of gene variants related to neuroinflammation (microglia and innate immunity) that impact on AD risk. The brain's innate immune system can help clear away amyloid plaques or cause inflammation, which arguably kills the most nerve cells in the brains of Alzheimer's patients. Genes such as TREM2 and CD33, which was identified in our Alzheimer's Genome Project, determine which of these innate immune events (amyloid clearance or neuroinflammation) will dominate in the brain. As a result, CureAlz has expanded its efforts in this area to initiate a new consortium aimed at understanding how to regulate the brain's innate immune system to govern neuroinflammation. It includes important projects on CD33 and TREM2 from Drs. Marco Colonna and David Holtzman, and from Dr. Christian Haass in collaboration with Dr. Beth Stevens; on microglial proteins with Dr. Greg Lemke, a new investigator for us; and on deactivation of neuroinflammation with Dr. Vishwa (Deep) Dixit, among many others.

If we can turn down neuroinflammation in the brain, we will have a much better chance to treat patients who already are suffering with symptoms of Alzheimer's-related cognitive impairment and dementia. This is because "resilient brain" studies have shown that we can live with large numbers of plaques and tangles in our brain and remain dementia-free, as long as neuroinflammation is kept in check. Along these lines, the CureAlz 3-D drug discovery effort is now using a new version of Alzheimer's in a Dish that recapitulates all three pillars of Alzheimer's pathology: not only the plaques and tangles of the original system, but also neuroinflammation. By integrating the Alzheimer's genes involved with neuroinflammation, such as CD33 and TREM2, into this system, the 3DDS consortium has been able to carry out screening for drugs that target neuroinflammation, and has identified a dozen approved drugs and natural compounds that were effective in

"If we can turn down neuroinflammation in the brain, we will have a much better chance to treat patients who already are suffering with symptoms of Alzheimer's-related cognitive impairment and dementia."

curbing neuroinflammation. These now are being tested in mouse models in the G2T program and are being considered for clinical trials in patients.

Meanwhile, my ongoing collaboration with Dr. Rob Moir exploring the role of amyloid as an antimicrobial peptide, essentially a soldier in the brain's innate immune response unit, also has made a great deal of progress during 2017. We have published data showing that amyloid plaques form quickly in response to microbial pathogens (bacteria, viruses, fungus) that are activated in the brain, or capable of crossing the blood-brain barrier into the brain. We now are working to catalog exactly which microbes most often are found in the brains of Alzheimer's patients and in healthy brains. If we can someday identify the main microbes driving amyloid formation in the brain, we may be able to specifically target them with antimicrobial drugs or even vaccination as a form of primary prevention of Alzheimer's disease. I will be eager to share more with you as 2018 progresses.

While every one of the 67 projects and 76 investigators we funded in 2017 deserves mention here, I cannot possibly do them all justice. I hope you will enjoy reading more about their work in this report. However, I cannot close without mentioning one researcher in particular: Dr. Ben Barres, a giant in the field and a true pioneer. Ben's seminal work on the role of glia in brain health and neuroinflammation was critical to the field's recognition of the key role played by the brain's innate immune system in health and disease. As the centrality of neuroinflammation to Alzheimer's emerged, he joined and became an invaluable member of the Cure Alzheimer's Fund Research Leadership Group. Ben passed away in December, but worked with us and with his colleagues at Stanford up until the very end; his devotion to science defined him through every day of his life. He will be missed as a scientist for his brilliant, incisive mind; he is missed as a colleague and a friend for his kindness, generosity and humility.

The tremendous developments of this past year remind us that science is not a straight-line process, and that Alzheimer's is an extremely complex disease. But, our investigators are decoding this disease, accelerating the path to effective treatments. I am proud to be a part of the CureAlz team, a group of world-class researchers tasked by you to work on the toughest questions of Alzheimer's disease in the most expedient manner to find a cure. While we had far too many exciting projects this year for me to discuss them all in this letter, I encourage you to read about all of them in this report.

In closing, I am grateful for another remarkable year of groundbreaking research made possible by CureAlz. What my Cure Alzheimer's Fund colleagues and I have been able to achieve in the fight against Alzheimer's is possible thanks to your unwavering commitment to this most noble of causes. While each of us is driven by the excitement of scientific discovery, we are always mindful of our true goal: helping patients and families, and ending the burden of Alzheimer's disease. Thank you for the opportunity to do so in partnership with all of you.

Sincerely yours,

Rudy Tanzi, Ph.D.
Research Leadership Group Chair

# Cure Alzheimer's Fund Loses
# AN EXCEPTIONAL RESEARCHER AND A DEAR FRIEND

**On December 27, 2017, Ben Barres lost his battle with pancreatic cancer at the age of 63.**

Ben was an acclaimed neuroscientist from Stanford University who changed our understanding of the brain. Ben's research was groundbreaking regarding the role of glia cells—those cells that make up the majority of the brain but are not nerve cells. A January 2, 2018, article about Ben and his life in *The Atlantic* described his work this way, "While most of his fellow neuroscientists studied neurons, the branching cells that carry electrical signals through the brain, Barres focused his attention on another group of cells called glia. Even though they equal neurons in number, glia were long dismissed as the brain's support crew—there simply to provide nutrients or structural scaffolding. But Barres showed that glia are stars in their own right. They help neurons to mature, producing the connections that are the basis for learning and memory, and then pruning those connections so that the most useful ones remain."

Throughout his life, Ben was a passionate mentor and teacher, and an outspoken advocate for gender equality in the sciences.

Ben, who was transgender, became a member of the Cure Alzheimer's Research Consortium in 2017. "The intellectual horsepower, innovative turn of mind and humanity Ben brought to some of the world's seemingly intractable medical mysteries had us all in awe. The world has lost an exceptional human being," said Cure Alzheimer's Fund President and CEO Tim Armour.

# The Research

## Our New Science Structure

When considering the science structure for Cure Alzheimer's Fund, the founders quickly identified that they did not want to direct the science—instead, experienced and accomplished scientists would play that very important and crucial role. Consequently, two classic scientific structures were put in place:

- The members of the *Research Consortium* were charged with identifying the most promising areas in the field of Alzheimer's disease research, as well as recommending other researchers with great work who should receive grants from Cure Alzheimer's Fund.
- The second group, the *Scientific Advisory Board*, was independent from the Research Consortium and would advise and counsel Cure Alzheimer's Fund leadership regarding the scientific soundness of the recommended research priorities. This group also would review grant proposals for consistency with the overall objectives of Cure Alzheimer's Fund.

As our organization grew, it became necessary to re-evaluate our approach to science direction and oversight. Cure Alzheimer's Fund engaged in a strategic assessment of our science oversight groups and, as a result of that assessment, implemented recommended changes.

First, our Research Consortium and Scientific Advisory Board have been merged into a new entity, the Research Leadership Group, with 29 of the world's leading scientists in the field of Alzheimer's disease. These leaders will continue to be the primary decision makers regarding our overall direction, as well as for consideration of specific proposals and projects.

We also have established a group called the Research Strategy Council, composed of extraordinary individuals with a wide range of relevant expertise. They will be tasked with assessing our entire portfolio of funded research to ensure we are active in the right topical areas, that we are continuing the right lines of investigation, and that our choices of what to fund are fully aligned with our goal of accelerating the development of a disease-altering treatment or cure for Alzheimer's disease. RSC members will work closely with the new Research Leadership Group and its Chair, Dr. Rudy Tanzi, and will report to our Board of Directors regarding their recommendations.

# Our Researchers

This gallery features researchers who received funding in 2017, as well as the members of our Research Leadership Group and Research Strategy Council.

**RANDALL J. BATEMAN, M.D.**

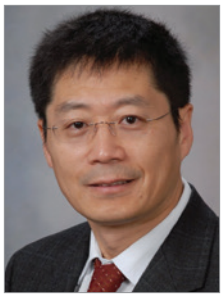
Washington University
School of Medicine

*Charles F. and Joanne Knight Distinguished Professor of Neurology*

**GEORGE S. BLOOM, PH.D.**

University of Virginia

*Professor of Biology, Cell Biology and Neuroscience*



**GUOJUN BU, PH.D.**

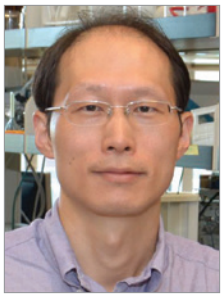
Mayo Clinic Jacksonville

*Professor of Neuroscience and Associate Director, Center for Regenerative Medicine*

**OLEG BUTOVSKY, PH.D.**

Brigham & Women's Hospital

*Assistant Professor of Neurology, Harvard Medical School*



**HANSANG CHO, PH.D.**

University of North Carolina
at Charlotte

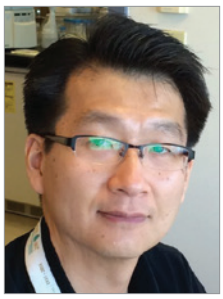
*Assistant Professor of Mechanical Engineering and Engineering Science*

**DENNIS CHOI, M.D., PH.D.**

Stony Brook University
School of Medicine

*Chair of the Department of Neurology; Director of the Institute for Advanced Neurosciences*

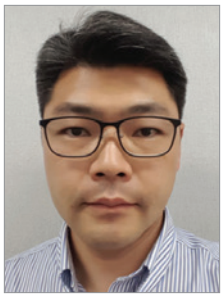
*Research Strategy Council*



**SE HOON CHOI, PH.D.**

Massachusetts General Hospital

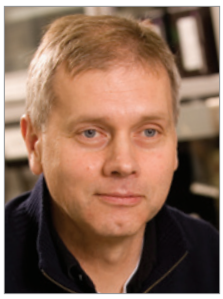
*Assistant Professor of Neurology, Harvard Medical School*



**WON-SUK CHUNG, PH.D.**

KAIST

*Assistant Professor, Biological Science*



**MARCO COLONNA, M.D.**

Washington University
School of Medicine

*Robert Rock Belliveau, M.D., Professor of Pathology and Immunology; Professor of Medicine*

*Research Leadership Group*

**BART DE STROOPER, M.D., PH.D.**

VIB-KU Leuven Center for Brain and Disease Research (Belgium)

*Director, VIB-KU Leuven Center for Brain and Disease Research; Professor of Molecular Medicine, Scientific Director, Department of Molecular and Developmental Genetics, KU Leuven*

*Research Leadership Group*

**MAARTEN DEWILDE, PH.D.**

VIB-KU Leuven Center for Brain and Disease Research (Belgium)

*Professor Faculty of Medicine, Head of the Laboratory for the Research of Neurodegenerative Diseases, KU Leuven*

**MARC DIAMOND, M.D.**

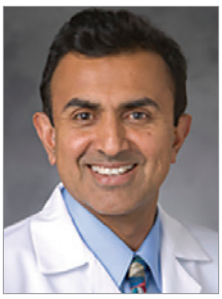
University of Texas Southwestern Medical Center

*Director, Center for Alzheimer's and Neurodegenerative Diseases; Professor and Director; Distinguished Chair in Basic Brain Injury and Repair*

**VISHWA DEEP DIXIT, D.V.M., PH.D.**

Yale School of Medicine

*Professor of Comparative Medicine and of Immunobiology*

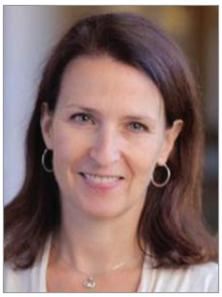


**MURALI DORAISWAMY, M.D.**

Duke University

*Professor of Psychiatry and Behavioral Sciences*

*Research Leadership Group*

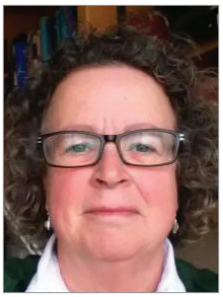


**KAREN DUFF, PH.D.**

Columbia University

*Deputy Director, Taub Institute for Research on Alzheimer's Disease and the Aging Brain; Professor of Pathology and Cell Biology*

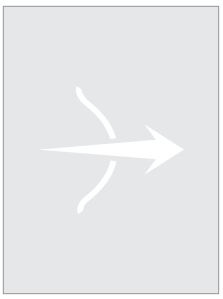
*Research Leadership Group*



**FRANCES EDWARDS, PH.D.**

University College, London

*Professor of Neurodegeneration*



**MICHELLE E. EHRLICH, M.D.**

Icahn School of Medicine at Mount Sinai

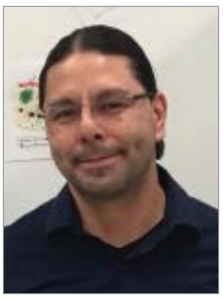
*Professor of Pediatrics and Neurology*

**CALEB FINCH, PH.D.**

University of Southern California

*ARCO/William F. Kieschnick Professor in the Neurobiology of Aging; University Professor*

*Research Leadership Group*



**GILBERT GALLARDO, PH.D.**

Washington University School of Medicine

*Assistant Professor, Department of Neurology*

**SAMUEL GANDY, M.D., PH.D.**

Icahn School of Medicine at Mount Sinai

*Professor of Alzheimer's Disease Research; Professor of Neurology and Psychiatry; Associate Director of the Mount Sinai Alzheimer's Disease Research Center*

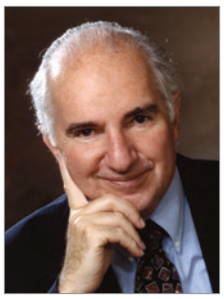
*Research Leadership Group*

**CHARLES GLABE, PH.D.**

University of California, Irvine

*Professor, Molecular Biology and Biochemistry*

*Research Leadership Group*



**ALFRED L. GOLDBERG, PH.D.**

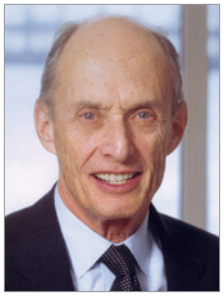
Harvard Medical School

*Professor of Cell Biology*

**PAULA GRAMMAS, PH.D.**

University of Rhode Island

*Thomas M. Ryan Professor of Neuroscience; Executive Director of the George & Anne Ryan Institute for Neuroscience*



**PAUL GREENGARD, PH.D., AND NOBEL LAUREATE**

The Rockefeller University

*Vincent Astor Professor and Head of the Laboratory of Molecular and Cellular Neuroscience; Nobel Prize in Physiology or Medicine, 2000*

*Research Leadership Group*

**ANA GRICIUC, PH.D.**

Massachusetts General Hospital

*Assistant Professor of Neurology, Harvard Medical School*

**VINCE GROPPI, PH.D.**

Life Sciences Institute, University of Michigan

*Director, Center for the Discovery of New Medicines*

*Research Strategy Council*

**CHRISTIAN HAASS, PH.D.**

DZNE Munich

*Head of the Laboratory of Neurodegenerative Disease Research; Member of the Center for Integrated Protein Science; Speaker of the German Center for Neurodegenerative Diseases; Speaker of the Collaborative Research Center 596*

*Research Leadership Group*

**JOHN HARDY, PH.D.**

University College, London

*Professor of Neuroscience; Head of the Department of Molecular Neuroscience; Chair of Molecular Biology of Neurological Disease*

**DAVID HOLTZMAN, M.D.**

Washington University School of Medicine

*Andrew B. and Gretchen P. Jones Professor and Chairman of Neurology; Associate Director of the Alzheimer's Disease Research Center; Scientific Director of the Hope Center for Neurological Disorders*

*Research Leadership Group*

**RICHARD L. HUGANIR, PH.D.**

Johns Hopkins University School of Medicine

*Director, Department of Neuroscience; Professor*

*Research Leadership Group*

**NANCY IP, PH.D.**

Hong Kong University of Science and Technology

*Head of the Department of Biochemistry; Director of Biotechnology Research Institute; Dean of Science*

*Research Leadership Group*

**DANIEL IRIMIA, M.D., PH.D.**

Massachusetts General Hospital

*Associate Professor of Surgery, Harvard Medical School; Associate Bioengineer, Massachusetts General Hospital; Deputy Director, BioMEMS Resource Center*

**RUDOLF JAENISCH, M.D.**

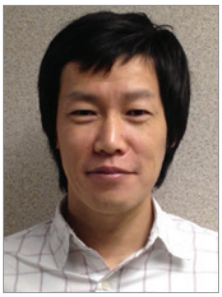
Whitehead Institute and Massachusetts Institute of Technology

*Professor of Biology*

**ROGER KAMM, PH.D.**

Massachusetts Institute of Technology

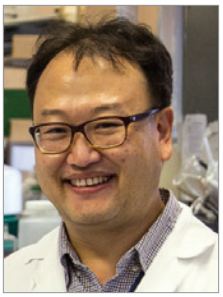
*Cecil and Ida Green Distinguished Professor of Biological and Mechanical Engineering*



**TAKAHISA KANEKIYO, M.D., PH.D.**

Mayo Clinic Jacksonville

*Assistant Professor of Neuroscience*



**DOO YEON KIM, PH.D.**

Massachusetts General Hospital

*Assistant Professor of Neurology, Harvard Medical School; Assistant in Neuroscience*

**TAE-WAN KIM, PH.D.**

Columbia University

*Associate Professor of Pathology and Cell Biology, Taub Institute for Research on Alzheimer's Disease and the Aging Brain*

**JONATHAN KIPNIS, PH.D.**

University of Virginia

*Harrison Distinguished Teaching Professor and Chair, Department of Neuroscience; Director, Center for Brain Immunology and Glia*

**DEEPAK VIJAYA KUMAR, PH.D.**

Massachusetts General Hospital

*Instructor in Neurology, Harvard Medical School*

**BRUCE LAMB, PH.D.**

Indiana University School of Medicine

*Executive Director, Paul and Carole Stark Neurosciences Research Institute*

*Research Leadership Group*

**CHRISTOPH LANGE, PH.D.**

Harvard School of Public Health

*Professor of Biostatistics*

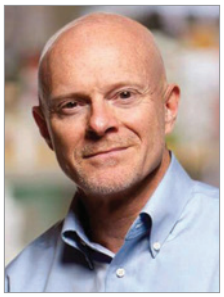
*Research Leadership Group*

**JOHN S. LAZO, PH.D.**

University of Virginia

*Distinguished Professor, Departments of Pharmacology, Chemistry, Biochemistry and Molecular Genetics*

*Research Leadership Group*



**GREG LEMKE, PH.D.**

Salk Institute for Biological Studies

*Professor, Molecular Neurobiology Laboratory; Françoise Gilot-Salk Chair*

**YUEMING LI, PH.D.**

Memorial Sloan Kettering Cancer Center

*Professor and Director of Graduate Program in Pharmacology*

**ROBERT C. MALENKA, M.D., PH.D.**

Stanford University School of Medicine

*Pritzker Professor of Psychiatry and Behavioral Sciences; Director of Pritzker Laboratory; Co-Director, Institute for Neuroscience Innovation and Translational Neurosciences*

*Research Leadership Group*

**ROBERTO MALINOW, M.D., PH.D.**

University of California, San Diego

*Shiley Endowed Chair in Alzheimer's Disease Research in Honor of Dr. Leon Thal; Distinguished Professor*

*Research Leadership Group*

**ECKHARD MANDELKOW, PH.D.**

DZNE Bonn

*Professor and Group Leader*

**EVA-MARIA MANDELKOW, M.D., PH.D.**

DZNE Bonn

*Senior Group Leader*

**FREDERICK R. MAXFIELD, PH.D.**

Weill Cornell Medical College

*Vladimir Horowitz and Wanda Toscanini Horowitz Distinguished Professor in Neuroscience, Biochemistry*

