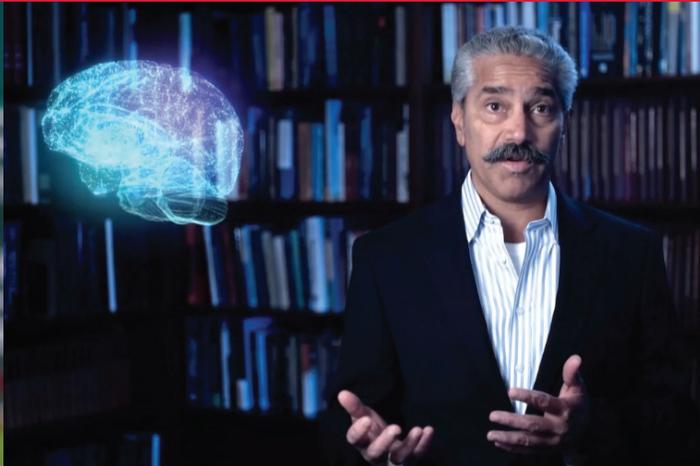


 **Cure Alzheimer's FUND**
15 years of breakthrough research

2019 ANNUAL REPORT



OUR MISSION

Cure Alzheimer's Fund is a non-profit organization dedicated to funding research with the highest probability of preventing, slowing or reversing Alzheimer's disease.

The photographs on the cover of this annual report represent 15 years of dedication to end Alzheimer's disease. We honor and are grateful to all who have brought us one step closer to a cure.

Annual Report 2019

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Dear Friends,

As we all know, we currently are living through an unanticipated and difficult period of our history, with the ultimate impact of COVID-19 on our society still unknown. Cure Alzheimer's Fund faces a paradox in this report—celebrating the outstanding results of last year, while simultaneously describing the actions we are taking to mitigate the impact of the pandemic on our research activities.

First, let us describe the situation going forward. Fortunately, due to the excellent fundraising results in 2019 and in the first few months of 2020, we have begun this year with substantial resources for research funding. Also, we have a dedicated group of directors committed to fully funding the operating expenses of the foundation so, unlike the vast majority of nonprofits, we expect to maintain our level of activities. We hope, however, that all of you will continue to support us during this difficult period, since it is your donations that fund our research.

Despite the anticipated continued support of many of our committed givers, we anticipate a reduction in fundraising. We should be able to fully fund ongoing research projects, but in the case of new projects, we must be careful to select only those with the most meaning. Dr. Rudy Tanzi, Tim Armour and Meg Smith, along with our Research Strategy Council, are working on prioritizing our research funding for the remainder of the year.

Tim and his wonderful team have made a smooth and impressive conversion to a virtual organization, with everyone now operating from their homes and not going into the office. This transition has proceeded without any major hitches, and our devoted staff continues to process research grants, review progress reports, accept and record donations and maintain contact with our donors. We are in good shape.

Due to the COVID-19 crisis, like business owners around the world, Cure Alzheimer's Fund-supported scientists were forced to temporarily close down their labs in mid-March. But that has not impeded our scientific progress in the fight to stop Alzheimer's disease. Cure Alzheimer's Fund research has continued throughout the pandemic and even has led to useful new research for fighting COVID-19. While the labs are physically



From left, Cure Alzheimer's Fund Co-Chairmen and Co-Founders Jeffrey L. Morby and Henry F. McCance, and Cure Alzheimer's Fund Research Leadership Group Chair Rudolph Tanzi, Ph.D.

shut down, it is important to note that—thanks to your generous funding—our scientists have been so prolific in their research findings that there is always a healthy backlog of fresh data to analyze, of studies being prepared for publication, and brainstorming and think tank sessions. Our investigators are conducting daily online meetings (e.g., Zoom sessions) with their lab members and each other.

Science does not stop—even for a pandemic.

Throughout the COVID-19 crisis, each lab has been able to appoint essential personnel who (in physically distanced shifts) keep the lab experiments ready to roll as soon as the lab fully reopens. This entails maintaining the lab mice that never stop breeding, the cells that never stop dividing and the equipment that never stops humming. In addition, a good number of experiments are performed on computers, e.g., statistical genetics, bioinformatics, artificial intelligence-based drug discovery and data mining. These activities continue unimpeded at home offices.