**WILLIAM C. MOBLEY, M.D., PH.D.**

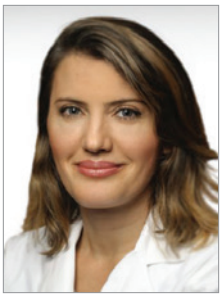
University of California, San Diego

*Associate Dean for Neurosciences Initiatives; Distinguished Professor of Neurosciences; Florence Riford Chair for Alzheimer Disease Research*

*Research Leadership Group*

**ROBERT MOIR, PH.D.**
Massachusetts General Hospital
*Assistant Professor of Neurology, Harvard Medical School*

**JOHN MORRIS, M.D.**
Washington University School of Medicine
*Director of the Charles F. and Joanne Knight Alzheimer's Disease Research Center, Memory and Aging Project; Harvey A. and Dorismae Hacker Friedman Distinguished Professor of Neurology; Professor of Pathology and Immunology*
*Research Strategy Council, Chair*



**NATURA MYEKU, PH.D.**
Columbia University
*Assistant Professor of Pathology and Cell Biology*

**MATTHIAS NAHRENDORF, M.D., PH.D.**
Massachusetts General Hospital
*Professor of Radiology, Harvard Medical School*

**MAIKEN NEDERGAARD, M.D., D.M.SC.**
University of Rochester Medical Center
*Co-Director, Department of Neurosurgery, Center for Translational Neuromedicine; Professor, Department of Neurology; Professor, Department of Neuroscience*

**ALEXANDRA NEWTON, PH.D.**
University of California, San Diego
*Professor of Pharmacology*

**ERIN H. NORRIS, PH.D.**
The Rockefeller University
*Research Assistant Professor*

**TAL NURIEL, PH.D.**
Columbia University
*Postdoctoral Research Fellow*

**STEVE PAUL, M.D.**
*Former President, Lilly Research Laboratories; Former Scientific Director, National Institute of Mental Health*
*Research Strategy Council*

**RONALD C. PETERSON, M.D., PH.D.**
Mayo Clinic
*Director, Alzheimer's Disease Research Center*
*Research Leadership Group*

**ANDREAS R. PFENNING, PH.D.**

Carnegie Mellon University

*Assistant Professor; Computational Biology Department*

**CHRISTIAN PIKE, PH.D.**

University of Southern California

*Professor in Gerontology, Division of Biogerontology*

**KAREN REEVES, M.D.**

AZ Therapies

*President and Chief Medical Officer*

*Research Strategy Council*

**STEPHEN R. SALTON, M.D., PH.D.**

Icahn School of Medicine
at Mount Sinai

*Professor of Neuroscience; Professor of Geriatrics and Palliative Medicine*

**ERIC E. SCHADT, PH.D.**

Icahn School of Medicine
at Mount Sinai

*Director, Institute for Genomics and Multiscale Biology; Chair of the Department of Genetics and Genomics Sciences; Professor of Genomics*

*Research Leadership Group*

**ELIZABETH R. SHARLOW, PH.D.**

University of Virginia

*Associate Professor of Research, Pharmacology; Co-Director, Fiske Drug Discovery Laboratory*

**SANGRAM S. SISODIA, PH.D.**

University of Chicago

*Thomas Reynolds Sr. Family Professor of Neurosciences; Director, Center for Molecular Neurobiology, Department of Neurobiology*

*Research Leadership Group*

**STEPHEN SNYDER, PH.D.**

National Institute of Aging
Division of Neuroscience

*Retired Deputy Director*

*Research Strategy Council*

**HERMANN STELLER, PH.D.**

The Rockefeller University

*Strang Professor; Head of the Laboratory of Apoptosis and Cancer Biology*

**BETH STEVENS, PH.D.**

Boston Children's Hospital

*Research Associate in Neurology, Associate Professor of Neurology, Harvard Medical School*

*Research Leadership Group*

**SIDNEY STRICKLAND, PH.D.**

The Rockefeller University

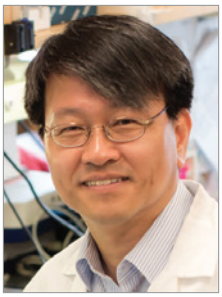
*Vice President for Educational Affairs; Dean of Graduate and Postgraduate Studies; Research Professor, Patricia and John Rosenwald Laboratory of Neurobiology and Genetics*

**THOMAS C. SÜDHOF, M.D., AND NOBEL LAUREATE**

Stanford University School of Medicine

*Avram Goldstein Professor in the School of Medicine; Professor of Neurology and Psychiatry and Behavioral Sciences*

*Research Leadership Group*



**JAEHONG SUH, PH.D.**

Massachusetts General Hospital

*Assistant Professor of Neurology, Harvard Medical School; Assistant Investigator, Massachusetts General Hospital*

**FILIP SWIRSKI, PH.D.**

Massachusetts General Hospital

*Associate Professor of Radiology, Harvard Medical School; Patricia and Scott Eston MGH Research Scholar*

**RUDOLPH TANZI, PH.D.**

Massachusetts General Hospital

*Joseph P. and Rose F. Kennedy Professor of Neurology, Harvard Medical School; Vice Chair, Massachusetts General Hospital Neurology Department; Director, Genetics and Aging Research Unit*

*Research Leadership Group, Chair*

**GIUSEPPINA TESCO, M.D., PH.D.**

Tufts University

*Associate Professor of Neuroscience, Tufts University School of Medicine*

**LI-HUEI TSAI, PH.D.**

Massachusetts Institute of Technology

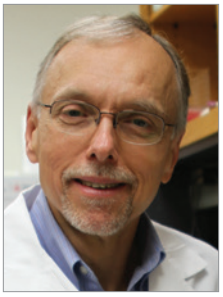
*Director, The Picower Institute for Learning and Memory; Professor of Neuroscience, Department of Brain and Cognitive Sciences; Senior Associate Member, Broad Institute*

*Research Leadership Group*

**MARK TUSZYNSKI, M.D., PH.D.**

University of California, San Diego

*Professor of Neurosciences; Director of the Center for Neural Repair; Attending Neurologist*



**ROBERT VASSAR, PH.D.**

Northwestern University

*Professor of Cell and Molecular Biology*

*Research Leadership Group*

**STEVEN L. WAGNER, PH.D.**

University of California, San Diego

*Associate Professor of Neurosciences*

*Research Leadership Group*

**WILMA WASCO, PH.D.**

Massachusetts General Hospital

*Associate Professor of Neurology, Associate Geneticist, Harvard Medical School*

**CHERYL WELLINGTON, PH.D.**

University of British Columbia

*Professor, Department of Pathology and Laboratory Medicine*

**NORELLE C. WILDBURGER, PH.D.**

Washington University
School of Medicine

*Postdoctoral Research Fellow*

**BENJAMIN WOLOZIN, M.D., PH.D.**

Boston University

*Professor, Department of Pharmacology and Experimental Therapeutics and Neurology*

**STEPHEN T. WONG, PH.D.**

Houston Methodist Research Institute

*John S. Dunn Sr. Distinguished Endowed Chair in Biomedical Engineering; Professor of Radiology, Pathology, Laboratory Medicine, Neurology and Neurosciences; Chief of Medical Physics and Chief Research Information Officer; Associate Director of Translational Research*

*Research Leadership Group*

**WEIMING XIA, PH.D.**

Boston University

*Research Associate Professor, Pharmacology and Experimental Therapeutics; Acting Associate Director of Research, Bedford Geriatric Research Education Clinical Center, Bedford VA Medical Center*

**HUAXI XU, PH.D.**

Sanford Burnham Prebys Medical Discovery Institute

*Jeanne and Gary Herberger Leadership Chair in Neuroscience Research; Professor and Director, Neuroscience Initiative; Professor, Degenerative Diseases Program, Neuroscience and Aging Research Center*

**ANDREW S. YOO, PH.D.**

Washington University
School of Medicine

*Assistant Professor, Department of Developmental Biology*

**ZHEN ZHAO, PH.D.**

University of Southern California

*Assistant Professor of Physiology and Neuroscience*

**BERISLAV ZLOKOVIC, M.D., PH.D.**

University of Southern California

*Chair and Professor of Physiology and Neuroscience*

*Mary Hayley and Selim Zilkha Chair in Alzheimer's Disease Research; Director, Zilkha Neurogenetic Institute*

*Research Leadership Group*

# 2017 Funded Research

Cure Alzheimer's Fund distributed **$15.7 million to support 67 research projects** across our focus areas, an all-time high record. Visit **CureAlz.org/the-research** to read about all of our current research projects.

| Project/Researcher | Distribution Amount |
|---|---|
| **Alzheimer's Genome Project™ and Functional Genomics** | |
| **Modeling DNA Methylation Changes in Alzheimer's Disease Using Human-Induced Pluripotent Stem Cells**<br>Rudolf Jaenisch, M.D., Massachusetts Institute of Technology | **$150,000** |
| **Gene Expression Throughout Development of Pathology in APPKI Mice; Effects of Human Tau and Aging**<br>John Hardy, Ph.D., and Frances Edwards, Ph.D., University College, London | **$198,987** |
| **Alzheimer's Genome Project™**<br>Rudolph Tanzi, Ph.D., Massachusetts General Hospital | **$1,500,000** |
| **Genes to Therapies™/Stem Cell Drug Screening: Translational studies investigating established and newly confirmed AD genes** | |
| **G2T Research Model and Materials**<br>Taconic Biosciences | **$1,390,209** |
| **Role of ATXN1 in Regulating BACE1 Activity**<br>Jaehong Suh, Ph.D., Massachusetts General Hospital | **$287,500** |
| **ABCA7 in Brain Homeostasis and Alzheimer's Disease**<br>Guojun Bu, Ph.D., and Takahisa Kanekiyo, M.D., Ph.D., Mayo Clinic Jacksonville | **$200,000** |
| **Molecular and Cellular Mechanisms of an ACE1 Variant in Alzheimer's Disease**<br>Robert Vassar, Ph.D., Northwestern University | Year 2: **$250,000**<br>Year 3: **$250,000** |
| **APOE Proteoforms in Human CNS and Validation of APOE Pharmacodynamic Translational Markers**<br>Randall J. Bateman, M.D., Washington University School of Medicine | **$250,000** |
| **The Role of PICALM Mutations in Alzheimer's Disease**<br>Berislav Zlokovic, M.D., Ph.D., and Zhen Zhao, Ph.D., University of Southern California | **$200,000** |
| ***In Vitro* and *In Vivo* Analysis of Amyloid Precursor Protein (APP) Variants**<br>Sangram Sisodia, Ph.D., University of Chicago | **$250,000** |
| **Effects of Peripheral APOE on Central Nervous System Functions and Alzheimer's Disease Pathogenesis**<br>Guojun Bu, Ph.D., Mayo Clinic Jacksonville | **$250,000** |
| **The Role of APOE in Microglia Regulation in Neurodegeneration**<br>Oleg Butovsky, Ph.D., Brigham and Women's Hospital | **$250,000** |
| **Impact of APOE and Sex on Vulnerable Neuron-Specific Functional Network**<br>Paul Greengard, Ph.D., The Rockefeller University | **$250,000** |
| **Understanding the Effect of APOE on Tau-Mediated Neurodegeneration**<br>David M. Holtzman, M.D., Washington University School of Medicine | **$300,000** |
| **Using Human Bioengineered Cerebral Vessels to Explore How Native APOE Affects Cerebrovascular Properties Relevant to Alzheimer's Disease**<br>Cheryl Wellington, Ph.D., University of British Columbia | **$248,458** |
| **Evaluation of Sleep-EEG in Transgenic Mice**<br>Psychogenics | **$27,500** |
| **Evaluation of Blood-Brain Barrier (BBB) Penetration of Alzheimer's Drug Targets, and Identification of BBB Integrity Enhancers**<br>Se Hoon Choi, Ph.D., and Roger Kamm, Ph.D., Massachusetts General Hospital/Massachusetts Institute of Technology | **$200,000** |
| **Compounds Modulating Microglial Uptake of Amyloid Beta and CD33-Targeted Immunotherapy for Alzheimer's Disease**<br>Ana Griciuc, Ph.D., and Rudolph Tanzi, Ph.D., Massachusetts General Hospital | **$250,000** |
| **High-Throughput Drug Screening for Alzheimer's Disease Using 3-D Human Neural Culture Systems**<br>Doo Yeon Kim, Ph.D., Massachusetts General Hospital | **$250,000** |
| **Alzheimer's Disease Stem Cell Drug Screening in 3-D**<br>Weiming Xia, Ph.D., Boston University School of Medicine | **$100,000** |

| Project/Researcher | Distribution Amount |
|---|---|
| **Genes to Therapies™/Stem Cell Drug Screening: Translational studies investigating established and newly confirmed AD genes (continued)** | |
| **Uncovering the Molecular Mechanism of Selected Drug Candidates Derived from Systemic Alzheimer's Drug Repositioning**<br>Stephen T. Wong, Ph.D., Houston Methodist Research Institute | **$150,000** |
| **Therapeutic Modulation of TREM2 Activity**<br>Christian Haass, Ph.D., DZNE Munich | **$112,000** |
| **SORLA Attenuates Amyloid Beta Toxicity Through Interactions with EphA4**<br>Huaxi Xu, Ph.D., Sanford Burnham Prebys Medical Discovery Institute | **$150,000** |
| **Discovery of CK1 Activators for Inducing the Autophagic Degradation of Amyloid Precursor Protein (APP) Beta-CTF**<br>Paul Greengard, Ph.D., The Rockefeller University | **$450,000** |
| **Functional Characterization of GGA3 Mutations Associated with Alzheimer's Disease**<br>Giuseppina Tesco, M.D., Ph.D., Tufts University | **$150,000** |
| **Investigating the Mechanism of APOE4-associated Neuronal Hyperactivity in the Entorhinal Cortex and its Effect on Tauopathy Propagation**<br>Karen Duff, Ph.D., and Tal Nuriel, Ph.D., Columbia University Medical Center | **$200,000** |
| **Genes to Therapies™ (G2T) Centralized Research Core**<br>Wilma Wasco, Ph.D., Massachusetts General Hospital | **$200,000** |
| **Protein Kinase C in Alzheimer's Disease**<br>Alexandra Newton, Ph.D., University of California, San Diego | **$250,000** |
| **TREM2: Role in Modulating Amyloid Beta and Tau-Related Pathologies and Neurodegeneration**<br>Marco Colonna, M.D., and David M. Holtzman, M.D., Washington University School of Medicine | **$300,000** |
| **Interactions Among TREM2, APOE and Sex**<br>Caleb Finch, Ph.D., and Christian Pike, Ph.D., University of Southern California | **$156,005** |
| **A Microfluidics-Based Human Brain Cell 3-D Culture System in Alzheimer's Disease**<br>Hansang Cho, Ph.D., University of North Carolina at Charlotte | **$152,350** |
| **Exploring Sex Differences in AD Pathogenesis Using 3-D Human Non-Cell-Autonomous Models**<br>Doo Yeon Kim, Ph.D., and Daniel Irimia, M.D., Ph.D., Massachusetts General Hospital | **$200,000** |
| **Identification: Early detection via biomarkers, imaging, etc.** | |
| **Amyloid Beta Kinetics and Enhancing the Diagnostic and Prognostic Cerebrospinal Fluid Biomarkers of Alzheimer's Disease**<br>Randall J. Bateman, M.D., and Norelle C. Wildburger, Ph.D., Washington University School of Medicine | **$50,000** |
| **Stable Isotope Labeling and Quantitative Mass Spectrometry Imaging of Alzheimer's Disease Pathology in Human Brain**<br>Randall J. Bateman, M.D., and Norelle C. Wildburger, Ph.D., Washington University School of Medicine | **$150,000** |
| **Immune System Structures and Processes: Role of inflammation and other responses in AD** | |
| **Early Role of Microglia in Synapse Loss in Alzheimer's Disease**<br>Beth Stevens, Ph.D., Boston Children's Hospital | **$150,000** |
| **Microglial TAM Receptors as Modulators of Alzheimer's Pathology**<br>Greg Lemke, Ph.D., Salk Institute for Biological Studies | **$150,000** |
| **Impact of Inflammasome Deactivation on Alzheimer's Disease**<br>Vishwa Deep Dixit, D.V.M., Ph.D., Yale School of Medicine | **$150,000** |
| **Synapse Pruning by Astrocytes: A Potential New Target for Treating Alzheimer's Disease**<br>Won-Suk Chung, Ph.D., KAIST | **$150,000** |
| **Systemic Inflammatory Networks in Alzheimer's Disease**<br>Filip Swirski, Ph.D., and Matthias Nahrendorf, M.D., Ph.D., Massachusetts General Hospital | **$150,000** |
| **The Role of the Contact System in Alzheimer's Disease**<br>Sidney Strickland, Ph.D., and Erin H. Norris, Ph.D., The Rockefeller University | **$150,000** |
| **Targeting Reactive Astrocytes for Therapeutic Intervention in Alzheimer's Disease**<br>Gilbert Gallardo, Ph.D., Washington University School of Medicine | **$150,000** |
| **Chronic Viral Neuroinfection Mediates Amyloid Beta Deposition in Transgenic Alzheimer's Disease Mice**<br>Robert Moir, Ph.D., Massachusetts General Hospital | **$350,000** |
| **Regulation of Microglial Lysosome Acidification**<br>Frederick R. Maxfield, Ph.D., Weill Cornell Medical College | **$150,000** |
| **VGF, a Novel Therapeutic Effector of Alzheimer's Disease Pathogenesis and Progression**<br>Michelle E. Ehrlich, M.D., and Stephen R. Salton, M.D., Ph.D., Icahn School of Medicine at Mount Sinai | **$150,000** |