While Alzheimer's disease research goes on, many of our scientists also are taking the opportunity to help out with the COVID-19 crisis in various ways. For example, at Massachusetts General Hospital and other medical centers, other clinical units were turned into intensive care units (ICUs) once it became clear there would not be enough critical care capacity to handle the huge influx of COVID-19 patients. But the new ICUs didn't have the centralized monitoring equipment necessary to keep track of all of the patients. So, lab researchers were redeployed as "listeners" to sit outside patients' rooms monitoring their vitals, oxygen levels and ventilator status. Other techs contributed with their foreign language skills, handing out personal protective equipment or bringing food to front-line caregivers. Many neurology doctors also have been redeployed as COVID-19 ICU doctors.

Alzheimer's disease labs currently are loaning unused equipment and providing supplies to labs carrying out critical COVID-19 testing to increase throughput. And, in some labs, like Dr. Rudy Tanzi's, Cure Alzheimer's Fund investigators are helping to develop new tools that someday will allow for home testing for COVID-19 exposure.

Cure Alzheimer's Fund researchers also are using their expertise and resources to contribute to COVID-19 research, in many cases thanks to the research tools and drugs our generous donors have made possible. This includes employing algorithms and programs developed for the Alzheimer's Genome Project™ (AGP) to determine the

genetic risk factors that make some resilient to COVID-19-related respiratory distress and others more susceptible. Other algorithms invented by AGP investigators have been used to analyze thousands of viral genome sequences from COVID-19 patients to successfully determine how many strains of COVID-19 virus exist, along with their relative severity and geographic origins.

“Cure Alzheimer's Fund studies also are being planned to assess whether COVID-19 infection will increase later-life risk for Alzheimer's disease along the lines of the 'Antimicrobial Protection Hypothesis.’”

Our scientists also are learning from Alzheimer's disease research about how inflammation inundates the lungs of some COVID-19 patients with what has been termed a “cytokine storm.” This is because in the brains of Alzheimer's patients, the biggest killer of nerve cells—neuroinflammation—also leads to cytokine storms; the underlying molecular and pathogenic mechanisms are remarkably similar. In Alzheimer's disease, although triggered by plaques and tangles, it is also the cytokine storm-triggering neuroinflammation that ultimately leads to dementia.

The Cure Alzheimer's Fund 3D Drug Screening Consortium has been successfully screening for drugs and natural compounds that protect against neuroinflammation in the brain. This

information now is being shared with COVID-19 researchers and ICU clinicians to test whether the same drugs can reduce inflammation and the resulting cytokine storm in COVID-19 patients. These include drugs that afford protection against inflammation, e.g., the Cure Alzheimer's Fund-supported Amylyx drug combination that was successful in a recent amyotrophic lateral sclerosis (ALS) clinical trial and that now is being tried in Alzheimer's patients. This also includes dozens of drugs and natural products that worked in our Alzheimer's in a Dish screens, e.g., cromolyn, cat's claw and exotic mushroom extracts. We also will be exploring whether the same lifestyle recommendations for reducing chronic neuroinflammation espoused by Cure Alzheimer's Fund, like S.H.I.E.L.D (sleep, handle stress, interact, exercise, learn new things, diet) may help with resilience to COVID-19.

Finally, Cure Alzheimer's Fund investigators also are asking whether COVID-19, once it enters the brain, can trigger amyloid plaques and tangles, along the lines of the “Antimicrobial Protection Hypothesis” championed by Cure Alzheimer's Fund researcher Rob Moir, whose groundbreaking studies are going strong in Rudy Tanzi's

lab. Cure Alzheimer's Fund studies also are being planned to assess whether COVID-19 infection will increase later-life risk for Alzheimer's disease along the lines of the "Antimicrobial Protection Hypothesis." When it comes to fighting COVID-19, as it is with Alzheimer's disease, it is an "all hands on deck" approach. Despite all of the chaos and heartbreak the COVID-19 virus has caused the world, you can be assured that throughout this terrible crisis, our researchers continue the fight to stop Alzheimer's disease while selflessly working more closely together than ever to apply our research expertise and tools to slowing the COVID-19 pandemic.

Our 15th Anniversary Year, Outstanding in All Respects

In 2019 we were able to fund \$19.9 million in research projects as we raised a total of \$25.2 million. The latter number represents a 23% increase in funds raised from 2018. Please see page 67 for a graph showing our fundraising and research investments over the last 15 years. As of March 2020, Cure Alzheimer's Fund had provided **\$110 million in Alzheimer's research grants.**

In recognition of our leadership role, for the **ninth consecutive year, Cure Alzheimer's Fund has achieved a 4-star rating from Charity Navigator**, awarded to only 3% of nonprofit organizations in the United States. Similarly, the Better Business Bureau and other charity rating agencies consistently recognize Cure Alzheimer's Fund with high ratings for effectiveness and efficiency. Through 2019, the 525 research papers funded by Cure Alzheimer's Fund have been cited 28,000 times, a measure of the importance of our breakthrough research, which few others can match.

Our Scientific Accomplishments and Activities

Below are described some of our research efforts in 2019, many of which will continue into 2020. Every one of the initiatives described below has the potential for new drug discovery, and with these projects we are getting closer and closer to finding a cure.

NEUROINFLAMMATION

We at Cure Alzheimer's Fund (through the Alzheimer's Genome Project, spearheaded by Rudy Tanzi, Ph.D.) identified inflammation as a primary cause of clinical Alzheimer's disease in 2008—far earlier than the field as a whole—with the discovery of the risk impact of the CD33 gene. In the labs of scientists like Drs. Marco Colonna (Washington University School of Medicine in St. Louis), Christian Haass (DZNE Munich), David Holtzman (Washington University School of Medicine in St. Louis) and Ana Griciuc (Massachusetts General Hospital), CureAlz scientists have gone on to investigate the functions of CD33 and another inflammation gene with AD risk variants, TREM2, and their interplay, and are seeking ways to intervene to inhibit the excess inflammation we now know causes the devastating loss of neurons and their networks.

ALZHEIMER'S IN A DISH AND DRUG SCREENING

The Alzheimer's in a Dish tool (ADiD), a breakthrough technology developed by Drs. Doo Yeon Kim and Rudy Tanzi of Massachusetts General Hospital in 2014 with CureAlz funding, empowers researchers with a human-derived neural cell system

to identify potential causes of Alzheimer's disease as well as to assess potential medications. The original ADiD innovation has been matched with a high-throughput testing system to allow our researchers to rapidly analyze natural compounds and drugs, including those developed for other diseases and proven to have a safe dose, for their impact on Alzheimer's pathology. Using ADiD, the CureAlz 3D Drug Screening Consortium now has completed initial analysis of thousands of FDA-approved drugs and natural compounds and has identified a number of candidates able to prevent up to 90% of expected amyloid and tau pathology from developing in the model. CureAlz now is funding the significant and challenging work of determining whether these compounds would be similarly effective in people at safe doses.

THE ANTIMICROBIAL PEPTIDE (AMP) HYPOTHESIS, A NEW PARADIGM

At the end of 2019, Rob Moir, Ph.D., a brilliant researcher at Massachusetts General Hospital, tragically passed away from brain cancer. He leaves an extraordinary legacy of creativity and rare insight from which the entire Alzheimer's community will forever benefit. Together with his close friend and career-long collaborator Rudy Tanzi, Ph.D., Rob originated the Antimicrobial Peptide Hypothesis of Alzheimer's Disease. This theory turns the classic understanding of Alzheimer's pathology on its head by positing that amyloid, tau and neuroinflammation are all components of the brain's innate immune system, whose purpose is to protect the brain from pathogens and other insults. In certain situations (including the presence of genetic variants that evolved to protect against historical pathogens but that now are deleterious), the normally protective innate immune system overreacts, generating the conditions for Alzheimer's disease. This breakthrough hypothesis has important implications for Alzheimer's drug development, since we now know that amyloid beta, tau tangles and inflammation are providing useful protection for the brain, so any medicines that attempt to totally eliminate them may be counterproductive. Many medications that have been under consideration will have to be reconsidered now that the goal is to modulate production and activity rather than totally inhibit them.