| Project/Researcher | Distribution Amount |
|---|---|
| **Microbiome: Interaction of the Microbiome with AD** | |
| **Gut Microbiome-Mediated Shifts in Amyloid Beta Deposition in a Humanized Alzheimer's Disease Mouse Model**<br>Deepak Vijaya Kumar, Ph.D., Massachusetts General Hospital | **$250,000** |
| **Mechanisms by Which the Gut Microbiome Influences Amyloid Deposition and Neuroinflammation in the APPswe/ PS1DE9 Mouse Model of Amyloid Beta Amyloidosis**<br>Sangram S. Sisodia, Ph.D., University of Chicago | **$175,000** |
| **Other: Novel approaches, targets or therapies aligned with the Cure Alzheimer's Fund mission** | |
| **Pathway Cross-talks Associated with Sex and Risk for Alzheimer's Disease**<br>Murali Doraiswamy, M.D., Duke University | **$152,276** |
| **Modeling Neuronal Aging in Specific Subtypes of Human Neurons by MicroRNA-Mediated Neuronal Reprogramming**<br>Andrew S. Yoo, Ph.D. , Washington University School of Medicine | **$150,000** |
| **Pathological Pathways and Systems** | |
| **Tau Missorting in Alzheimer's Disease—Causes and Consequences**<br>Eva-Maria Mandelkow, M.D., Ph.D., and Eckhard Mandelkow, Ph.D., DZNE Bonn | **$172,500** |
| **The Role of Meningeal Lymphatics in Cleansing the Brain: Implications for Alzheimer's Disease**<br>Jonathan Kipnis, Ph.D., University of Virginia | **$150,000** |
| **Genetic Targets to Block Tau Propagation: Test Knockdown of Heparan Sulfate Proteoglycan Genes *in Vivo***<br>Marc Diamond, M.D., University of Texas Southwestern Medical Center | **$150,000** |
| **Inhibition of Tau Pathology in Human Neurons**<br>Benjamin Wolozin, M.D., Ph.D., Boston University | **$100,000** |
| **Propagation of Tauopathy and Ubiquitin Proteasome System Dysfunction: Impact and Rescue with a UPS Activator**<br>Karen Duff, Ph.D., and Natura Myeku, Ph.D., Columbia University Medical Center | **$320,106** |
| **Will Restoration of Normal Glymphatic Function Slow Progression of Cognitive Decline and Amyloid Plaques in a Murine Alzheimer's Model?**<br>Maiken Nedergaard, M.D., D.M.Sc., University of Rochester Medical Center | **$150,000** |
| **Cerebrovascular Dysfunction in AD: Targeting the Mechanisms of Vascular Activation**<br>Paula Grammas, Ph.D., University of Rhode Island | **$150,000** |
| **Stimulating Proteasome Activity for the Treatment of Alzheimer's Disease**<br>Hermann Steller, Ph.D., The Rockefeller University | **$150,000** |
| **Targeting Cell Cycle Re-entry Using 3-D Neuron Cultures**<br>George S. Bloom, Ph.D., John S. Lazo, Ph.D., and Elizabeth R. Sharlow, Ph.D., University of Virginia Medical Center | **$190,681** |
| **Therapeutic Strategies and Drug Discovery** | |
| **A Combination of Anti-Amyloid Beta and Growth Factor Therapy for Alzheimer's Disease**<br>Mark Tuszynski, M.D., Ph.D., University of California, San Diego | **$125,000** |
| **Activation of the 26S Proteasome for the Treatment of Alzheimer's Disease**<br>Alfred L. Goldberg, Ph.D., Harvard Medical School | **$150,000** |
| **Nanobodies to Cross the Blood-Brain Barrier**<br>Bart De Strooper, M.D., Ph.D., and Maarten Dewilde, Ph.D., VIB-KU Leuven Center for Brain and Disease Research (Belgium) | **$150,000** |
| **Biochemical Mapping of the GSM Binding Site of Novel Pyridazine-Derived Small Molecule Gamma-Secretase Modulators**<br>Steven L. Wagner, Ph.D., and Yueming Li, Ph.D., University of California, San Diego/Memorial Sloan Kettering Cancer Center | **$300,000** |
| **Novel Chemical Modulators for BACE1-Mediated Cleavage of Amyloid Beta Precursor Protein**<br>Tae-Wan Kim, Ph.D., Columbia University | **$150,000** |
| **Treating with Gamma-Secretase Modulators (GSMs) to Prevent Neurodegeneration in Mouse Models of Down Syndrome**<br>William C. Mobley, M.D., Ph.D., and Steven L. Wagner, Ph.D., University of California, San Diego | **$150,000** |
| **Validation of Endogenous Human Antibodies That are Correlated With Avoiding Alzheimer's Disease and Their Corresponding Antigens, for Immunotherapeutic Development**<br>Charles Glabe, Ph.D., University of California, Irvine | **$150,000** |
| **Whole Genome Sequencing and Epigenetics** | |
| **Analytical and Statistical Tools for Sequence Analysis for Alzheimer's Disease**<br>Christoph Lange, Ph.D., Harvard School of Public Health | **$250,000** |
| **CIRCUITS: Interpreting Alzheimer's Disease-Associated Genetic Variation at Enhancer Regions**<br>Andreas R. Pfenning, Ph.D., Carnegie Mellon University | **$193,786** |

# Alzheimer's Genome Project and Functional Genomics

## Modeling DNA Methylation Changes in Alzheimer's Disease Using Human-Induced Pluripotent Stem Cells

**RUDOLF JAENISCH, M.D.,** Massachusetts Institute of Technology

Alzheimer's disease is associated with changes to DNA methylation, a modification of DNA that can alter the expression of genes in the brain. How DNA methylation changes contribute to Alzheimer's disease, however, has been hard to determine. Our proposed work aims to study the causes of DNA methylation changes in Alzheimer's disease and aims to better understand how these changes might affect Alzheimer's disease patients. To do this, we are using a "disease-in-a-dish" approach of generating human neurons with the hallmarks of Alzheimer's disease from human-induced pluripotent stem cells.

## Gene Expression Throughout Development of Pathology in APPKI Mice; Effects of Human Tau and Aging

**JOHN HARDY, PH.D.,** University College, London
**FRANCES EDWARDS, PH.D.,** University College, London

As the huge investments into cardiac and cancer research pay off with successful prevention and treatment of these common diseases, the average age of the world population continues to rise. This has the unfortunate consequence that age-related diseases, such as Alzheimer's disease, are rising rapidly. The increased prevalence of Alzheimer's disease in our aging population is becoming a crippling burden, both personally and financially for the families affected, and also for government health services across the world. This, the most urgent health problem of our time, must be solved. Understanding the underlying causes is the only way to develop effective treatments. Here we take advantage of recent improvements in animal models and technical advances in analysis of gene expression to achieve this goal, with the aim of finding new drug targets to tackle this ever-growing problem.

Alzheimer's disease starts decades before the problem of brain deterioration becomes apparent. During this time amyloid beta builds up in the brain and is increasingly deposited as amyloid plaques. But the disease only becomes problematic as further changes happen and tau tangles start to appear inside the brain cells. The most likely window of opportunity for preventing the loss of memory and other brain functions in Alzheimer's disease is the long period when amyloid beta has started to rise as the plaque load increases, but before tau tangles and brain degeneration set in. By the time Alzheimer's disease is diagnosed, substantial loss of brain tissue already has occurred, particularly in the hippocampus, a structure important for memory. In this study we concentrate on the effects on the hippocampus of rising amyloid beta before and during the increase of plaque load. Using new improved mouse models expressing genes that cause

Alzheimer's disease in humans, and taking advantage of recent technological advances, we will study the gene expression from the earliest stages, relating it directly to the first development of plaques and their progress throughout the life of the mice through to old age. In addition, we will investigate what is important about human compared with mouse tau, and assess whether it is critical for the final steps of the disease.

By comparing normal mice to mice with genes that cause different rates of rising amyloid beta, with and without human tau, we can work out which genes change their activity and how they are influenced by aging, giving us clues to which factors may be manipulated to prevent or delay disease progression. The data will be analyzed and published in the scientific literature, but it also will be added to a publicly available database that we have previously created for a study on dementia (www.mouseac.org). Anyone worldwide can look up any gene of interest and find out how it changes, and what other factors change with it, under these different conditions. This allows our data to benefit not only our research, but the research of scientists across the world, heading to a cure for Alzheimer's disease.

## Alzheimer's Genome Project™

**RUDOLPH TANZI, PH.D.,** Massachusetts General Hospital

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 amyloid precursor protein 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™ 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.

# Genes to Therapies™/Stem Cell Drug Screening

Translational studies investigating established and newly confirmed AD genes

## G2T Research Models and Materials

**TACONIC BIOSCIENCES**

Taconic Biosciences GMBH, a global provider of genetically modified mouse models and associated services, is providing customized mouse models (transgenic, conventional/conditional knock out, conventional/conditional knock in) for each specific gene and type of mutation that will be studied in the Genes to Therapies™ project.

## Role of ATXN1 in Regulating BACE1 Activity

**JAEHONG SUH, PH.D.,** Massachusetts General Hospital

A recent genetic study from our research group revealed that the Ataxin-1 gene (ATXN1) is genetically associated with Alzheimer's disease. ATXN1 encodes a nuclear protein, Ataxin-1, and DNA mutations that increase the CAG trinucleotide repeat in ATXN1 known to cause spinocerebellar ataxia type 1 (SCA1). SCA1 is a neurodegenerative disease that primarily impairs coordinated movement and later deteriorates the cognitive function of patients. In a preliminary study with mouse models, we found the deletion of ATXN1 elevates BACE1 expression in the brain. BACE1 cleaves amyloid precursor protein (APP) and initiates the generation of amyloid beta, the main culprit in senile plaques in Alzheimer's disease brains. In this proposed study, we will attempt to uncover the molecular mechanism by which Ataxin-1 regulates BACE1 expression and the amyloidogenic cleavage of APP in the brain. We will further investigate how Ataxin-1 affects Alzheimer's disease-related phenotypes such as amyloid beta plaque deposition, altered neuron generation and axonal path-finding in the brain.

## ABCA7 in Brain Homeostasis and Alzheimer's Disease

**GUOJUN BU, PH.D.,** Mayo Clinic Jacksonville
**TAKAHISA KANEKIYO, M.D., PH.D.,** Mayo Clinic Jacksonville

Genetic and environmental factors influence the risk of late-onset Alzheimer's disease; genetic studies have identified novel risk genes for the disease. ABCA7 is the gene encoding ATP-binding cassette sub-family A member 7; variants of ABCA7, which shares a homology with ABCA1, have shown a strong association with increased risk for late-onset Alzheimer's disease. Importantly, loss-of-function variants in ABCA7 also have been demonstrated to significantly increase Alzheimer's disease risk. While ABCA7 is expressed in neurons and

microglia in the brain, our knowledge of ABCA7 function in those cell types is limited. Our recent studies using knockout mice have implicated novel functions of ABCA7 in regulating amyloid beta production, cellular stress responses and the brain's immune system. Thus, we will further investigate how cell type-specific ABCA7 loss of function impacts known Alzheimer's disease-related pathways, to identify novel ones through nontargeted approaches. Specifically, we will examine ABCA7 function using primary neurons and microglia/macrophages using human-induced pluripotent stem cell (iPSC) models. We currently are generating iPSC lines where the ABCA7 gene is edited by CRISPR/Cas9 technology to model disease-associated mutations. We also are generating neuron- or microglia-specific ABCA7 knockout mice. Using these new models, we will comprehensively investigate how ABCA7 in each cell type regulates brain homeostasis, and how disturbances of these mechanisms contribute to the development of Alzheimer's disease. Our studies should lead to new therapeutic strategies targeting ABCA7 in Alzheimer's disease.

## Molecular and Cellular Mechanisms of an ACE1 Variant in Alzheimer's Disease (Years 2 and 3)

**ROBERT VASSAR, PH.D.,** Northwestern University

Alzheimer's disease is a complex genetic disorder that is the leading cause of dementia in the elderly. The Cure Alzheimer's Fund Alzheimer's Genome Project™ has identified a new mutation in a gene called ACE1 that is associated with increased risk for AD. How the ACE1 gene causes AD is completely unknown. The overarching goal of this project is to understand the role of the ACE1 gene in AD using cell-based models and genetically engineered mice. The information gathered from this study is expected to provide greater insight into the causes of AD in people and could lead to new AD therapeutic approaches.

## APOE Proteoforms in Human CNS and Validation of APOE Pharmacodynamic Translational Markers

**RANDALL J. BATEMAN, M.D.,** Washington University School of Medicine

APOE is the single greatest risk factor for Alzheimer's disease and causes up to half of all AD. The reasons for this genetic risk factor are uncertain, but there are several key ways APOE could cause AD. This includes different kinds, function, stability or amounts of APOE causing increased risk of amyloidosis and neurodegeneration. However, until recently, it has been challenging to accurately compare the amounts and kinds of different forms of APOE (there are three common forms called APOE2, APOE3 and APOE4). The first part of this study will determine the amounts and structure, including fragments, of each APOE form in the brain, cerebrospinal fluid and blood samples from AD and control participants. We will assess which kinds of APOE exist and whether there are specific forms associated with AD. The second part of this study will use these measurement techniques in mouse models to develop drug-specific biomarkers that then could be used in human clinical trials to determine whether a drug targeting APOE is working.

# The Role of PICALM Mutations in Alzheimer's Disease

**BERISLAV ZLOKOVIC, M.D., PH.D.,** University of Southern California
**ZHEN ZHAO, PH.D.,** University of Southern California

The search for biological understanding of Alzheimer's disease (AD) has expanded to include new risk factors, particularly genes. Thanks to breakthroughs in human genetics and high-throughput genome sequencing, PICALM, the gene encoding phosphatidylinositol binding clathrin assembly protein, has been identified as a new risk gene for AD. As a key player in clathrin-mediated endocytosis and intracellular trafficking, PICALM critically regulates amyloid beta brain metabolism and neuronal toxicity. Our group recently reported that reduction of PICALM in cerebral vasculature was strongly associated with AD progression in patients, and with accelerated disease progression in an animal model of AD. However, it still is unclear whether genetic variations or mutations of the PICALM gene directly contribute to the disease. Fortunately, the Alzheimer's Genome Project™, led by Dr. Rudy Tanzi at Harvard University, discovered three novel PICALM genetic mutations strongly associated with AD through whole genome sequencing (WGS). We have expanded our work for our renewal grant to investigate an additional 14 variants supplied by the Tanzi lab. The biological functions of these rare mutations need to be examined urgently, especially in a cell type-specific manner, in order to determine their direct contributions to the pathogenesis of AD.

Our recent study, using both transgenic models and CRISPR-mediated genomic editing in human induced pluripotent stem cells (iPSCs), has demonstrated that PICALM plays a key role in mediating the clearance of amyloid beta at the blood-brain barrier (BBB), as well as mitigating amyloid beta toxicity in neurons, providing molecular and cellular bases to investigate the amyloid beta-dependent and independent functions of novel PICALM mutations. We hypothesize that these mutations may represent loss-of-function (LOF) or gain-of-function (GOF) mutations that affect amyloid beta metabolism and toxicity in different brain cell types, particularly the brain endothelial cells and neurons. In this proposed study, we will investigate the functions of the novel PICALM mutations using both endothelial cells and neurons derived from CRISPR-engineered iPSCs, as well as in transgenic animal models, and examine their impact on trans-vascular clearance and neuronal toxicity of amyloid beta. We expect to generate unique new insights into AD-related PICALM mutations that will have important impact on our understanding of the disease and implications to the development of new PICALM-targeted therapies for AD.

# *In Vitro* and *In Vivo* Analysis of Amyloid Precursor Protein (APP) Variants

**SANGRAM SISODIA, PH.D.,** University of Chicago

It is widely accepted that amyloid beta peptides, the principal component of senile plaques, play a causative role in the pathogenesis of Alzheimer's disease (AD). Amyloid beta is derived from larger amyloid precursor proteins (APP). Early-onset, familial AD (FAD) is caused by inheritance of mutations in genes encoding APP or presenilin (PS1 or PS2) variants. Mutations in APP lead to the production of elevated levels of amyloid beta or the ratio of amyloid beta$_{42}$/$_{40}$ peptides. Importantly, all of the known APP mutations reside proximal to, or within, the amyloid beta peptide sequence. Very recently, Rudy Tanzi and colleagues (unpublished) have identified additional mutations in APP that co-segregate with two early-onset FAD pedigrees, but surprisingly, these mutations are quite a distance from the amyloid beta sequence. The mechanism(s) by which these novel variants influence amyloid beta production and/or deposition is not known, but our current proposal seeks to clarify these important issues in cell culture and transgenic mouse models.

# Effects of Peripheral APOE on Central Nervous System Functions and Alzheimer's Disease Pathogenesis

**GUOJUN BU, PH.D.,** Mayo Clinic Jacksonville

Alzheimer's disease, as the leading cause of dementia, has become a growing epidemic in our aging society. While aging is the greatest risk factor for AD development, a growing list of genetic and environmental factors also contributes to the risk. Among them, a gene called APOE is the strongest genetic risk factor for AD. The goal of the APOE consortium is to collectively address how a specific gene form called APOE4, which encodes the APOE4 protein, drives up the risk, and how we can target this protein for the development of new therapy. Interestingly, APOE protein is present not just in the brain, but also at a high concentration in the blood, produced primarily by the liver to transport cholesterol and other lipids among different organs. Along with their increased AD risk, individuals carrying the APOE4 gene also are at a greater risk of developing hypercholesterolemia and atherosclerosis compared with those carrying the APOE3 gene. Despite critical knowledge gained in the past two decades in understanding how brain APOE4 regulates AD-related pathologies, we know very little about how peripheral APOE circulating in the blood impacts brain functions and AD-related pathways.

Toward this goal, we recently have developed a new set of animal models that allow for expression of APOE only in the liver but not in the brain, thus allowing studies on how liver APOE populated in the blood affects brain functions and AD pathologies. In these animals, we also can turn on or turn off APOE expression during different disease states to address the timing at which APOE4 has the greatest impact. Our hypothesis is that blood APOE4 impairs brain functions and increases AD pathology by injuring blood vessels and by driving up harmful inflammation. This will be pursued through two specific aims:

- In Aim 1, we will compare how blood APOE3 (good form) and APOE4 (bad form) modulate inflammatory responses, blood vessel integrity, and brain functions measured by electrical signals and memory performance.
- In Aim 2, we will address how blood APOE3 and APOE4 affect the clearance of the amyloid component called amyloid beta, the buildup of which forms amyloid plaques thought to be the central driver of the AD disease process.

We have established multiple innovative technologies and tools to achieve our goals. This project will include close collaboration with other consortium projects. In particular, the Bu lab has a longstanding collaboration with the Holtzman lab to address how APOE4 drives AD risk. This collaboration will be further strengthened within this APOE consortium using complementary approaches. Collaboration with other consortium projects also will include those with the Wellington team to address vascular effects, the Bateman team to analyze the different forms of APOE in the blood, the Butovsky team to address inflammation, and the Greengard team to study new APOE-related genes and pathways. Our studies will for the first time investigate how blood APOE affects brain functions and AD-related pathways, and how we can develop new AD therapies targeting APOE in the blood.

# The Role of APOE in Microglia Regulation in Neurodegeneration

**OLEG BUTOVSKY, PH.D.,** Brigham and Women's Hospital

Microglia, the primary immune cells and the sensors of the brain, play a pivotal role in the maintenance of brain homeostasis, but lose their functionality during the course of aging and neurodegenerative diseases. There is a gap in our knowledge about how microglial function is maintained in healthy brain and how and why it is prone to dysregulation in Alzheimer's disease. There is also a lack of understanding of how the prominent genetic risk factor, APOE, is involved in microglia regulation and function. Human APOE has three common alleles, and the e4 allele is the major genetic risk factor for sporadic late-onset AD; its impact is even greater on women than men. The functional mechanisms underlying the genetic association of APOE4 with AD remain elusive. One mechanism by which APOE influences AD risk is by affecting amyloid beta clearance and accumulation. However, whether APOE directly regulates microglia functions in AD has not been investigated. This application will investigate the role of APOE in microglia as potential therapeutic targets of AD. Since APOE4 is the major risk factor of the disease, we will study the role of APOE4 in microglia regulation by employing novel tools, including new mouse models and techniques to specifically target APOE in order to restore microglia-mediated protein clearance and brain function in animal models of AD.

# Impact of APOE and Sex on Vulnerable Neuron-Specific Functional Network

**PAUL GREENGARD, PH.D.,** The Rockefeller University
*Nobel Prize in Physiology or Medicine, 2000*

APOE, the most important genetic predisposition factor for sporadic Alzheimer's disease, long has been known for its effect on the formation of amyloid plaques. There is evidence for another role of APOE on neuron function independent of amyloid beta. We have developed tools to make the full inventory of all proteins present in a specific type of neuron, in particular in neurons that display differential vulnerability to neurodegeneration. Entorhinal cortex layer II (ECII) and hippocampal CA1 neurons are both crucial for new memory formation, and are the most susceptible to degeneration. This proposal will comprehensively profile ECII and CA1 neurons in mice bred to carry the different human alleles of APOE, and investigate whether the human risk allele of APOE is putting ECII neurons in an increased vulnerability state compared with the neutral or the protective alleles of APOE. We also have evidence that ECII neurons could display different profiles in males and females, because they are equipped with sensors for estrogen. In light of the increased prevalence of AD for women, we will investigate if APOE and sex interact to alter the vulnerability of ECII neurons. Potential proteins modulated by APOE and/or sex that make ECII neurons more vulnerable could represent new drug targets to prevent ECII neurons from degenerating.