IMPLICATIONS OF THE AMP HYPOTHESIS—PATHOGENS ARE A TRIGGER FOR AD

The AMP Hypothesis implies that one potential way of significantly reducing the number of Alzheimer's patients in our population would be to start with the very beginning of the problem—the triggers, thought to include pathogens of various types such as viruses, fungi and bacteria. As our research based on the work from the Moir and Tanzi labs continues, we will learn more about whether these triggers or the innate immune overreaction to them can be stopped at the outset. Some viruses are present in our genomes from birth, but other pathogens invade the brain during our lifetime. CureAlz has long supported work in the lab of Berislav Zlokovic, M.D., Ph.D., at the University of Southern California, a leader in the investigation of how the blood-brain barrier becomes more porous as we age, potentially allowing easier entry by pathogens. Knowing which invasive pathogens are key triggers for AD pathology would enable us to focus efforts on fighting them—potentially with vaccines, antivirals, and other preventive measures and treatments—so CureAlz is dedicating significant resources to identify the pathogens potentially overrepresented in the brains of Alzheimer's patients.

BRAIN PERIPHERY INTERACTIONS AND THE CUREALZ BERG BRAIN ENTRY AND EXIT CONSORTIUM

Jony Kipnis, Ph.D., of Washington University School of Medicine in St. Louis, several years ago made the startling discovery that the brain has a long-unrecognized lymphatic system. His work has tremendous implications for Alzheimer's research, because the lymphatic system in the brain acts as a clearing mechanism for amyloid and other proteins. More recently, a CureAlz-funded lab discovered a series of small channels in the skull that allow immune cells to travel from the skull's bone marrow into the brain.

These discoveries, along with the field's new recognition that more pathogens and immune cells travel in and out of the brain than historically recognized, led CureAlz to convene a new consortium to address the passage of materials into and out of the brain. Thanks to generous funding provided by the Berg family, six labs on two continents are collaborating to investigate how the brain's fluid systems interact, and how different cellular actors function together in these systems. The answers to these questions should create a wide range of new opportunities, from improved resistance to pathogenic invasion of the brain, to therapeutic improvement of protein clearance, to new ways to ameliorate inflammatory side effects from AD therapeutics.

CONTINUING INSIGHTS FROM THE ALZHEIMER'S GENOME PROJECT

The CureAlz Alzheimer's Genome Project continued to generate important scientific data in 2019. Beginning with the formation of Cure Alzheimer's Fund 15 years ago, we have always maintained a leadership position in understanding the genomics of AD, thanks to our scientific leader, Rudy Tanzi. We were the first to do an AD family-based scan of the entire genome to identify novel AD genes beginning in 2005, and 10 years later were among the first to carry out more sophisticated (whole genome sequencing) scans of AD families and cases employing the latest next-generation genome sequencing technology. We now have one of the most comprehensive databases in the world for the genomics of AD and are constantly adding dimensions to that database to permit us to perform a great variety of state-of-the-art analyses using sophisticated algorithms developed by our scientists. In 2019, Drs. Christoph Lange (Harvard T.H. Chan School of Public Health) and Rudy Tanzi (Massachusetts General Hospital) published four novel sex-specific genetic loci associated with different levels of risk for Alzheimer's disease for men than for women, loci that they identified by developing a new complex biostatistical analytics and filtering approach. They also published this approach, and it will serve both the Alzheimer's field and others looking for risk differences arising from genetic sex.