## Understanding the Effect of APOE on Tau-Mediated Neurodegeneration

**DAVID M. HOLTZMAN, M.D.,** Washington University School of Medicine

APOE is the strongest genetic risk factor for Alzheimer's disease, with the APOE4 isoform greatly increasing risk. We still do not completely understand how APOE increases AD risk. We have recently found that APOE4 greatly increases brain degeneration and neuronal loss that is mediated by a key protein in AD, tau, in a mouse model. We will try to better understand how APOE4 is resulting in greater brain damage. In addition, we will determine whether we can decrease APOE levels in the brain and, by doing so, block nerve cell loss and neurodegeneration. If successful, this could lead to new therapeutic approaches to target APOE to prevent the brain damage that leads to dementia in AD.

## Using Human Bioengineered Cerebral Vessels to Explore How Native APOE Affects Cerebrovascular Properties Relevant to Alzheimer's Disease

**CHERYL WELLINGTON, PH.D.,** University of British Columbia

The brain contains approximately 400 miles of specialized blood vessels that protect and nourish it. One important function of these cerebral vessels is to allow amyloid beta, a peptide central to Alzheimer's disease, to exit the brain. As people age, this function often becomes impaired, and amyloid beta then becomes stuck in the vessels and contributes to other changes that lead to full-blown AD. Risk factors for AD, including genetic (APOE) and lifestyle (exercise, cholesterol) issues, can affect function of cerebral vessels in ways we don't yet understand. My lab therefore has invented a way to grow human cerebral blood vessels with proper anatomy and function in a test tube. These three-dimensional vessels contain human endothelial cells that form the blood-brain barrier, smooth muscle cells that control blood flow and astrocytes that produce APOE. In this project we will study how APOE affects amyloid beta clearance through and inflammation of cerebral vessels.

## Evaluation of Sleep-EEG in Transgenic Mice

**PSYCHOGENICS**

PsychoGenics is acting as a contract research organization for the "Molecular and Cellular Mechanisms of an ACE1 Variant in Alzheimer's Disease" project of Robert Vassar, Ph.D.

# Evaluation of Blood-Brain Barrier (BBB) Penetration of Alzheimer's Drug Targets, and Identification of BBB Integrity Enhancers

**SE HOON CHOI, PH.D.,** Massachusetts General Hospital
**ROGER KAMM, PH.D.,** Massachusetts Institute of Technology

The blood-brain barrier (BBB) is a highly selective membrane barrier, formed by brain endothelial cells, that separates the brain from circulating blood, preventing harmful materials in the blood from entering the brain. BBB disruption occurs in various neurological disorders, including Alzheimer's disease (AD), which is the most common form of dementia among older people. Therefore, there has been great interest in cell models to closely mimic human BBB function in order to understand its roles not only in normal healthy conditions, but also BBB-related disorders. Supported by CAF, we developed the most physiologically relevant BBB models for use to study the role of BBB on AD pathogenesis (referred to as "3D AD-BBB monolayer model"). We think our BBB model will be of great significance to researchers investigating BBB function not only in health, but also in BBB-related diseases, such as AD. We also think our model will provide a well-controlled platform for a therapeutic screening of new drugs, mimicking a human-like environment in which the drugs must pass through the BBB to get to the brain. The Cure Alzheimer's Fund 3-D Drug Screen Consortium has finished the screening of 2,600 drugs and selected more than 38 potential AD drugs. We propose to test whether these selected drugs can pass the BBB and have effects on AD pathology in our 3D AD-BBB monolayer model. We also propose to screen compounds that reverse BBB breakdown in AD. These drugs are compelling candidates for repurposing as therapeutic agents that could rectify the dysfunctional BBB associated with AD.

# Compounds Modulating Microglial Uptake of Amyloid Beta and CD33-Targeted Immunotherapy for Alzheimer's Disease

**ANA GRICIUC, PH.D.,** Massachusetts General Hospital
**RUDOLPH TANZI, PH.D.,** Massachusetts General Hospital

The microglial regulator CD33 controls brain amyloid beta clearance in Alzheimer's disease. We previously performed an unbiased high-throughput screen of FDA-approved medications and CD33-specific antibodies in microglia to identify effective CD33 inhibitors. We found medications that modulated amyloid beta clearance and microglial activation state. We also found CD33-specific antibodies that dramatically reduced CD33 protein levels. Here, we propose to investigate the mechanisms through which the FDA-approved medications modulate amyloid beta clearance and the levels of pro-inflammatory mediators in microglia. We also will determine the effects of CD33-specific antibodies on amyloid beta clearance, microglial activation state and CD33-mediated signaling. The development of effective CD33 inhibitors might provide a novel therapeutic approach for this devastating disease.

## High-Throughput Drug Screening for Alzheimer's Disease Using 3-D Human Neural Culture Systems

**DOO YEON KIM, PH.D.,** Massachusetts General Hospital

Recently, we developed a novel cellular Alzheimer's disease (AD) model based on a unique 3-D culture system and genetically modified human neural stem cells. This 3-D human neural cell culture model of AD has great potential to innovate and accelerate current AD drug discovery. In the first and second years of this project, we focused on 1) developing a high-throughput drug screening system based on our 3-D culture models and 2) screening/validating 38 primary-hit compounds that decrease either tau and/or amyloid beta pathology. These hits originally were identified by screening an approximately 2,500-drug library by the Wong lab (a part of the 3-D Drug Screen Consortium). In the third year, we will continue our efforts validating additional AD drug candidates selected by 1) analyzing AD-specific gene sets and drug prediction using connectivity MAP and L1000CDS2 search engines (Kim lab) and by 2) artificial intelligence-based bioinformatics approaches (Wong lab). Next, we will explore the impact of validated hits on pathological changes to AD neurons in 3-D culture models, including Ca2+ influx, kinase activities, hyperexcitability, synaptic loss and cell death. Our study will provide mechanistic insights into how to block the pathological cascade of AD in human neural cells, and may contribute to finding novel AD drug candidates that can be directly entered in human clinical trials.

## Alzheimer's Disease Stem Cell Drug Screening in 3-D

**WEIMING XIA, PH.D.,** Boston University School of Medicine

The search for drugs that would be effective in the treatment of Alzheimer's disease (AD) has been extremely slow and time consuming. In order to hasten the process, we propose to use stem cells derived from Alzheimer's patients to test drugs previously approved by the U.S. Food and Drug Administration for the treatment of other diseases. In addition to investigating the effect of these drugs on the levels of the toxic proteins found in the brains of Alzheimer's disease patients, we will study changes in relevant proteins that may cause potential toxic side effects for these candidate Alzheimer's therapeutics. The importance of this project is that it will lay the foundation for developing FDA-approved drugs as novel therapeutics for the prevention and treatment of AD, and do so in an efficient, cost-effective manner.

## Uncovering the Molecular Mechanism of Selected Drug Candidates Derived from Systemic Alzheimer's Drug Repositioning

**STEPHEN T. WONG, PH.D.,** Houston Methodist Research Institute

Partnering with the research consortium led by Massachusetts General Hospital, we successfully developed the SysteMatic Alzheimer's disease drug ReposiTioning (SMART) framework to identify candidate drugs for repurposing for Alzheimer's in a previous grant from Cure Alzheimer's Fund. A high-throughput screening using the Alzheimer's in a Dish model and a library of more than 2,000 compounds identified 38 preliminary hits, three of which can achieve almost complete inhibition of accumulation of phosphorylated

tau (p-Tau). Using these preliminary hits as "baits," SMART took advantage of publicly available large cellular perturbation response data (more than 20,000 drugs and compounds) and predicted and validated nine clinically used compounds beyond the original library that can ignite a similar cellular phenotype as the original top three preliminary hits, i.e., almost complete inhibition of p-Tau accumulation. Compared with the high-content drug screening, SMART improved the success rate of hit identification by more than 50-fold en route to quadrupling the panel of candidates for fast-track drug repositioning study. Thus, the integrative neurobiology framework has shown its potential as a powerful, cost-effective platform for drug discovery and mechanism study in Alzheimer's disease (AD).

In this proposal, we will expand the modeling capability of SMART with a mechanism discovery module grounded on advanced machine learning techniques to investigate and validate novel mechanism for inhibition of p-Tau accumulation regarding the drug hits discovered in the prior funding period. The proposed study has two specific aims: Aim 1 will construct an image-omics workflow to uncover the molecular mechanism underlying representative FDA-approved compounds that block AD neuropathogenic events, while Aim 2 will evaluate the selected drug hits in cell assays with validation results feeding back to Aim 1 to ensure the efficacy of drug repositioning and mechanism discovery. The success of this research would enable better understanding of novel mechanisms of known drugs identified and lead to new, cost-effective treatment targets for Alzheimer's.

## Therapeutic Modulation of TREM2 Activity

**CHRISTIAN HAASS, PH.D.,** DZNE Munich

There is strong evidence that inflammation occurs in different stages of Alzheimer's disease (AD), and understanding this process can help us to design new therapeutic approaches. TREM2 is a protein that is directly related to the inflammation process that occurs in the brain of patients with AD, and mutations in this protein increase the risk to develop AD up to threefold. A fragment of this protein, namely soluble TREM2 (sTREM2), increases at very early stages of AD, and this increase occurs in parallel to an increase of biomarkers for neuronal cell death. We have evidence that increased sTREM2 reflects a protective response which, however, could not be maintained in later stages of AD. We now want to enhance TREM2 activity during later disease stages. To do so, we want to prevent its cleavage and thus increase TREM2 levels on the surface of brain cells, which are involved in clearance of amyloid deposits and cellular debris. We now have identified the site where the protein is cleaved. Interestingly, a disease-causing mutation occurs in AD patients exactly at this site. This mutation increases the cleavage and consequently reduces the function of TREM2. Successful identification of the cleavage site enables us now to generate therapeutic antibodies, which block the access of the cleaving enzyme to TREM2. A patent and a scientific publication emerged out of the first-year funding.

## SORLA Attenuates Amyloid Beta Toxicity Through Interactions with EphA4

**HUAXI XU, PH.D.,** Sanford Burnham Prebys Medical Discovery Institute

SORLA is a genetic risk factor in Alzheimer's disease (AD), but it is currently unclear how changes in SORLA abundance can trigger the onset of AD in the elderly. So far, studies have shown that SORLA can limit the amount of neurotoxic amyloid beta generated in the brain. However, since high levels of amyloid beta also are seen in aged individuals without symptoms of dementia or cognitive decline, neuroprotective mechanisms are likely in place to protect neurons from amyloid beta damage. We describe here that SORLA can limit the activation of a cell surface component EphA4 that is activated in the presence of amyloid beta, which can damage synaptic function in the brain. Our preliminary results indicate that SORLA overexpression can limit amyloid beta-dependent activation of EphA4 in response to normal EphA4 activators such as Ephrin ligands, and amyloid beta in cultured neurons, and our pilot experiments indicate that mouse models overexpressing SORLA are less vulnerable to amyloid beta injected into the mouse hippocampus. Our study here will confirm whether SORLA can limit toxic signals from EpahA4 in response to amyloid beta, and whether molecular strategies to enhance SORLA/EphA4 interactions can further protect neurons from synaptic damage from amyloid beta. This study potentially will provide insight into a new pathway to protect neurons from amyloid beta damage, which may lead to strategies to improve cognition in AD patients.

## Discovery of CK1 Activators for Inducing the Autophagic Degradation of Amyloid Precursor Protein (APP) Beta-CTF

**PAUL GREENGARD, PH.D.,** The Rockefeller University
*Nobel Prize in Physiology or Medicine, 2000*

Alzheimer's disease affects more than 5 million people in the United States. Unlike the other top 10 causes of death in the United States, Alzheimer's disease remains the only one in this category that cannot be cured, prevented or slowed. Multiple lines of evidence suggest that a defective clearance mechanism is involved in the pathogenesis of Alzheimer's disease. Our laboratory has discovered a novel molecular pathway regulating protein clearance, which represents an attractive therapeutic target for developing drugs for Alzheimer's disease. This project represents a direct effort to search for small molecule compounds that can restore protein clearance.

## Functional Characterization of GGA3 Mutations Associated with Alzheimer's Disease

**GIUSEPPINA TESCO, M.D., PH.D.,** Tufts University

Neurons, highly organized brain cells, are characterized by specialized projections called dendrites and axons. The axon is the longest neuronal projection where proteins move like along a highway, in two different directions and at different speeds. Scientists demonstrated that in the brain of subjects affected by Alzheimer's disease (AD), a disorder characterized by memory loss, this coordinate traffic doesn't work properly, so neurons start to be

unhealthy and die. Our goal is to try to understand why this traffic no longer is functioning in order to find a way to prevent the neuronal traffic disruption and possibly find a treatment for Alzheimer's disease. The aim of this study is to determine the extent to which mutations in a trafficking molecule called GGA3 may lead to disruption of protein movements in the axon, ultimately causing neuronal death.

## Investigating the Mechanism of APOE4-associated Neuronal Hyperactivity in the Entorhinal Cortex and its Effect on Tauopathy Propagation

**KAREN DUFF, PH.D.,** Columbia University Medical Center
**TAL NURIEL, PH.D.,** Columbia University Medical Center

Carriers of the APOE4 gene are at significantly increased risk for developing Alzheimer's disease. We have shown that aging mice that express the APOE4 gene have increased activity in a region of the brain that is implicated in the development of Alzheimer's disease, and we believe this increased activity may be an important link between APOE4 and Alzheimer's disease pathology. In order to understand why this increased activity occurs, we will perform a series of experiments. In addition, we will study the effect of this APOE4-linked brain activity on the spread of tau, an important protein whose accumulation and spread in the brain plays a vital role in Alzheimer's disease. We anticipate that the results of this study will yield significant insights into the biology of APOE4 and Alzheimer's disease, as well as how Alzheimer's disease may be treated or prevented in these individuals.

## Genes to Therapies™ (G2T) Centralized Research Core

**WILMA WASCO, PH.D.,** Massachusetts General Hospital

Of the currently identified Alzheimer's disease (AD) genes and candidate genes, 59 have been or are currently being screened and analyzed for mutations/functional variants in the Whole Genome Sequencing (WGS) project. Of these, approximately 15 that clearly fit the criteria for immediate and thorough investigation will be prioritized for study. Ultimately, Cure Alzheimer's Fund will pursue and encourage others to pursue investigations of each of the identified genes to determine their potential role in Alzheimer's pathology; however, resources first will be focused on the most important top 15 genes, to determine how these identified Alzheimer's risk genes are involved in Alzheimer's pathology as well as how that information can be used to facilitate more rapid development of effective therapeutic interventions.

The Cure Alzheimer's Fund Steering Committee believes the quickest and most effective way to generate valid therapeutic targets and approaches is to recruit investigators who have the appropriate background and scientific expertise for each gene of interest. To decrease the overall time and cost of the studies, recruited investigators will be supplied with all of the resources necessary to successfully carry out functional biological studies on a specific gene. As a first step toward this goal, Cure Alzheimer's Fund has established a relationship with Taconic Biosciences, which is generating customized mouse models for each gene to be studied. Providing these mouse models and other appropriate reagents to investigators not only will obviate the time and effort necessary for each investigator to generate his or her own mouse models and reagents, but importantly, it will ensure

all investigators are working with animal models that are consistently and reliably generated, documented and maintained. This process will be supervised by the research operations manager based at Massachusetts General Hospital and overseen by the Steering Committee.

## Protein Kinase C in Alzheimer's Disease

**ALEXANDRA NEWTON, PH.D.,** University of California, San Diego

The research supported by Cure Alzheimer's Fund has shown that a key protein turned off in cancer is excessively active in Alzheimer's disease. This protein, called protein kinase C, is an information processor, or "signal transducer," that regulates cellular activities. Its activity needs to be exactly balanced to maintain normal cellular function. Reduced function promotes cell survival, a hallmark of cancer. Analysis of genetic mutations identified in the Genes to Therapies™ program by Rudy Tanzi reveals that mutations found in some patients with Alzheimer's disease actually enhance the function of protein kinase C. Indeed, enhanced signaling by protein kinase C generally may be associated with the pathology of Alzheimer's disease, identifying this protein as a promising therapeutic target.

## TREM2: Role in Modulating Amyloid Beta and Tau-Related Pathologies and Neurodegeneration

**MARCO COLONNA, M.D.,** Washington University School of Medicine
**DAVID M. HOLTZMAN, M.D.,** Washington University School of Medicine

Recently it has become apparent that the innate immune cells in the brain, microglia, play an important role in the overall response during Alzheimer's disease. Despite the fact that much effort has been expended on ascertaining the precise nature of the role of microglia in AD, much remains unknown. TREM2 is an important molecule expressed by microglia. TREM2 appears essential to maintaining microglial function in AD, and genetic variants of TREM2 have been linked to an increase in the risk of developing late-onset AD. Our work will focus on understanding the role of TREM2 on microglia using two models of AD, a model of the early development of AD and a model that combines both the early- and late-phase pathology in AD. The overall goal of this work is to better understand the role that microglia play in AD and how TREM2 may impact microglial function in AD. In particular, this work will help answer the question of whether a robust microglial response in AD is good, bad or dependent upon the timing of the response relative to the stage of disease. Ultimately these studies hope to inform the development of new and effective treatments for AD.

## Interactions Among TREM2, APOE and Sex

**CALEB FINCH, PH.D.,** University of Southern California
**CHRISTIAN PIKE, PH.D.,** University of Southern California

Men and women differ in their vulnerability, clinical manifestation and neuropathological progression of Alzheimer's disease, with women typically exhibiting worse outcomes. Understanding the role of sex differences in AD is essential for developing effective interventions to prevent and treat the disease. In this project, we investigate how female sex modulates interactions between two significant genetic risk factors for AD, APOE4 and TREM2.

## A Microfluidics-Based Human Brain Cell 3-D Culture System in Alzheimer's Disease

**HANSANG CHO, PH.D.,** University of North Carolina at Charlotte

The roles of microglia, resident immune cells in brains, have not been fully elucidated yet in the progression of Alzheimer's disease neurodegeneration due to the multiplex microgliosis and the challenge of *in vitro* culture in a regulatory manner. In our human AD 3-D brain model, we could regulate and measure microgliosis, including morphogenesis, recruitment, phenotype change and expressed pro-inflammatory factors. Most interestingly, cellular interactions between AD neurons and engaged microglia, including microglial cleavage of axons and retraction of neurite, could be observed in a real-time and single cellular resolution for the first time. Our human AD brain model will be expanded into an array format to serve as a valid platform for screening and evaluating drug candidates with a high-throughput.

## Exploring Sex Differences in AD Pathogenesis Using 3-D Human Non-Cell-Autonomous Models

**DOO YEON KIM, PH.D.,** Massachusetts General Hospital
**DANIEL IRIMIA, M.D., PH.D.,** Massachusetts General Hospital

Alzheimer's disease is twice more common in women than men. Moreover, women experience faster age-related cognitive decline than men. However, the precise reasons behind these differences in Alzheimer's disease between women and men are unknown. In this application, we will explore the differential impact of sex on AD pathogenesis. We will employ two emerging technologies to quantify pathological sex-dependent changes in neurons during AD in relevant *in vitro* models. In preliminary work, these models have been validated to recapitulate the key pathogenic cascades of AD in normal human neurons. This proposal will address the urgent need to address the gap in knowledge of understanding the role of sex differences in AD. Ultimately, it will lead to new insights into AD pathogenesis, which ultimately will result in better interventions to prevent, monitor and treat AD.