The "crossruffing" of genetic information with other biochemical information and information from the human biome is allowing us to more fully understand the causes of Alzheimer's disease. Our many Genes to Therapies™ (G2T) projects

"Thanks to generous funding provided by the Berg family, six labs on two continents are collaborating to investigate how the brain's fluid systems interact, and how different cellular actors function together in these systems."

thus are investigating the variants identified by AGP. Now, in 2020, sequencing and analysis of AGP data have expanded to include the 96% of the genome that includes regulatory elements. Gene regulation is emerging as a key question in Alzheimer's disease because it can change as an organism ages and in response to its environment. These "epigenetic" changes thus can alter how the presence of a particular gene variant changes the function of a cellular pathway even though the underlying gene—the DNA—does not change. The combination of the specific variant of a person's gene and how the expression of that gene is regulated thus offers new complexity, but

also new opportunity for understanding and intervening in cellular pathways implicated in Alzheimer's. The six labs of our CureAlz CIRCUITS consortium, led by Drs. Manolis Kellis and Li-Huei Tsai of the Massachusetts Institute of Technology, are addressing this complexity in partnership with AGP.

"CureAlz's determination to take smart risks on rigorously identified promising early research has led us to be respected leaders in the Alzheimer's field; ... in 2019, significant funding far beyond what our resources alone could provide flowed to labs and research thanks to data and prominence enabled by our early support."

NEW PROJECTS STARTED IN 2019

CureAlz continued its commitment to a number of longstanding projects in 2019 due to their continued outstanding progress, but we also initiated support for an impressive group of new investigations. We will provide a few examples here but hope you will discover all of the others as you read this report. Drs. Len Petrucelli (Mayo Clinic Jacksonville) and Anthony Fitzpatrick (Columbia University) are applying new technology, cryo-electron microscopy, to define the unique shape of tau filaments in different tauopathies, including Alzheimer's. Our microbiome support expanded to new researchers, Howard Weiner and Laura Cox at Brigham and Women's Hospital. We initiated support for our second clinical trial, an assessment of the use of commonly available equipment to examine key cells in the eye for changes that could be diagnostic for Alzheimer's disease, under the leadership of Dr. Shirley Wray (Massachusetts General Hospital). We added a new G2T project in the lab of John Fryer at the Mayo Clinic Arizona, who is looking at the role of the clusterin gene in tau pathology. We are excited to see what these new efforts in the labs of highly experienced and productive scientists will yield.

LEVERAGE AND LEADERSHIP

In 2019, we partnered with the Alzheimer's Association and Alzheimer's Drug Discovery Foundation to finance a stage two human Alzheimer's trial of a drug developed by Amylyx; our participation has allowed the trial to double its originally planned size. Despite the challenges to clinical trials posed by COVID-19, Amylyx in May 2020 announced full enrollment of this PEGASUS Alzheimer's trial, which is seeking to improve cognition by redressing mitochondrial and endoplasmic reticulum function in patients with mild AD. Amylyx also announced late in 2019 that its trial of the same combinatorial therapeutic in ALS demonstrated statistically significant benefits to patients over placebo, a wonderful achievement for the ALS community, and we believe a positive sign that the Amylyx drug will similarly help AD patients. Amylyx is

a wonderful example of CureAlz's commitment to supporting the highest potential wet lab research on the path to patients: back in 2015, we were one of Amylyx's first funders, and we are excited about the leverage our investment has generated.

CureAlz's determination to take smart risks on rigorously identified promising early research has led us to be respected leaders in the Alzheimer's field; we are proud that in 2019, significant funding far beyond what our resources alone could provide flowed to labs and research thanks to data and prominence enabled by our early support. The work leading to the publication of the sex-linked Alzheimer's gene variants by Drs. Lange and Tanzi, for example, was funded by CureAlz in partnership with the Rotary Foundation. Influenced in large part by the work of Drs. Moir and Tanzi, the National Institutes of Health has newly dedicated funding for projects investigating pathogens as causes of Alzheimer's.

CureAlz long has supported work in the labs of Drs. Moir, Tanzi and Sam Sisodia (University of Chicago) on the connection between the gut microbiome and AD pathology in the brain; this research now is frequently highlighted at Alzheimer's conferences and catalyzed Open Philanthropy's ongoing \$10.5 million program in five labs also funded by CureAlz. Finally, the National Institute on Aging will decide soon whether it will follow its large Blueprint grant investment in the gamma-secretase modulator (GSM) developed by Drs. Tanzi and Steve Wagner (University of California, San Diego) with CureAlz funding by fully funding its phase 1 clinical trial at a cost of more than \$5 million. CureAlz is committed to working with all possible partners to fight a disease that is too big for any one entity to conquer.