# Identification

Early detection via biomarkers, imaging, etc.

## Amyloid Beta Kinetics and Enhancing the Diagnostic and Prognostic Cerebrospinal Fluid Biomarkers of Alzheimer's Disease

**RANDALL J. BATEMAN, M.D.,** Washington University School of Medicine
**NORELLE C. WILDBURGER, PH.D.,** Washington University School of Medicine

The pathological process of Alzheimer's disease begins decades before cognitive decline. It has become apparent that for disease-modifying therapies to be effective, early intervention is required. In order to screen those at risk, improved biomarkers of AD pathology are urgently needed to identify individuals early, while damage is not too severe and is potentially reversible. We are using the most advanced technology to identify a new generation of biomarkers.

## Stable Isotope Labeling and Quantitative Mass Spectrometry Imaging of Alzheimer's Disease Pathology in Human Brain

**RANDALL J. BATEMAN, M.D.,** Washington University School of Medicine
**NORELLE C. WILDBURGER, PH.D.,** Washington University School of Medicine

Our goal is to measure, for the first time in human Alzheimer's disease brain, the metabolism of neurons (brain cells) and how they are affected by AD, and if this is directly related to tau accumulation inside the neuron affecting function and overall health. Further, we will measure plaque pathology and tau tangle growth. We have developed an advanced imaging protocol called SILK-SIMS, which enables us to image and measure neuron metabolism and plaque growth at the nanometer level; this allows us to see structures much smaller than cells and quantify changes during life and the disease process.

Neuronal metabolism and plaque growth is measured with a label given to patients (like a dye that tags newly made plaques and tangles), which we then image with SILK-SIMS, noting both the location and amount of neuronal metabolism or hypo-metabolism and plaque toxicity. We aim to measure neuronal metabolism (a proxy for function), tangle growth and plaque toxicity, using SILK-SIMS imaging, in the brains of people with mild to severe AD, and compare these measurements with those taken from patients without dementia. These findings will enable us to model how fast AD pathology occurs in the living human brain. This research is unique in that we will be providing the first direct measures of growth of AD pathology in the human AD brain by utilizing cutting-edge methodologies never before leveraged in the AD field. The outcomes will provide new insights in order to better understand tau and amyloid pathology, which can accelerate drug development and inform clinical trials. In addition, we will establish a blueprint for the investigation of other devastating such neurodegenerative diseases as Parkinson's disease, frontal-temporal dementia and amyotrophic lateral sclerosis (ALS; also known as Lou Gehrig's disease).

# Immune System Structures and Processes

Role of inflammation and other responses in AD

## Early Role of Microglia in Synapse Loss in Alzheimer's Disease

**BETH STEVENS, PH.D.,** Boston Children's Hospital

In Alzheimer's disease (AD), synaptic connections are lost early and in specific areas of the brain, including the hippocampus, where memory is formed and stored; however, what makes synapses vulnerable in AD and other neurodegenerative diseases remains elusive. In the healthy developing brain, synaptic loss (also known as synaptic pruning) is a normal process required for proper brain development. We previously found a key role for a group of immune molecules called complement in synaptic pruning. These proteins localize to synapses during periods of active synapse elimination and are required for normal brain wiring. Interestingly, the function of complement proteins in the brain appears analogous to their function in the immune system: they "tag" cellular material to be eliminated. Synapses tagged with complement proteins are eliminated by microglia, resident immune cells that express complement receptors. We showed that synapse loss in AD mouse models is mediated by an abnormal reactivation of this developmental pruning pathway, and that blocking complement or microglial complement receptors resulted in protection of synapse loss and memory defects in AD models (Hong et al., Science 2016). We predict that proteins in this pruning pathway could serve as biomarkers in AD to detect the disease early. To test this hypothesis, we will determine whether complement and microglia localize to synapses in human brains of early stages of AD, and whether complement proteins are abnormally upregulated in the cerebrospinal fluid (CSF) of AD patients. Our preliminary data suggest that C1q, the initiating protein of the complement pathway, is associated with synapses in late stages of the disease. We plan to continue investigating the role of complement in earlier stages of human AD. Moreover, we aim to study the role of other microglial receptors in aberrant synapse loss. Recent genome-wide association studies have identified several microglial and complement proteins as AD susceptibility genes, including TREM2; however, it is not known whether TREM2 plays a role in synapse loss or dysfunction. Using established assays, we are investigating whether TREM2 acts as a receptor through which microglia engulf synapses in AD mouse models. We found that TREM2 is involved in activating microglia and may be involved in synaptic engulfment. Understanding the function of TREM2 and other immune-related risk genes in early synapse loss can provide novel insight into new biomarkers and therapeutic targets.

## Microglial TAM Receptors as Modulators of Alzheimer's Pathology

**GREG LEMKE, PH.D.,** Salk Institute for Biological Studies

Protein aggregates of amyloid beta peptides accumulate in the brain in Alzheimer's disease and contribute to disease pathology by directly damaging neurons and by activating microglia, the resident immune cells of the brain. We will employ genetic methods to study the function of TAM receptors expressed in microglia, and hypothesize that TAMs act to dampen the activation of these immune cells

and therefore prevent inflammation in the brain during Alzheimer's disease. We furthermore hypothesize that these TAM receptors enable microglia to ingest amyloid beta aggregates as they are forming and thereby indirectly protect neurons against aggregate-mediated damage. Boosting TAM activation or expression in microglia may therefore be of therapeutic benefit in Alzheimer's disease.

## Impact of Inflammasome Deactivation on Alzheimer's Disease

**VISHWA DEEP DIXIT, D.V.M., PH.D.,** Yale School of Medicine

This project emanates from the findings from the Dixit lab that the NLRP3 inflammasome gene controls age-related inflammation and cognitive decline. Inflammasome is a high molecular weight protein complex that assembles in the cytosol of microglia and myeloid-lineage cells upon encounter with such "damage-associated molecular patterns" as amyloids, lipotoxic fatty acids or extracellular ATP derived from necrotic cells. Upon assembly, this causes caspase-1 dependent release of pro-inflammatory cytokines IL-1beta, IL-18 and special form of cell death called pyroptosis. Studies from our lab have identified that the NLRP3 inflammasome controls development of inflammation-associated degenerative diseases during aging. Consistent with our data, independent studies also have demonstrated the increased activation of NLRP3 inflammasome in AD in humans, and that genetic loss of NLRP3 protects against dementia in amyloid precursor protein/presenilin 1 mouse model.

Although it is established that inflammation plays a pivotal role in the development of Alzheimer's disease (AD), the therapeutic approaches that impact specific innate immune mechanisms in the microglia remain to be identified. Interestingly, our preliminary results show that a subset of elderly are protected from age-related inflammation and microglial activation despite the presence of amyloid beta plaques. This implies that there must be endogenous protective mechanisms that maintain homeostasis in aging by preventing the sensing of aberrant amyloid beta deposits in microglia resulting in reduced inflammatory damage. Therefore, the long-term goal of this proposal is to identify and harness anti-inflammasome regulators as therapeutic targets to prevent or treat AD.

This proposal is based on our discovery that ketone metabolite beta hydroxybutyrate (BHB) and NLRP3 inflammasome constitutes an immunometabolic checkpoint of binary opposition—endogenous polar signals that work in concert to regulate the innate immune response. Ketone bodies, BHB and acetoacetate (AcAc) support mammalian survival during periods of starvation by serving as a source of ATP in tricarboxylic acid (TCA) cycle for brain function. Intriguingly, we have found that macrophages and microglia highly express the key ketogenic enzyme 3-Hydroxy-3-MethylGlutaryl-CoA Lyase (HMGCL). This suggests that microglia can produce ketone bodies, and that local levels of BHB in brain may function as a regulatory metabolite that restrains the runaway inflammasome activation. In addition, this suggests that medium chain triglycerides (MCTs), which can cross the blood-brain barrier, serve as substrates for production of BHB in microglia. Given that MCTs are under investigation to lower AD severity, the mechanism of microglial-derived BHB as regulatory anti-inflammasome metabolite has high clinical impact. Thus, based on our findings, the central hypothesis of this project is that ketogenic substrate switch underlies the regulatory microglial responses that protects against AD by inhibition of CD33 and deactivation of the NLRP3 inflammasome. The corollary is that elevating central nervous system ketogenesis and BHB signaling may serve as an anti-inflammatory intervention against AD.

## Synapse Pruning by Astrocytes: A Potential New Target for Treating Alzheimer's Disease

**WON-SUK CHUNG, PH.D.,** KAIST

There is profound synapse loss in the early stages of Alzheimer's disease progression. However, it is unclear what triggers synapse loss and how we can prevent this process. Recently, we have found that astrocytes phagocytose and eliminate synapses in the developing and adult healthy brain, suggesting astrocytes may maintain synaptic/brain homeostasis by constantly cleaning up unnecessary synapses and synaptic debris. In this proposal, we will investigate whether the phagocytic capacity of astrocytes is impaired in the initiation and progression of Alzheimer's disease, and whether we can develop new therapies to stimulate phagocytosis by astrocytes.

## Systemic Inflammatory Networks in Alzheimer's Disease

**FILIP SWIRSKI, PH.D.,** Massachusetts General Hospital
**MATTHIAS NAHRENDORF, M.D., PH.D.,** Massachusetts General Hospital

Brains of Alzheimer's disease (AD) patients contain inflammatory cells, but the relevance of inflammation to disease development and exacerbation is unknown. Inflammation is a biological response to damage, stress and infection. It is a natural defense process that manifests itself as heat, pain, redness and swelling, playing an essential role in disease. Depending on the extent, type and duration of inflammation, the process can be either helpful or harmful, because it can remove the offending pathogen, but it also can cause damage to healthy tissue. This grant will investigate how inflammation in the body and inflammation in the brain influence AD. The main hypothesis of this grant is that inflammation exacerbates AD, and is thus a major component of AD pathology and a potential therapeutic target.

## The Role of the Contact System in Alzheimer's Disease

**SIDNEY STRICKLAND, PH.D.,** The Rockefeller University
**ERIN H. NORRIS, PH.D.,** The Rockefeller University

Many Alzheimer's disease (AD) patients have problems with the blood vessels in the brain. These problems could contribute to the cognitive decline observed in AD. We have been studying the role of a blood-based system called the contact system in AD. This system leads to blood clotting and inflammation, is activated in AD patients and contributes to the severity of disease in mouse models. We will investigate how the contact system contributes to AD pathology using mouse models. A better understanding of the effects of the contact system in AD could help better diagnose which patients have a vascular component in their disease, and help to design novel treatments for these patients.

# Targeting Reactive Astrocytes for Therapeutic Intervention in Alzheimer's Disease

**GILBERT GALLARDO, PH.D.,** Washington University School of Medicine

Reactive astrocytes and neuroinflammation are well-known features of Alzheimer's disease that are associated with disease manifestation, pathology and brain atrophy. Yet, despite a compelling association with AD and reactive astrocytes, their impact on disease pathogenesis and their therapeutic potential remains largely unknown. Our goal is to clarify reactive astrocytes, contributions to the pathogenesis of AD, as this knowledge may be key in delaying or perhaps preventing neuronal cell death. We previously discovered a complex composed of the ion pump α2-Na/K ATPase and the protein α-Adducin is enriched in reactive astrocytes that promotes a neurotoxic response. In the proposed study, we will investigate the role of the astrocytic α2-Na/K ATPase/α-Adducin complex in AD and determine whether pharmacological inhibition is beneficial.

# Chronic Viral Neuroinfection Mediates Amyloid Beta Deposition in Transgenic Alzheimer's Disease Mice

**ROBERT MOIR, PH.D.,** Massachusetts General Hospital

The hallmark pathology in Alzheimer's disease is deposition of amyloid beta peptide in brain as insoluble amyloid. Amyloid beta typically is characterized as a functionless byproduct of metabolism with an intrinsically abnormal propensity for self-association that drives AD pathology. However, antimicrobial peptides are a family of critically important natural antibiotics that self-associate and generate amyloids as part of their normal protective activities. Our recent report on amyloid beta's protective actions against infection suggest the protein may be an antimicrobial peptide. Our findings revealed aggregation and generation of amyloid are important parts of amyloid beta's role in immunity, mediating the capture and neutralization of pathogens in brain.

In our experiments, genetically modified cells, nematode worms, fruit flies and AD mice expressing human amyloid beta were protected from infection by amyloid-mediated entrapment of the invading pathogens. Our findings raise the intriguing possibility that chronic neuroinfection may be driving amyloid beta amyloid deposition in AD brain. Evidence also has begun to emerge of high microbial burdens in the brain of AD patients, with neurotropic viruses the pathogens most frequently linked to the disease. New data generated with our collaborators at Mount Sinai (laboratories of Eric Schadt, Sam Gandy and Joel Dudley) show brain regions showing AD pathologies contain high levels of genetic material from herpesviridae viruses. Our preliminary studies have confirmed herpes viruses can seed amyloid beta amyloid deposition in experimental AD models.

We are currently exploring a novel theoretical amyloidosis model in which sustained, elevated replication by herpesviridae enhance amyloidosis, accelerating the cascade of pathologies that lead to neurodegeneration and dementia. Our planned studies will characterize herpes-seeded amyloid generation in a 3-dimensional human neural cell culture system (dubbed Alzheimer's in a Dish in recent media reports). In addition, we will develop a humanized experimental AD mouse model that can be infected by the species of herpes virus we identified as involved in Alzheimer's disease. We believe our proposed study will add significantly to an emerging model of a protective/harmful duality to amyloid beta's activities in brain, as well as better inform current and future AD therapeutic strategies aimed at preventing pathological amyloid beta accumulation.

# Regulation of Microglial Lysosome Acidification

**FREDERICK R. MAXFIELD, PH.D.,** Weill Cornell Medical College

Microglial cells are the scavenger cells of the brain, and they are responsible for clearance of dead cells, denatured proteins and other debris. We have studied the ability of microglial cells isolated from the brains of newborn mice to degrade the amyloid beta that accumulates in the brains of Alzheimer's patients. We found that microglia could take up small particles of amyloid beta efficiently and deliver them to lysosomes, which are the digestive organelles of cells. However, the microglia in our cell culture experiments were unable to degrade the amyloid beta even though it was in the lysosomes. We found that the reason for poor degradation was that the lysosomes in microglia were not as acidic as lysosomes in other cells. The digestive enzymes in lysosomes require acid conditions for their activity. Treatments that activated the microglia led to good acidification and rapid degradation of internalized amyloid beta.

The goal of this project is to determine whether the same lysosomal pH regulation occurs *in vivo*. To measure the lysosomal pH, we put a pH-sensitive fluorescent dye and a pH-insensitive fluorescent dye on a biocompatible polymer called dextran. When cells deliver the dextran to lysosomes, we can use the ratio of the two types of fluorescence to determine the pH. We have verified that the fluorescent dextran injected into the upper spinal cord can diffuse into the brain and be taken up by the microglia in a living mouse. We image the cells in the brain using a method called multiphoton microscopy, which allows us to see detailed images relatively deeply in a mouse brain. In order to selectively measure the lysosomal pH in microglia, we need to label these cells by expressing a fluorescent protein in them that does not interfere with our pH measurements. We will determine whether activation of the microglia in living mice has the same effect on lysosome acidification *in vivo* as it does in cell culture. (These same treatments have been shown by another laboratory to clear amyloid plaque in mouse brains.) We also will test the molecular mechanism for the improved acidification using mice lacking a key regulator protein called Clc-7. Finally, we will begin to measure the effects of increased lysosome acidification on degradation of amyloid plaques. We believe this regulation of the degradative capacity of microglia is a potential site of therapeutic regulation.

# VGF, a Novel Therapeutic Effector of Alzheimer's Disease Pathogenesis and Progression

**MICHELLE E. EHRLICH, M.D.,** Icahn School of Medicine at Mount Sinai
**STEPHEN R. SALTON, M.D., PH.D.,** Icahn School of Medicine at Mount Sinai

Alzheimer's disease is the most common form of dementia and is characterized by a progressive decline in cognitive function. Neurotrophic growth factors, including brain-derived neurotrophic factor (BDNF), are well-known modulators of synaptic plasticity and neuroprotection, and have been a major research interest in age- and disease-related cognitive dysfunction. VGF (nonacronymic), a secreted neuronal and endocrine protein whose expression is induced by BDNF, is processed into several bioactive peptides that function in memory formation and neuroprotection. Biomarker studies have identified decreased levels of VGF-derived peptides in the cerebrospinal fluid of AD patients, and large-scale genomics studies by the Accelerating Medicines Partnership-Alzheimer's Disease consortium have recently converged on VGF as a critical regulator in the signaling networks that underlie AD pathogenesis and progression in human patients. Recent data collected in our labs further demonstrate that VGF overexpression or administration of VGF-derived peptides to the 5XFAD mouse model of AD reduce amyloid plaque load, microgliosis and astrogliosis in the brain, in a region-specific manner. We propose to investigate how the VGF-derived peptide TLQP-21 delays or reverses neuropathology in the 5xFAD brain by studying its interaction with the complement C3a receptor (C3aR1) on cultured microglia, its regulation of microglial amyloid uptake and gene expression, and potential modulation of VGF actions by beta-adrenergic receptor (AR) signaling, which reportedly increases beta amyloid phagocytosis and generally reduces amyloid load in AD models (although this is controversial). In addition, we will determine the underlying pathways by which VGF or VGF-derived peptide TLQP-21 blocks or delays development of neuropathology and impacts microglial function in mouse tauopathy (PS19) and amyloid (5XFAD) models, utilizing large-scale genetics approaches to analyze gene expression and to construct signaling networks. The proposed experiments will validate a novel AD target, and will test new approaches to reduce neuroinflammation in neurodegenerative disease.

# Microbiome

Interaction of the microbiome with AD

## Gut Microbiome-Mediated Shifts in Amyloid Beta Deposition in a Humanized Alzheimer's Disease Mouse Model

**DEEPAK VIJAYA KUMAR, PH.D.,** Massachusetts General Hospital

Microorganisms of the human gastrointestinal tract are collectively referred to as the gut microbiota or microbiome. More than a century ago, Nobel laureate Elie Metchnikoff first proposed manipulation of the gut microbiome as a possible treatment for neurological disorders. However, only recently have procedures emerged that allow the microbiome to be reproducibly changed in ways that provide reliable and specific benefits for patients with neurological disease.

Among the most successful approaches has been fecal transplantation. In fecal transplantation, the gut microbiota from healthy subjects is transferred to patients suffering disease. Our own studies, and recent findings reported by other laboratories, suggest cerebral amyloid deposition, the hallmark pathology for Alzheimer's disease (AD), may be among the brain pathologies linked to gut microbiota. In this study, we propose to extend our study of the connection between AD amyloidosis and the gut microbiome. Previously, we have shown the gut microbiome of genetically modified AD mice is shifted toward abnormal bacterial species linked to health disorders. In this study, we propose to extend our investigations and test whether fecal transplants that replace abnormal amyloid-associated gut microbiota with the microbiome of normal mice can reduce AD amyloidosis.

Our study will use humanized AD mice that recapitulate mechanisms that normally regulate amyloid generation in humans. In previous AD mouse models, amyloid-generating pathways are artificially maintained at abnormally high levels. We also will investigate whether gut microbial metabolic products known to travel to the brain are responsible for modulating amyloidosis. Confirmation that gut microbiome manipulation may be able to delay the onset of AD amyloid pathology would be a major advance for the field. Moreover, it would open the possibility of adapting existing approved medical procedures for the treatment, and possible diagnosis, of AD. To that end, we hope to include experiments to screen ingestible agents that could be helpful in slowing cerebral deposition of harmful amyloid.

# Mechanisms By Which the Gut Microbiome Influences Amyloid Deposition and Neuroinflammation in the APPswe/ PS1DE9 Mouse Model of Amyloid Beta Amyloidosis

**SANGRAM S. SISODIA, PH.D.,** University of Chicago

We have generated and characterized mouse models of Alzheimer's disease that recapitulate the severe amyloid beta amyloidosis and neuroinflammation evident in the human disease. It has long been assumed that inflammation associated with amyloid deposition reflects the activation of astrocytes and microglia that adopt pro-inflammatory phenotypes, but there is a paucity of information regarding the potential role of peripheral tissues and, more importantly, the gut microbiota in regulating innate immunity that in turn leads to central nervous system (CNS) dysfunction. Indeed, it has become increasingly evident that psychiatric developmental disorders co-exist with common gastrointestinal conditions. Moreover, the microbiome has been implicated in neuroprotection after ischemic lesions, as well as to immunologically mediated neurological conditions such as multiple sclerosis.

Over the past two years, we tested the hypothesis that the composition of the intestinal microbiome might play a key role in modulating neuroinflammation and amyloid beta deposition. We treated male and female APPSWE/PS1ΔE9 transgenic mice with an antibiotic (ABX) cocktail either postnatally alone, or throughout life, and we reported that while total bacterial abundance was unchanged in either the cecum or feces, there is a distinct perturbation in gut microbial diversity. We demonstrated that amyloid plaque deposition and plaque size are significantly reduced in the brains of male ABX-treated animals, but not in female animals. Finally, ABX-induced perturbations in gut microbial diversity also paralleled by alterations in the morphology of microglia, scavenger cells that play an important role in removal of amyloid beta plaques.

Having established a strong correlation between alterations in the gut microbiota and decreased levels of amyloid beta deposition in male APPSWE/PS1ΔE9 transgenic mice, there remain several outstanding issues pertinent to the biological mechanism(s) that underlie the observed phenotypes. First, the difference in outcomes between male and female mice is remarkable, and we seek to identify sex-specific genetic changes that could account for the observed differences. Second, we propose to generate APPSWE/PS1ΔE9 mice that are devoid of gut microbes ("germ-free"; GF mice) and evaluate amyloid deposition and neuroinflammation in this model. Third, it is well established that microglia are considered the primary responders to amyloid beta deposition in the brain and initiate neuroinflammation. We feel it is important to evaluate the genetic changes that occur in these cells as a function of changes in the microbiome. For this purpose, we have obtained a novel transgenic "Ribo-Tag" mouse line from Dr. Jasna Kriz at University of Laval that will allow us to determine the levels of actively translated microglial cell mRNAs and protein products. This new understanding of the role of gut bacteria in modulating amyloid beta amyloidosis and microglial function in neurodegeneration offers a powerful new approach to identify new targets and/or mechanisms that could be of therapeutic relevance.

# Other

Novel approaches, targets or therapies aligned with the Cure Alzheimer's Fund mission

## Pathway Cross-talks Associated with Sex and Risk for Alzheimer's Disease

**MURALI DORAISWAMY, M.D.,** Duke University

Although women may constitute some 60 percent of all cases of Alzheimer's disease (AD) in the United States, we still don't understand the reasons why. We are using data from a large national biomarker study called the Alzheimer's Disease Neuroimaging Initiative to study this issue more systematically. Their initial results suggest that among people with mild cognitive impairment, women may decline at faster rates than men. In addition, their preliminary results also suggest that the presence of amyloid beta and tangle pathology in the brain may have a bigger effect in women than in men. Using sophisticated computational approaches to model how various genes and chemicals interact in the bodies of older people with memory problems, they are doing further analyses to confirm these early findings. Understanding the basis for gender differences will in turn help us develop highly personalized ways to reduce the risk for Alzheimer's.

## Modeling Neuronal Aging in Specific Subtypes of Human Neurons by MicroRNA-Mediated Neuronal Reprogramming

**ANDREW S. YOO, PH.D.,** Washington University School of Medicine

The ability to derive and grow human neurons in tissue culture from elderly individuals will offer invaluable tools to study how advancing aging, the strongest risk factor for Alzheimer's disease, affects neuronal properties later in life. My research team developed an experimental approach to convert (reprogram) skin fibroblast cells from human individuals directly into neurons without the usual requirement of reverting the cells back to stem cell stages. Our method utilizes small molecules called microRNAs, which can be combined with additional genetic factors to generate specific types of neurons. Here, we propose to devise a microRNA-based reprogramming technique to generate neuronal subtypes affected in early stages of Alzheimer's disease with high efficiency and specificity. Using this approach, we will generate human neurons from the donors of multiple age groups, and analyze age-related signatures in converted neurons across the age spectrum. If this project succeeds, we will be able to generate human neurons reflecting all ages, and discover the biological changes that occur at different stages of life. With these powerful tools in hand, we will be able to elucidate how neurons age and function differently across the age spectrum. Our work eventually will offer insights into cellular properties intrinsic in aging neurons that make them susceptible to neurodegenerative diseases later in life. By devising biomarkers that indicate the aging status of neurons, our work ultimately will lead to an experimental platform to screen for drugs that one day may promote healthy brain function throughout life.

# Pathological Pathways and Systems

## Tau Missorting in Alzheimer's Disease—Causes and Consequences

**EVA-MARIA MANDELKOW, M.D., PH.D.,** DZNE Bonn
**ECKHARD MANDELKOW, PH.D.,** DZNE Bonn

During the development of Alzheimer's dementia, multiple changes occur in brain cells, making the search for and treatment of underlying causes difficult. Therefore, a key goal of Alzheimer's disease (AD) research is to identify early changes occurring long before cognitive deficits become apparent. One such event is the so-called "missorting" of tau protein, which normally is found in the axons of neurons, but which in AD accumulates in the "wrong" compartments, the cell bodies and dendrites. This project aims to analyze the reasons for this pathological change and to find ways to prevent it. The mechanism of a second phenomenon in AD, the propagation of tau pathology between neurons, also is currently unclear. This propagation leads to the spread of tau neurofibrillary tangles from the transentorhinal regions of the brain to others, which Braak staging measures as a signifier of disease progression and which correlates with cognitive decline. The analysis of individual neuronal compartments observed via microfluidic devices we will perform in this project should provide evidence of whether tau propagation is caused by pathological signaling cascades or by the release and reuptake of pathological forms of tau between cells.

## The Role of Meningeal Lymphatics in Cleansing the Brain: Implications for Alzheimer's Disease

**JONATHAN KIPNIS, PH.D.,** University of Virginia

The (re)discovery of the meningeal lymphatic vessels prompted a close reassessment of the pathways of waste clearance in the brain. Unraveling the contribution of this newly characterized route of drainage to brain homeostasis will offer insights into how its healthy function can be harnessed to address the accumulation of toxic proteins seen in Alzheimer's and other neurodegenerative diseases. We now show that meningeal lymphatic function is intrinsically modulating brain perivascular cerebrospinal fluid/interstitial fluid recirculation, and that decreased drainage by the meningeal lymphatics leads to increased amyloid beta deposition in the brain and accelerates memory decline in models of Alzheimer's disease. The next step will be to understand whether the cognitive decline observed in old or AD mice can be improved by boosting meningeal lymphatic function and, if that is the case, which molecular mechanisms may account for it.

# Genetic Targets to Block Tau Propagation: Test Knockdown of Heparan Sulfate Proteoglycan Genes *In Vivo*

**MARC DIAMOND, M.D.,** University of Texas Southwestern Medical Center

Trans-cellular propagation of tau pathology has been implicated in the progression of Alzheimer's disease and other tauopathies. We previously have determined the mechanism by which tau aggregates bind the cell surface to trigger uptake via macropinocytosis. This involves direct binding of tau to heparan sulfate proteoglycans (HSPGs) on the cell surface. HSPGs are glycolipid-anchored and transmembrane core proteins that are extensively glycosylated and sulfated by a defined set of cellular enzymes. In prior published and unpublished work, we have determined that disruption of EXT1, a gene that plays a proximal role in the extension of sugar chains on HSPG core proteins, strongly inhibits tau aggregate uptake, seeding and transcellular propagation *in vitro* and *in vivo*. We hypothesize that individual HSPG synthetic genes required for tau uptake will represent viable drug targets.

Aim 1: We will individually test each of 24 genes associated with HSPG synthesis using Cas9/CRISPR-mediated gene knockout in HEK293T cells. We will confirm hits in HEK293T cells and primary cultured neurons.

Aim 2: We will test candidate genes in an in vivo model of spreading tau pathology by AAV-shRNA knockdown. If we are successful, a limited number of candidates will represent important new drug targets to block Alzheimer's disease progression.

# Inhibition of Tau Pathology in Human Neurons

**BENJAMIN WOLOZIN, M.D., PH.D.,** Boston University

The work proposed in this application stems from dramatic advances in our understanding of reasons that nerve cells die in Alzheimer's disease. This work derives from new insights into how our bodies respond to stress. We have discovered a group of proteins, termed RNA-binding proteins (RBPs), that bind directly to tau protein (one of the major proteins that accumulates in the brains of patients with Alzheimer's disease). Binding of these RBPs causes tau to form small clumps, termed oligomers, which are very harmful. In parallel studies, we have found that reducing one of these RBPs prevents disease and prolongs survival in an animal model of Alzheimer's disease. However, there actually are multiple RBPs that associate with tau in disease, and we don't know which RBP is the best target for therapeutic development. In this proposal, we will test each of the RBPs that we find associated with tau pathology and determine which is the best target for future drug development. This project also will address another key part of testing the utility of our approach for therapeutic development. Until now, our studies all have been done in mouse models. Recently, scientists have figured out how to grow human nerve cells from patients with Alzheimer's disease in culture in a way where the nerve cells develop some of the aspects of Alzheimer's disease. In this project, we will import this technology and test whether reducing RBPs in human nerve cells (similar to those in our brain) also protects against the changes seen in the brains of patients with Alzheimer's disease.

# Propagation of Tauopathy and Ubiquitin Proteasome System Dysfunction: Impact and Rescue with a UPS Activator

**KAREN DUFF, PH.D.,** Columbia University Medical Center
**NATURA MYEKU, PH.D.,** Columbia University Medical Center

The brain of a patient with Alzheimer's disease shows two abnormalities: clumps of a protein called amyloid into what is known as amyloid plaques, and clumps of a protein called tau into what is known as neurofibrillary tangles. One of the features of Alzheimer's disease is that the tangles start in one part of the brain (areas involved in memory and learning), but they infect new regions and spread through the brain, contributing to the worsening of the disease. This project will investigate the impact of tau propagation on the functioning of the ubiquitin proteasome system (UPS), the process by which cells break down proteins in order to use and dispose of/clear their component parts, and whether it can be rescued by an already-approved drug either by acting on the tau pathology itself or on its impact on the UPS.

We have spent several years studying how the tangles spread through the brain and what effect tangles have on brain function. We recently have described a way to prevent tangles forming in the brain by enhancing a molecular method known as "clearance," which is a natural way that brain cells remove ("clear") toxic or abnormal proteins. We have identified several drugs that can boost clearance and improve the brain's ability to clear abnormal tau, thereby removing tangles. While we have been able to clear tangles to some extent at various stages of disease in a mouse model, we have not yet shown whether these drugs can prevent the spread of the tangles within the brain. This could be very important if we want to prevent tangles from taking hold, or making the disease worse. We propose to test whether the spread of tangles through the brain is a result of abnormal tau overwhelming the cell's ability to clear it from cells, and if we can boost the cell's defenses against tangles using drugs. If our drugs do prevent the spread of tangles through the brain by enhancing clearance, they would be good candidates for clinical trial in AD patients, as well as in patients suffering with tangles that cause a different dementia, frontotemporal dementia (FTD).

# Will Restoration of Normal Glymphatic Function Slow Progression of Cognitive Decline and Amyloid Plaques in a Murine Alzheimer's Model?

**MAIKEN NEDERGAARD, M.D., D.M.SC.,** University of Rochester Medical Center

We proposed to map glymphatic function as a function of aging in a mouse model of Alzheimer's disease, and to test whether improved sleep can slow the progression of cognitive decline by improving glymphatic clearance. We have made considerable progress and the pilot data suggests that improved sleep indeed can slow the progression of Alzheimer's disease. Our methodological studies refining glymphatic analysis will be key for translating glymphatic studies into a diagnostic platform.

# Cerebrovascular Dysfunction in AD: Targeting the Mechanisms of Vascular Activation

**PAULA GRAMMAS, PH.D.,** University of Rhode Island

Our laboratory has worked for almost 30 years to understand how brain blood vessels may be involved in Alzheimer's disease (AD). Our work is timely and important, as a large body of evidence indicates that cardiovascular risk factors, i.e., conditions that affect blood vessel (vascular) function, increase one's risk for developing AD. We were the first to show that brain blood vessels in AD are a source of toxic proteins; a process we term "vascular activation." If blood vessel-derived toxic factors contribute to a cascade of events that lead to dementia in the AD brain, then blocking "vascular activation" should be beneficial to cognitive (memory) function. This idea is novel, testable and is supported by our preclinical study, which showed that inhibiting vascular activation did improve cognitive performance in AD transgenic mice. In the current project we will determine how cardiovascular risk factors (such as diabetes and cholesterol) in mice carrying a gene associated with late-onset AD lead to vascular activation by identifying the cellular pathways and biochemical proteins that drive this pathologic process. Results from this study will reveal novel therapeutic targets for AD and other neurodegenerative diseases. Identification of new therapeutic targets is a critical barrier to progress in the AD field. Results from this project would, for the first time, identify a cascade linking cardiovascular risk factors to brain blood vessel activation, and highlight novel targets for improving vascular function with wide-ranging implications for brain health.

# Stimulating Proteasome Activity for the Treatment of Alzheimer's Disease

**HERMANN STELLER, PH.D.,** The Rockefeller University

Alzheimer's disease (AD) poses a major unmet health need, since neither cures nor treatments that address the root cause of AD currently exist. AD is caused by the accumulation of toxic proteins that impair cell function and eventually lead to the death of nerve cells. All our cells have potent clearance mechanisms to degrade unwanted and potentially dangerous proteins. Unfortunately, this "trash removal" process becomes less efficient with age. We recently discovered a novel mechanism that stimulates the activity of "proteasomes," the nano-machines responsible for the removal of unwanted proteins, and we found that this mechanism is essential for the maintenance of neuronal health and brain function. Moreover, this process becomes less efficient with age, and mutations in this pathway are found in human patients suffering from age-related neurological diseases. Importantly, stimulating the activity of this protein clearance pathway can prevent neuronal degeneration and extend life span in animal models. Finally, we identified an inhibitor of this pathway that represents a promising drug target for the treatment of AD. This project will allow us to extend our investigation of this pathway and potential therapeutic interventions in more advanced animal models and human AD samples. This work has the potential to radically transform the field and yield a novel class of drugs that promote clearance of toxic proteins and thereby prevent age-related neuronal degeneration.

# Targeting Cell Cycle Re-entry Using 3-D Neuron Cultures

**GEORGE S. BLOOM, PH.D.,** University of Virginia Medical Center
**JOHN S. LAZO, PH.D.,** University of Virginia Medical Center
**ELIZABETH R. SHARLOW, PH.D.,** University of Virginia Medical Center

The loss of connections among neurons that control memory and cognition, and the death of those neurons, account for the well-known behavioral symptoms of Alzheimer's disease. Our laboratories have been attempting to unravel the seminal molecular pathways that convert normal healthy neurons into neurons destined to die long before the AD patients themselves. In the past two years, in large part due to the generous support of Cure Alzheimer's Fund, we made major progress toward understanding what may be the most common pathway for neuron death in AD: cell cycle re-entry (CCR), which represents the aberrant reactivation of innate processes for neuronal cell replication.

Whereas normal neurons in most of the brain never attempt to divide, up to 5 percent to 10 percent of the neurons in brain regions affected by AD show signs of CCR over the course of many years. Ironically, instead of dividing, these CCR neurons eventually die, and may account for as much as 90 percent of the neuronal loss seen in AD. We have found that CCR is initiated by soluble amyloid beta oligomers, which are the building blocks of the insoluble amyloid plaques that accumulate in AD brain, and that it requires soluble forms of tau, the protein that aggregates inside AD neurons to form insoluble neurofibrillary tangles.

In the previous funding period, we established the conditions for maximal CCR in human and mouse neurons that grow in three dimensions (3-D) and model many features of AD neurons in human brain. We have successfully identified several protein modifications and molecular pathways that participate in CCR in these cells. In the next funding period, we will exploit these innovative 3-D models to screen "libraries" of small molecules for compounds that can inhibit CCR, and thus have the potential to become drugs that prevent or slow progression of AD.

# Therapeutic Strategies and Drug Discovery

## A Combination of Anti-Amyloid Beta and Growth Factor Therapy for Alzheimer's Disease

**MARK TUSZYNSKI, M.D., PH.D.,** University of California, San Diego

We propose to test a combination of two potentially potent therapies for Alzheimer's disease (AD): Brain-Derived Neurotrophic Factor (BDNF) and an anti-amyloid treatment (gamma secretase modulator, GSM). In numerous animal models, modulation of amyloid beta levels (by immunotherapy or secretase blockade/modulation) has exhibited an ability to reduce AD-related neuropathology and improve functional outcomes. However, amyloid beta-modifying therapies have yielded disappointing results in clinical trials in which treatment is initiated after disease onset; for this reason, current clinical approaches are focusing on treating pre-symptomatic patients. Separately, we and others have shown that the nervous system growth factor BDNF can reduce neuronal loss, stimulate synaptic markers, improve transcriptional activity and ameliorate behavioral deficits in animal models of AD, ranging from APP transgenic (APP tg) mice to aged nonhuman primates. We propose to test whether a combination of these therapies will exhibit additive or multiplicative benefits in animal models of AD on molecular, cellular, biochemical and functional outcomes. The combination will be tested in APP tg mice (line 41) and on human iPSC-derived neurons from AD patients.

Thought leaders in the AD field, together with the National Institutes of Health and the Food and Drug Administration, are encouraging the exploration of combinatorial therapies for AD. We propose to pursue this promising approach, using two potent candidate therapies. We have performed first-in-human clinical trials of gene therapy in AD, and positive results of this work could similarly lead to human translation.

## Activation of the 26S Proteasome for the Treatment of Alzheimer's Disease

**ALFRED L. GOLDBERG, PH.D.,** Harvard Medical School

It has been widely assumed that rates of degradation of proteins by the ubiquitin-proteasome system (UPS) are regulated solely at the ubiquitination step. We recently discovered a novel biochemical mechanism, proteasome phosphorylation, that cells utilize to enhance their capacity to degrade misfolded proteins, such as mutant tau and phospho-tau (p-tau). We have shown that the 26S proteasome's capacity to degrade ubiquitinated proteins is enhanced in cells and mouse brains by agents (e.g., inhibitors of phosphodiesterase 4) that raise cAMP and activate protein kinase A-dependent phosphorylation of a subunit of the proteasome's 19S regulatory complex, Rpn6/PSMD11.