TO OUR FRIENDS

Thank you so much for both your financial and other support in so many different ways. We are honored that in 2019 we received 4,800 memorial gifts, totaling \$1.1 million, paying tribute to friends and relatives brought down by Alzheimer's disease. On behalf of them and you, our supporters, we are committed to winning the battle against Alzheimer's disease.

Best wishes,

Jeffrey L. Morby
Henry F. McCance
Founders
Co-Chairmen
Cure Alzheimer's Fund

Rudy Tanzi, Ph.D.
Chair, Cure Alzheimer's Fund Research Leadership
Group; Professor of Neurology, Harvard Medical
School; Director, Genetics and Aging Research Unit,
Massachusetts General Hospital



Dr. Robert Moir Changed the World's Understanding of Alzheimer's Disease

Cure Alzheimer's Fund Has Lost a Cherished Friend

On Dec. 20, 2019, at the age of 58, Robert Moir, Ph.D., passed away from glioblastoma, an aggressive form of brain cancer.

Rob was a brilliant scientist whose pioneering research led to a fundamental shift in the understanding of Alzheimer's disease. Born in Australia, he immigrated to the United States in 1994 to begin what would become a distinguished career. He joined the Genetics and Aging Research laboratory of Dr. Rudy Tanzi at Massachusetts General Hospital as an Alzheimer's biochemist and continued working in his lab as a post-doctoral fellow.

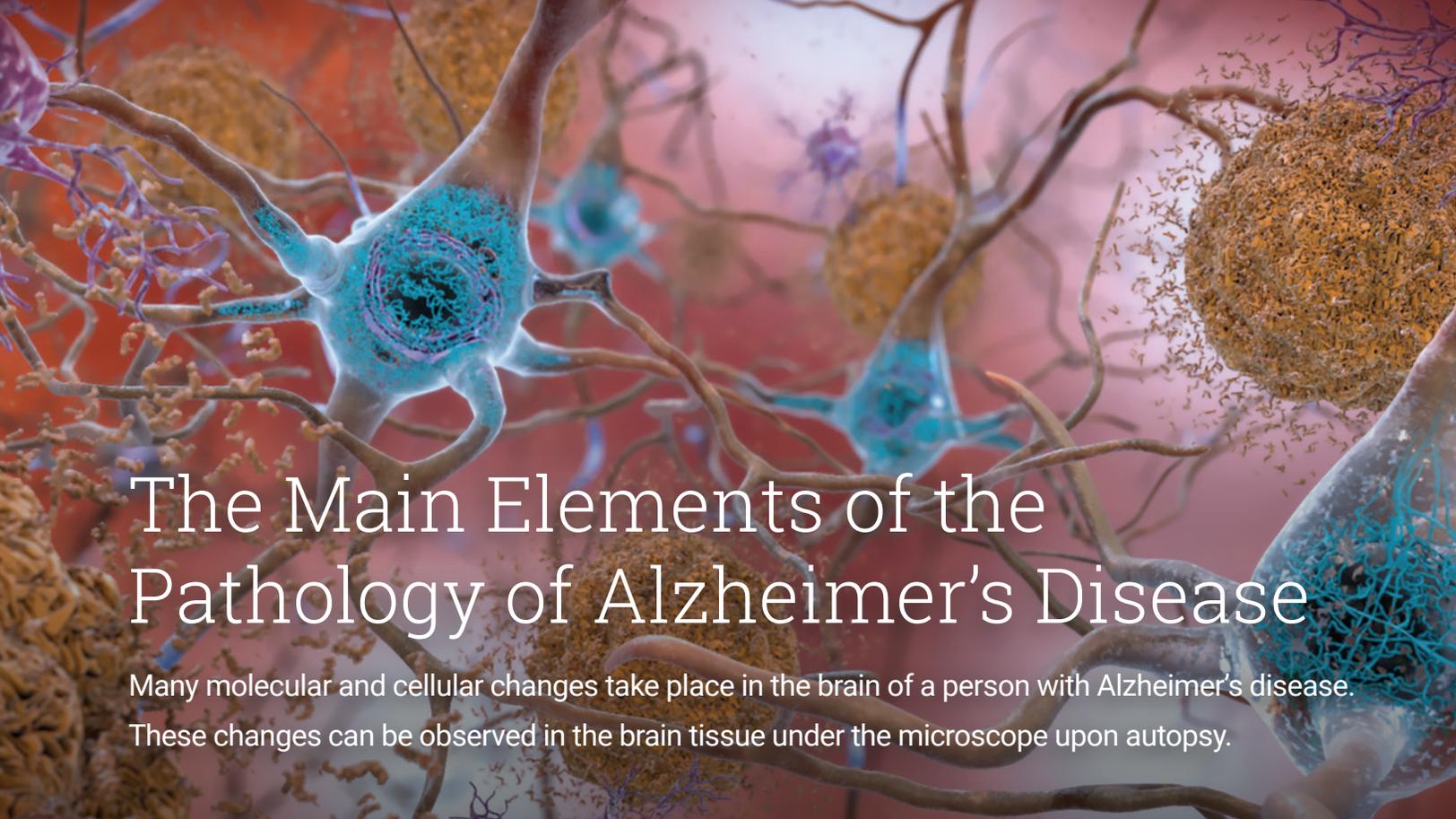
Rob challenged conventional wisdom that the buildup of amyloid in the brain was intrinsically pathological and aided the development of Alzheimer's. While amyloid is understood to have a destructive role in