These new insights into the mechanisms regulating proteasome function and the degradation of misfolded proteins indicate a very promising approach for development of novel drugs to inhibit the progression of Alzheimer's disease and other tauopathies. Moreover, such treatments are potentially applicable to other

neurodegenerative diseases caused by the accumulation of aggregation-prone proteins. Also, these approaches build on the well-characterized cAMP-PKA signaling pathway, and a variety of phosphodiesterase 4 (PDE4) inhibitors have been developed that raise cAMP levels in cells. Because our recent studies also indicate that proteasome function in several disease models is somehow inhibited by the accumulation of aggregated proteins, it seems likely that impaired proteostasis contributes to disease pathogenesis. Consequently, pharmacological activation of proteasomes should directly counter this important disease mechanism and merits further in-depth study. Although PDE4 inhibitors appear to be a very promising means to promote clearance of mutant tau and to enhance memory, such agents can have undesirable side effects. One immediate goal of these studies is to compare the efficacy of different PDE4 inhibitors in activating brain proteasomes. We also shall test whether other cyclic nucleotides and other cellular kinases have a similar capacity to activate 26S proteasomes and promote the clearance of mutated proteins. Additional studies will attempt to clarify how protein aggregates can impair proteasome function and how neurons may compensate for the impaired proteostasis.

## Nanobodies to Cross the Blood-Brain Barrier

**BART DE STROOPER, M.D., PH.D,** VIB-KU Leuven Center for Brain and Disease Research (Belgium)
**MAARTEN DEWILDE, PH.D.,** VIB-KU Leuven Center for Brain and Disease Research (Belgium)

The blood-brain barrier (BBB) is a vital barrier between the bloodstream and the brain. This barrier tightly controls which molecules can enter the brain. As a consequence of this barrier, the majority of currently available drugs can't enter the brain. Importantly, to treat Alzheimer's disease, drugs need to reach the brain. The aim of this project is to generate a universal tool that can transport drug molecules to the brain. During the first period we have mainly been generating tools and validating our platform to generate such a transport tool.

## Biochemical Mapping of the GSM Binding Site of Novel Pyridazine-Derived Small Molecule Gamma-Secretase Modulators

**STEVEN L. WAGNER, PH.D.,** University of California, San Diego
**YUEMING LI, PH.D.,** Memorial Sloan Kettering Cancer Center

A promising series of pyridazine-derived gamma-secretase modulators (GSMs) have been discovered in our labs at the University of California, San Diego and Massachusetts General Hospital that inhibit the formation of the aggregation-prone amyloid beta 42 peptide in favor of shorter, less pathogenic amyloid beta isoforms. Despite the development of numerous potent GSMs, the molecular target and the mechanism of action of these compounds remain nascent. Previously, we synthesized an active GSM-photoaffinity probe based on our GSM currently undergoing preclinical development to be used in cross-linking studies in order to identify the binding site of these ligands within the gamma-secretase enzyme. Initial studies have demonstrated that our novel GSMs selectively bind to the PS1-NTF domain of the gamma-secretase enzymatic complex. Additional experiments have been planned, with the goal of broadening our understanding of these specific target-ligand interactions by mapping of the bind site of our novel GSMs. The identification of the critical sites of contact will foster an improved understanding of the mechanism by which these therapeutically relevant small molecules affect the production of amyloid beta peptides. Furthermore, these experiments then will permit the use of in silico modeling of the dynamics of enzymatic processing of amyloid precursor protein

(APP), as well as other important substrates of gamma-secretase. The successful mapping of the GSM binding site within gamma-secretase in conjunction with the recently attained 3.4 Å resolution cryo-electron microscopy structure of gamma-secretase will enable compound docking facilitating rational structural modifications in order to identify more potent, as well as novel, alternative clinical candidates in the event of any untoward safety/toxicological events in the upcoming clinical trials with BPN-15606.

## Novel Chemical Modulators for BACE1-Mediated Cleavage of Amyloid Beta Precursor Protein

**TAE-WAN KIM, PH.D.,** Columbia University

The beta-site amyloid precursor protein (APP)-cleaving enzyme 1 (BACE1) is a promising drug target in Alzheimer's disease (AD). BACE1 is a membrane-bound proteolytic enzyme that mediates the first step in producing the amyloid beta peptide. A number of genetic and pathophysiological studies have shown the essential role for BACE1 in AD. Despite its clinical importance, mechanisms regulating BACE1 functions in the brain are unknown and thus under intense investigation. We first developed an assay using neuronal cells that can monitor the proteolytic cleavage of APP by BACE1 by detection of the direct cleavage product sAPPbeta. Using this assay, we screened for small molecules and identified a number of chemical compounds that can suppress the BACE1-mediated cleavage of APP through previously unknown mechanisms (yet sparing the catalytic activity of BACE1). In this proposal, we will further validate the identified small molecules and use them as chemical tools to uncover new biological pathways regulating BACE1 in the brain. Given high relevance of BACE1 to AD pathogenesis, the successful completion of our proposed studies may yield new insight to help devise more efficacious and safe ways for controlling BACE1 activity for therapeutic means.

## Treating with Gamma-Secretase Modulators (GSMs) to Prevent Neurodegeneration in Mouse Models of Down Syndrome

**WILLIAM C. MOBLEY, M.D., PH.D.,** University of California, San Diego
**STEPHEN WAGNER, PH.D.,** University of California, San Diego

The products of the amyloid precursor protein (APP) play a defining role in Alzheimer disease (AD) in people with Down syndrome (AD-DS), as well as in other types of AD. We aim to mitigate neurodegeneration in AD-DS using small molecules called gamma-secretase modulators (GSMs). We have found that GSMs reduced the levels of the toxic products of APP. Here, we propose to validate the effects of a GSM, UCSD776890, in a mouse model of AD-DS to ask whether or not we can prevent and/or rescue neurodegeneration and AD-related pathologies. UCSD776890 has excellent pharmacological characteristics and is well suited for clinical trials. Our findings will provide valuable insights into the efficacy of this GSM, and in so doing support an IND filing and inform the design of future trials for AD-DS.

# Validation of Endogenous Human Antibodies That are Correlated With Avoiding Alzheimer's Disease and Their Corresponding Antigens, for Immunotherapeutic Development

**CHARLES GLABE, PH.D.,** University of California, Irvine

Immunotherapy is a leading strategy for preventing cognitive decline in Alzheimer's disease. In 2015, the first disease-modifying treatment that prevented cognitive decline in human trials was reported. The trial showed that high doses (10 mg/kg) of a monoclonal antibody that targets amyloid beta amyloid aggregates, Aducanumab, prevented cognitive decline in mild cognitively impaired patients over a one-year period. While this is an exciting breakthrough, there are a number of problems that need to be overcome before this therapy is widely available. A number of side effects were noted that may be associated with the high amount of antibody administered and the high costs associated with the amount of antibody required will interfere with its widespread utilization. More effective antibodies and cheaper treatments would be a great benefit to AD patients.

In the previous award period, we identified an antibody, mH, which is highly correlated with avoiding AD or having AD ($P < .005$) by using the immunoreactivity of human serum samples on a microarray of 458 different amyloid binding sites that are called epitopes or antigens. We hypothesize mH is protective against disease and we will test this hypothesis in this proposal.

We will test whether mH prevents AD pathology and improves cognitive performance in transgenic mouse models of AD pathology. Since the peptide epitope or antigen for this antibody is a non-natural random peptide sequence, it is unlikely to have the side effects previously observed for immunization against human amyloid beta, so we also will test whether active immunization with the mH antigen elicits a protective immune response in transgenic mouse models. The results of these investigations have the potential of leading to the development of more effective antibodies or active vaccines as a cost-effective therapy that can be widely administered. Other potential outcomes and deliverables include diagnostics that can detect onset of disease before cognitive deficits, and the ability to distinguish different subtypes of disease, such as vascular AD and AD with Lewy body disease. A "theranostic" approach to AD treatment, where antibodies or vaccines are tailored to a patient's disease type based on microarray screening of patient serum samples, is also possible. The theranostic approach also can be used to monitor patient immune response to active vaccination and either change antigens or supplement antibody levels with monoclonal antibody administration for individuals with low immune response.

# Whole Genome Sequencing and Epigenetics

## Analytical and Statistical Tools for Sequence Analysis for Alzheimer's Disease

**CHRISTOPH LANGE, PH.D.,** Harvard School of Public Health

The availability of next-generation sequencing data in large-scale association studies for Alzheimer's disease provides a unique research opportunity. The data contains the information that is required to identify causal disease susceptibility loci (DSL) for Alzheimer's disease and many other mental health phenotypes and psychiatric diseases. In order to translate the wealth of information into DSL discovery for Alzheimer's disease, powerful statistical methodology is required. So far, a large number of rare variant association tests have been proposed. However, they do not incorporate all the important information about the variants. So far, none of the existing approaches takes the physical location of the variant into account. Under the assumption that deleterious DSLs and protective DSLs cluster in different genomic regions, we will develop a general association analysis framework for Alzheimer's disease that is built on spatial clustering approaches. The framework will be able to handle complex phenotypes, e.g. binary, quantitative, etc., and be applicable to different study designs, i.e. family-based studies and designs of unrelated subjects. If the DSLs cluster indeed, the increase of statistical power of the approach will be of practical relevance, enabling the discovery of DSLs. In the absence of DSL clustering, our approach will achieve similar power levels as existing methodology. Furthermore, in order to test larger genomic regions for association, we will develop network-based association methodology. The network-based approach will have sufficient power for larger genomic regions than existing approaches and, at the same time, provide an intuitive understanding of the complex relationships between the variants that drive the association, fostering new biological insights. The approach can incorporate complex phenotypes and different design types. All the proposed methodology will be implemented in user-friendly software packages with existing user-communities, i.e. PBAT, NPBAT and R. We will test, validate and compare the proposed approaches with the existing methodology, using large-scale simulation studies and by applications to the whole genome sequencing family study for Alzheimer's disease from the Tanzi lab.

## CIRCUITS: Interpreting Alzheimer's Disease-Associated Genetic Variation at Enhancer Regions

**ANDREAS R. PFENNING, PH.D.,** Carnegie Mellon University

Treating Alzheimer's disease is one of the greatest challenges we face in the coming years; it has the potential to have an enormous impact on human health. Despite its importance, there still are no highly effective treatments for Alzheimer's disease, due in large part to a limited understanding of the underlying disease mechanisms. Our laboratory, as a member of CIRCUITS (Consortium to Infer Regulatory Circuits and to Uncover Innovative Therapeutic Strategies), aims to make progress toward a cure using genomic approaches. Starting from recent insights into the genetic basis of Alzheimer's disease, we will use a combination of machine learning and experimental techniques to systematically work toward the underlying biological processes, cell types, pathways and potential drug targets.

**A MESSAGE FROM**

# Dr. Rudy Tanzi on Drug Development

**As I am sure you have read in the popular press, several large pharmaceutical companies have halted or reported failures from clinical trials, primarily involving therapies aimed at preventing amyloid plaque formation. Most of these phase 2 and phase 3 clinical trials involve thousands of patients and hundreds of millions of dollars of investment.**

Some big pharma companies, such as Pfizer, even have announced they are exiting the Alzheimer's drug development market. The many clinical trial failures in Alzheimer's disease are extremely disappointing. However, they were not unexpected; they reflect an unfortunate consequence of clinical trials aimed at central nervous system disorders. The good news is that we are learning from them.

To be deemed successful, clinical trials have been required to show improvement in memory deficits and other cognitive symptoms, including the ability to manage daily functioning. As a result, only patients who already were experiencing cognitive decline have been eligible to participate in most Alzheimer's clinical trials. Over the past decade, brain imaging studies have shown that amyloid accumulates in the brain up to 20 years before any symptoms of cognitive impairment appear. The failure of so many anti-amyloid drugs to improve cognition in patients suffering with dementia mainly has taught us that unfortunately, it is too late to simply stop plaques and expect any significant degree of cognitive improvement. This is the most likely reason for why even the best anti-amyloid drugs have failed in clinical trials to improve cognition in clinically diagnosed Alzheimer's patients.

Despite these setbacks, many of the failed amyloid-targeting drugs still may merit additional testing; they just may need to be administered before, or at the latest, as soon as symptoms of cognitive impairment arise. Over the past 10 to 15 years, brain imaging has advanced to the point that we can detect plaques in asymptomatic individuals. This, together with testing of plaque- and tau tangle-related biomarkers in spinal fluid (and soon, blood), is allowing us to more reliably predict who is at risk for dementia in future years. It is at this stage of the disease—when subjects have brain pathology but no signs of cognitive impairment—that we need to begin treating them with drugs targeting plaques and tangles.

To determine whether plaque and tangle treatments will prevent subsequent symptoms of dementia, 10- to 15-year prevention trials would be required. For a variety of reasons, most big pharma companies are unlikely to conduct such extended prevention trials. The first reason is financial—the cost of long prevention trials would be in the hundreds of millions to more than a billion dollars. Second, by the time such trials would be completed, the drug being tested likely would be off patent and already generic, disallowing the company to recoup the costs of clinical development. Third, some companies are not yet convinced that stopping amyloid deposition in the brain will prevent subsequent Alzheimer's-related dementia.

Since the 1990s, there has been a heated debate in the field as to whether amyloid beta causes the disease. This is because in transgenic mouse models of Alzheimer's, the initial Alzheimer's genes that we and others discovered in the '80s and '90s led to abundant brain plaques, but not to the "tau tangles" that kill nerve cells. Thanks to Cure Alzheimer's Fund (CureAlz), we were able to develop Alzheimer's in a Dish using mini-brain organoids that could recapitulate the disease in a Petri dish in less than two months.

"Since its inception, the foundational mantra of CureAlz as been *'early prediction, early detection, early intervention,'* as a strategy for stopping Alzheimer's disease."

Those groundbreaking experiments settled the debate. They showed that plaques do, indeed, lead to tangles, if we use a human brain organoid model instead of mice. These seminal experiments conducted by Dr. Doo Yeon Kim and myself at Massachusetts General Hospital, together with dramatic advances in imaging and biomarkers, largely thanks to CureAlz Research Leadership Group member Dr. David Holtzman and his colleagues at Washington University, St. Louis, have helped to establish a greater degree of agreement in the field that if we stop amyloid early on, we can stop the subsequent progression of the disease.

Yet, the problem of having to carry out a decadelong prevention trial to show that blocking amyloid prevents downstream cognitive issues remains. In recent efforts, co-led by Dr. Holtzman, new research-based definitions of Alzheimer's disease now have been proposed to help guide smarter clinical trials based on targeting early plaque and tangle pathology in subjects who do not yet suffer from cognitive impairment. For the past several years, we at CureAlz and others in the Alzheimer's research community have proposed that the FDA should consider this approach and be open to approval of safe drugs shown in clinical trials to reduce plaque or tangles, regardless of effects on cognition. The approval of such drugs would allow us to treat this disease when pathology first occurs, and not wait until the brain has degenerated to the point that cognitive impairment or dementia has ensued.

The CureAlz Research Leadership Group routinely has recommended that treatment of Alzheimer's disease should begin before symptoms emerge, similarly to how we treat heart disease, cancer and diabetes, targeting presymptomatic biomarkers of pathology. A new release from the FDA has taken a huge step in this direction. In February 2018, the FDA published new draft guidelines for conducting clinical trials of Alzheimer's disease suggesting that therapies designed to act earlier in the disease process (prior to symptoms) could be effectively tested in clinical trials. In such trials, success would be defined as improving an Alzheimer's biomarker, e.g., reducing numbers of plaques or tangles in the brain based on imaging and spinal fluid biomarkers. Approval then could be considered for drugs reducing levels of plaques and/or tangles regardless of whether they are shown to improve cognition in symptomatic patients with dementia. The FDA now appears willing to consider clinical trials that reflect our longtime understanding of the disease at CureAlz—that Alzheimer's starts long before symptoms emerge, and that's when we need to treat it!

The new announcement also means therapeutic options that failed in the past to improve cognition in symptomatic patients now may be revisited to test whether they will curb plaque pathology when administered much earlier, prior to onset of cognitive impairment. Since its inception, the foundational mantra of CureAlz as been *"early prediction, early detection, early intervention"* as a strategy for stopping Alzheimer's disease. With the newly proposed research-based criteria of the disease and corresponding new FDA guidelines, we have begun a new era, in which achieving the goals of this mantra now seem possible—and Cure Alzheimer's Fund researchers are perfectly situated to help make it happen.

# Dear Friends,

**Numbers alone cannot tell the story of the commitment, the passion and the expertise brought to the battle to end Alzheimer's by the Board, staff, donors and researchers of Cure Alzheimer's Fund. But numbers can help us to appreciate the progress made by this team to alleviate the suffering of the millions of patients and families afflicted with Alzheimer's.**

As documented in our growth chart on the following page, our rapid increase in research investments continues to be driven by equally strong increases in overall contributions. In fact, our compound average growth rate (CAGR) for the years 2015, 2016 and 2017 is 25 percent for both research AND contributions.

The absolute dollar figure for investment in research of $15.7 million is made possible by $18.5 million total contributions from about 12,000 donors; this has made a significant impact in the support of 67 researchers in 2017 whose work has changed the understanding of Alzheimer's disease pathology.

The Cure Alzheimer's Fund Board of Directors also has grown in membership, as referenced by the Co-Chairmen (page 2). Our Board continues its policy of funding all operating costs for Cure Alzheimer's Fund. Those operating costs have also increased, but at a CAGR of 18 percent over the same three-year period referenced above, in which contributions and research increased by 25 percent.

Specifically, our Board has contributed from inception in 2004 through the end of 2017 $31.5 million to support operating expenses totaling $18.3 million through the same period. The difference has been used to augment research spending, to provide for growth in future operating expenses and to continue to fuel strong growth in research.