the progression of Alzheimer's disease, Rob proposed that amyloid defended against toxicity by trapping harmful microbes.

After years of rejection, Rob's research was published in *Science Translational Medicine* in 2016. His work was recognized as one of the top five discoveries in neurology for 2016.

"Rob always thought outside of the box—he didn't even know there was a box!," said Tanzi. "He was a great, personal friend who never let anything stand in his way. He enjoyed life and always had a smile on his face."

Cure Alzheimer's Fund was privileged to begin working with Rob in 2006 and awarded 12 grants to fund his research over the course of the next 13 years. His work continues in the Moir Lab at Massachusetts General Hospital.



The Main Elements of the Pathology of Alzheimer's Disease

Many molecular and cellular changes take place in the brain of a person with Alzheimer's disease. These changes can be observed in the brain tissue under the microscope upon autopsy.

Amyloid Plaques

The amyloid plaques involved in Alzheimer's come in several different molecular forms that collect between neurons. Such plaques are formed from the breakdown of a larger protein, called amyloid precursor protein. In the Alzheimer's brain, abnormal levels of this naturally occurring protein clump together to form plaques that collect between neurons that disrupt cell function.

Neurofibrillary Tangles

Neurofibrillary tangles are abnormal accumulations of a protein called tau that collect inside neurons. Healthy neurons, in part, are supported internally by structures called microtubules. In Alzheimer's disease, however, abnormal chemical changes cause tau to detach from microtubules and stick to other tau molecules, forming threads that eventually join to form tangles inside neurons. These tangles block the neuron's transport system, which harms the synaptic communication between neurons.

Emerging evidence suggests that Alzheimer's-related brain changes may result from a complex interplay among abnormal tau and amyloid plaque proteins and several other factors. It appears that abnormal

tau accumulates in specific brain regions involved in memory. Amyloid clumps into plaques between neurons. As the level of amyloid plaques reaches a tipping point, there is a rapid spread of tau throughout the brain.

Chronic Inflammation

Research suggests that chronic inflammation may be caused by the buildup of glial cells normally meant to help keep the brain free of debris. One type of glial cell, microglia, engulfs and destroys waste and toxins in a healthy brain. In Alzheimer's, microglia fail to clear away waste, debris and protein collections, including amyloid plaques.

Loss of Neuronal Connections and Cell Death

In Alzheimer's disease, as neurons are injured and die throughout the brain, connections between networks of neurons may break down, and many brain regions begin to shrink. By the final stages of Alzheimer's, this process—called brain atrophy—is widespread, causing significant loss of brain volume.