Tim Armour

This growth, and the integrity with which it has been achieved, has attracted high-level recognition from several charity rating agencies:

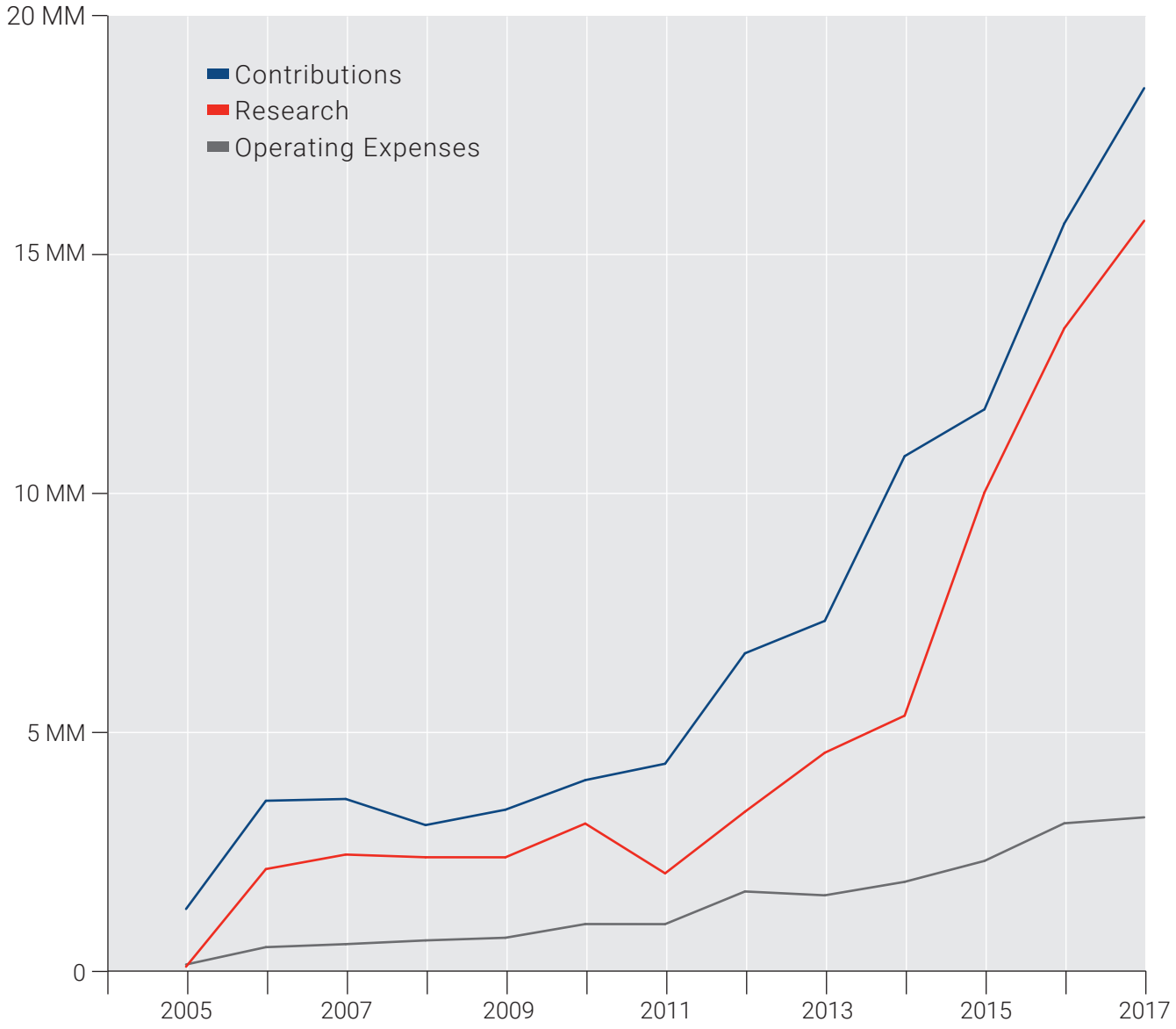
- Charity Navigator has awarded Cure Alzheimer's Fund its highest rating—4 stars—for seven consecutive rating periods.
- GuideStar has awarded Cure Alzheimer's Fund its highest designation of "Platinum."
- Give.org (a division of the Better Business Bureau) has given Cure Alzheimer's Fund a rating of 20 out of 20 standards achieved.

This recognition is a tribute to the Board of Directors for its guidance, our staff for its dedication and professionalism, our donors for their generosity and trust in our organization, and the researchers these donors have supported for delivering results that provide science-based hope for the development of safe and effective therapies.

To all those who have brought us this far, thank you. And to those who will join us, welcome.

Sincerely,
Tim Armour
President and CEO

# Growth: Inception Through 2017



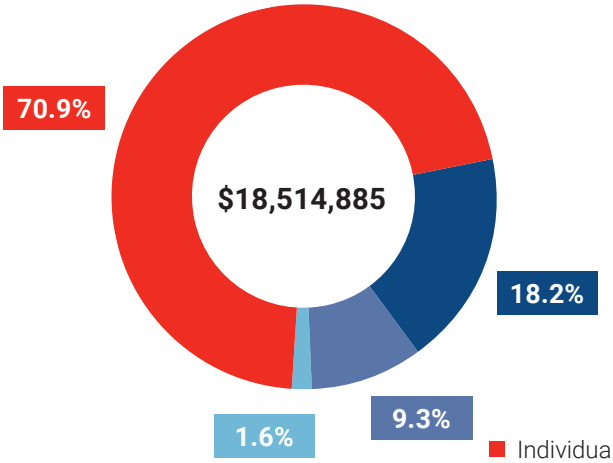

**A Record of Extraordinary Growth:**

Cure Alzheimer's Fund's rapid increase in research investments continues to be driven by equally strong increases in overall contributions.

# 2017 Fundraising

In 2017, Cure Alzheimer's Fund received 17,398 gifts—from individuals, corporations and foundations—totaling $18,514,885 in cash and in-kind revenues. Cumulative contributions from inception given by the Founders and Board total $31,508,821.Cumulative expenses from inception paid by the Founders and Board total $18,293,104.

**SOURCE OF FUNDS**




- Individuals **$13,131,677**
- Board **$3,367,945**
- Foundations/Trusts/Bequests **$1,728,611**
- Corporations **$286,652**

**USE OF FUNDS**

- Research Distributions and Support **$15,706,984**
- Programs **$2,005,066**
- Management and General **$751,416**
- Fundraising **$539,850**

Cure Alzheimer's Fund has no endowment or investment fund—our objective is to move money from donors to research as quickly as possible.
Source: Internal records.

# 2017 Financials (Year ended Dec. 31, 2017)

## Statement of Financial Position

| | |
|---|---|
| ASSETS | |
| Cash and cash equivalents | $4,250,228 |
| Restricted cash, documentary program project funds (temporarily restricted) | 25,164 |
| Investments | 3, 990,040 |
| Contributions receivable, undeposited funds | 929,151 |
| Pledges receivable (temporarily restricted) | 1,508,177 |
| Deposits – donor-advised funds | 10,136 |
| Equipment, net | 42,857 |
| Other assets | 183,265 |
| TOTAL ASSETS | 10,939,018 |
| LIABILITIES AND NET ASSETS | |
| LIABILITIES | |
| Accounts payable and accrued expenses | 530,632 |
| Total liabilities | 530,632 |
| NET ASSETS | |
| Unrestricted | 8,303,832 |
| Temporarily restricted | |
| Pledges receivable | 1,508,177 |
| Documentary program project | 25,164 |
| Personnel | 120,297 |
| Research in African American Population | 450,916 |
| | 2,104,554 |
| TOTAL NET ASSETS | 10,408,386 |
| TOTAL LIABILITIES AND NET ASSETS | $10,939,018 |

## Statement of Activities

| | |
|---|---|
| UNRESTRICTED NET ASSETS | |
| REVENUE AND OTHER SUPPORT | |
| Contributions | $17,501,551 |
| Net assets released from restrictions (pledges) | 1,010,314 |
| Donated services | 3,762 |
| Investment income | 13,021 |
| Realized (loss) gain in sale of stocks | (20,105) |
| Unrealized gain on investments | 10,314 |
| Other income | 3,644 |
| Net assets released from restrictions (other) | 16,235 |
| Net assets released from restrictions (documentary program project) | 58,172 |
| TOTAL REVENUE AND OTHER SUPPORT | 18,596,908 |
| EXPENDITURES | |
| Program expenses | |
| Research distributions and support | 15,706,984 |
| Documentary program project expenses | 58,172 |
| Operating program expenses | 1,946,894 |
| | 17,712,050 |
| Management and general | 751,416 |
| Fundraising | 539,850 |
| TOTAL EXPENDITURES | 19,003,316 |
| (DECREASE) INCREASE IN UNRESTRICTED NET ASSETS | (406,408) |
| TEMPORARILY RESTRICTED NET ASSETS | |
| Net assets released from restrictions | (1,084,721) |
| (DECREASE) INCREASE IN TEMPORARILY RESTRICTED NET ASSETS | (1,084,721) |
| CHANGES IN NET ASSETS | (1,491,129) |
| NET ASSETS BEGINNING OF YEAR | 11,899,515 |
| NET ASSETS AT END OF YEAR | $10,408,386 |

From the 2017 audited financial statements which, along with IRS Form 990, are available online at **curealz.org**.

# Our People

Cure Alzheimer's Fund is governed by a Board of Directors and administered by a small staff of full-time and part-time employees. We are guided by a Research Leadership Group and a Research Strategy Council to ensure that the funded projects are consistent with the mission of the organization. To read the biographies of our Board members and staff, please visit **CureAlz.org/our-impact/our-people**.

## BOARD OF DIRECTORS

**JEFFREY L. MORBY**

*Co-Chairman, Board of Directors*

*Founding Board Member*

*Former Vice-Chairman of Mellon Bank, President of Mellon Bank Europe*

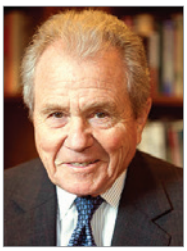
*Chairman of the Morby Family Charitable Foundation*

**TIM ARMOUR**

*President and Chief Executive Officer*

**BILL BENTER**

*Founder of Acusis*



**ROBERT F. GREENHILL**

*Chairman and Founder Greenhill & Company*

**JAY JESTER**

*Managing Director for Audax Private Equity*

**HENRY F. McCANCE**

*Co-Chairman, Board of Directors*

*Founding Board Member*

*Chairman Emeritus of Greylock Partners*

*Trustee of the McCance Family Foundation*

**JACQUELINE C. MORBY**

*Founding Board Member*

*Senior Advisor of TA Associates*

**PHYLLIS RAPPAPORT**

*Treasurer*

*Founding Board Member*

*Chair of the Phyllis and Jerome Lyle Rappaport Charitable Foundation*

*Director of New Boston Fund, Inc.*

**SHERRY SHARP**

*Christian Writer*

*President and Director of The Rick Sharp Alzheimer's Foundation*

## ADMINISTRATION

**TIM ARMOUR**
*President and Chief Executive Officer*

**LISA BIDA**
*Marketing Manager*

**JOYCE CANTOW**
*Accounting Assistant*

**BARBARA CHAMBERS**
*Senior Vice President*

**KRISTEN HAWLEY**
*Manager of Meetings and Events*

**AMANDA LACEY**
*Office Manager/Executive Assistant*

**LAUREL LYLE**
*Vice President, Development Operations and Fundraising Programs*

**JESSICA MUTCH**
*Chief Financial Officer*

**LAURA PELLETRINO**
*Development Assistant*

**SALLY ROSENFIELD**
*Senior Vice President*

**CAITLIN SAIA**
*Program Assistant*

**SHARON SEVRANSKY**
*Gift Processing Associate*

**JOHN SLATTERY**
*Senior Vice President*

**MEG SMITH**
*Senior Vice President*

**CONNOR SWAN**
*Development Associate*

**CINDY TURNER**
*Bookkeeper*

**DOROTHY VACARO**
*Gift Processing Associate*

# Our Heroes

**So many have been affected by Alzheimer's disease and every year we learn of those individuals who selflessly reach out to their friends and families to organize events that provide contributions to our fund. We are amazed—and humbled—by all of our donors and by these heroes. We thank all of our 2017 heroes, and share a few of their stories on the following pages.**

Alan Arnette
Alan Zhong
All Heart Cosmetics
All Set
Brandon Key
Carriage House at Lee's Farm
Cure Alzheimer's Mid-Atlantic
David K. Johnson Foundation
Diana Fiske
Family of John Ferrero
Freeburg Community High School
Gabrielle de Weck
Gil Stubbs
J. McLaughlin
Jog Your Memory
Keynote Sisters
Lauren Jiggetts, WGN Chicago
Lili and Tanya Cantu
Lisa Genova
Mary Schaus
Meadows Farms
Morgan Middleton
Nicki Rutishauser
Northbridge Companies
ONEHOPE Wine
Pro-Life Sports
Rebecca Carter and Kyle Fitzpatrick
Rick Sharp Alzheimer's Foundation
Running Road Trip
Shannon Roland
SingStrong A cappella Festival
Springbok Puzzles
Stacy Hull India Hicks
Sunset Halters
Talbots
Tina Kohnen
Trail Animals Running Club
Whit Collier
Wendy Hinden
Worldwide Wine & Spirits

# Mongol Musketeers

In the summer of 2017, Sam Bowers, Brigette Miller and Grady Northrup joined the Mongol Rally and started a 20,000-mile journey from Ireland to Mongolia—and back—to raise money for Cure Alzheimer's Fund. As they made their journey, we watched them via social media cool off in the North Sea, roll through Slovenia and cross through Russia. They encountered camels, fixed flat tires and enjoyed local cultures and people along the way. And, after their trek had concluded, they made a very generous donation to our organization.

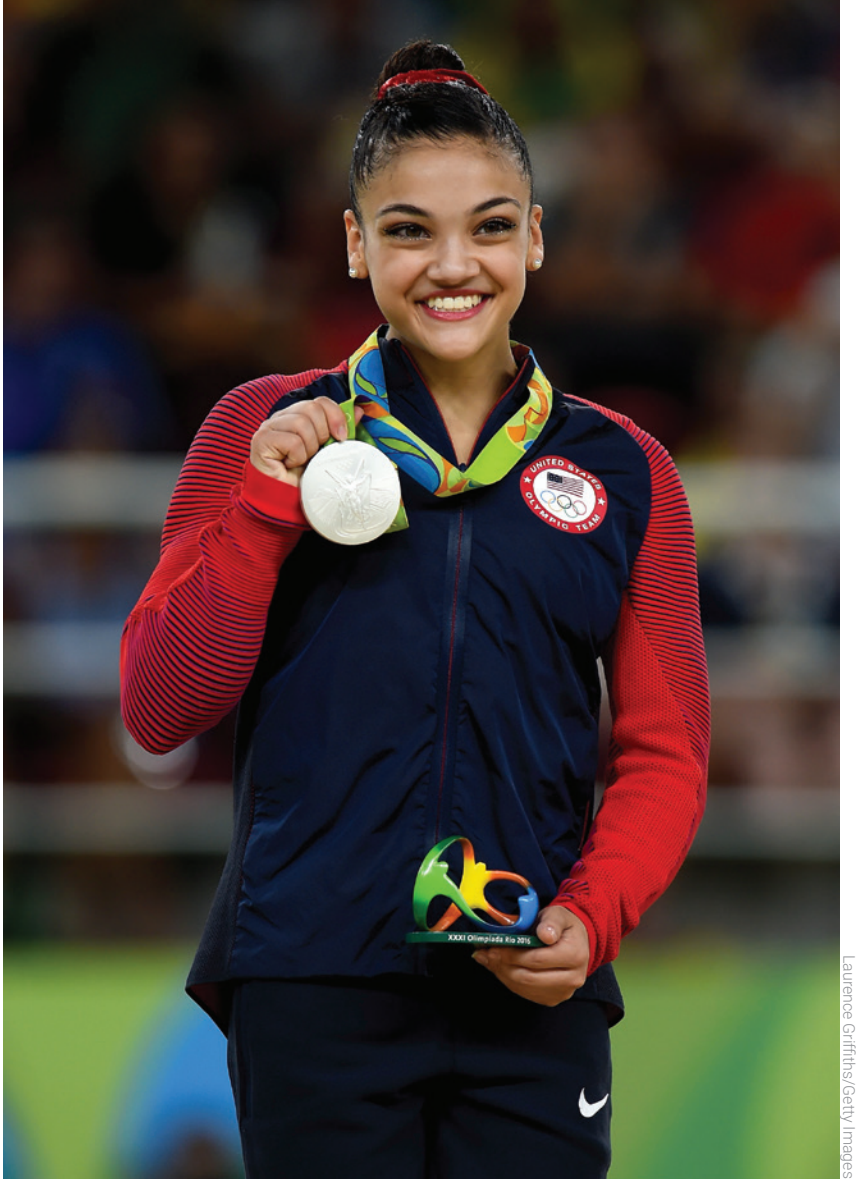
# Carolyn Mastrangelo and Barbara Geiger

Carolyn Mastrangelo and Barbara Geiger have held their annual Running4Answers Race and Fun Run in Roseland, New Jersey, since 2010. Carolyn's mother, Patricia Ann Lepofsky, was diagnosed with early-onset Alzheimer's in 1998 at age 54, inspiring Carolyn and Barbara to start the event to support research for a cure.

Lepofsky passed away in October 2015 from complications due to Alzheimer's disease. The Running4Answers team carries on. Through the years, hundreds of runners and walkers have come together each spring to raise awareness and important research dollars. Since its inception, Running4Answers has donated more than $250,000 to Cure Alzheimer's Fund and to the research that will lead to a cure. We are truly grateful for the extraordinary efforts of these two women and for their unwavering commitment.

# Laurie Hernandez Interstate Dance and Gymnastics

Olympic gold medalist and American gymnast Laurie Hernandez knows firsthand the impact of Alzheimer's disease. Laurie was close to her grandmother, who succumbed to the disease in 2016. Since then, Laurie has been involved in many awareness and fundraising initiatives. Interstate Dance and Gymnastics in Methuen, Massachusetts, sponsored an event encouraging their students to raise funds for Alzheimer's research and attend a special afternoon and lunch with Laurie as their reward.



Laurence Griffiths/Getty Images

# Fire Fighters Local 792

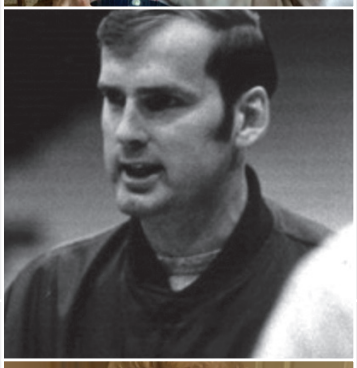
Quincy, Massachusetts, is home to an exceptional group of firefighters. They make sacrifices every day to protect the citizens of their community. Then, in their off time, they continue their service by giving back in extraordinary ways. For the past three years, International Association of Fire Fighters (IAFF) Local 792 has held an event at Olindy's bowling lanes and hundreds have participated to drive donations for our research.

# In Honor and In Memory

Cure Alzheimer's Fund receives many gifts in honor or in memory from the families and friends of those with Alzheimer's disease; these gifts are a reminder of the scale of Alzheimer's disease and that a cure must be found.

Giving a gift in honor or in memory of a family member or friend is an extraordinary way to pay tribute to someone special in your life while supporting the mission of finding a cure. If you would like to designate a memorial gift, you can do so on our website, or by mail or telephone. We will gratefully acknowledge each gift by notifying the individuals you have designated without disclosing the amount of the donation. At your request, we also will publish memorial photos we receive to the In Memory section of our website at **CureAlz.org/giving/in-memory/**.

If you have any questions about our In Memory program, please contact Laurel Lyle, Vice President of Development Operations and Fundraising Programs, at **LLyle@curealz.org**, or call **781-237-3800**. Thank you.



Cure Alzheimer's FUND

# SUPPORT OUR RESEARCH

Cure Alzheimer's Fund believes it is imperative to focus on and fund research that is innovative, collaborative and results oriented. The research we have funded has provided for tremendous advancements in understanding Alzheimer's disease and the search for a cure.

**But there is much more work to be done.**

To make a gift, or for additional ways to give, please visit **CureAlz.org/giving/donate/** or call **877-CURE-ALZ (287-3259)**.

**100% of your donation goes directly to research.**

Thank you.

★★★★ CHARITY NAVIGATOR Four Star Charity

Cure Alzheimer's Fund has been awarded the highest rating of 4 stars and has been in the top 3% of all charities for 7 consecutive years.

GUIDESTAR PLATINUM PARTICIPANT

Cure Alzheimer's Fund is a Platinum-level GuideStar participant, the highest level of recognition offered by GuideStar.

BBB ACCREDITED CHARITY

Cure Alzheimer's Fund is an accredited charity and meets all 20 Standards for Charity Accountability.

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Cure Alzheimer's FUND

**Main Office**
34 Washington St., Suite 200
Wellesley Hills, MA 02481
Phone: (781) 237-3800
info@curealz.org

**Office of the Co-Chairman**
Centre City Tower
650 Smithfield St., Suite 2015
Pittsburgh, PA 15222
Phone: (412) 261-2785

**CureAlz.org**
**WomenandAlzheimers.org**



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