Reprinted in part from information provided on the website of the National Institute of Aging/ National Institutes of Health. www.nia.nih.gov/health/what-alzheimers-disease

The Research

Our Science Structure

When considering the science structure for Cure Alzheimer's Fund, our 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. We now have two scientific entities acting on behalf of Cure Alzheimer's Fund.

First, our **Research Leadership Group** includes 34 of the world's leading scientists in the field of Alzheimer's disease. These leaders are the primary decision makers regarding our overall direction, as well as for specific proposals and projects.

Second, the **Research Strategy Council** is composed of extraordinary individuals with a wide range of relevant expertise. They are 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. They work closely with our Research Leadership Group and its Chair, Dr. Rudy Tanzi, and report to our Board of Directors regarding their recommendations.

Our Researchers

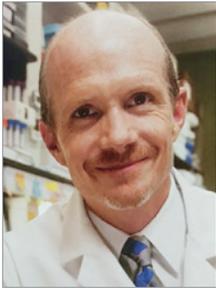
This gallery features researchers who received funding in 2019, as well as the members of our Research Leadership Group and Research Strategy Council.



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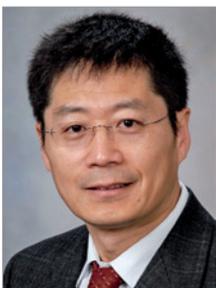
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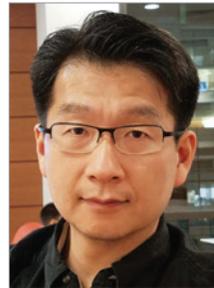
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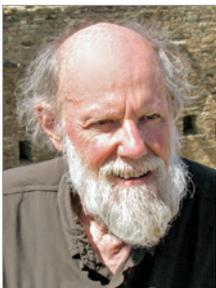
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Professor, Molecular Biology and Biochemistry
Research Leadership Group



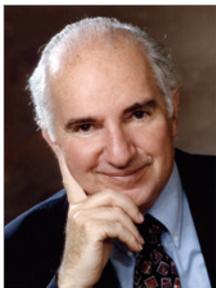
ANA GRICIUC, PH.D.
Massachusetts General Hospital
Assistant Professor of Neurology



CHRISTOPHER K. GLASS, M.D., PH.D.
University of California, San Diego
Distinguished Professor of Medicine and Cellular and Molecular Medicine; Ben and Wanda Hildyard Chair in Hereditary Diseases



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University of Michigan
Director, Michigan Drug Discovery
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ALFRED L. GOLDBERG, PH.D.
Harvard Medical School
Professor of Cell Biology



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 (DZNE); Speaker of the Collaborative Research Center 596
Research Leadership Group



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University of Rhode Island
Executive Director, George and Anne Ryan Institute for Neuroscience; Thomas M. Ryan Professor of Neuroscience; Professor of Biomedical and Pharmaceutical Sciences



BRIAN HEAD, PH.D.
University of California, San Diego
Professor, Anesthesiology



FANNY HERISSON, M.D., PH.D.
 Massachusetts General Hospital
Instructor in Neurology



RICHARD L. HUGANIR, PH.D.
 Johns Hopkins University
 School of Medicine
Bloomberg Distinguished Professor of Neuroscience and Psychological and Brain Sciences; Director, Department of Neuroscience; Co-Director, Brain Science Institute
Research Leadership Group



WINSTON HIDE, PH.D.
 Beth Israel Deaconess Medical Center
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 Washington University
 School of Medicine in St. Louis
Andrew B. and Gretchen P. Jones Professor and Chairman of Neurology; Professor of Developmental Biology; Associate Director, Knight Alzheimer's Disease Research Center; Scientific Director, Hope Center for Neurological Disorders
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JACOB M. HOOKER, PH.D.
 Massachusetts General Hospital
Phyllis and Jerome Lyle Rappaport MGH Research Scholar; Professor of Radiology, Harvard Medical School; Director of Radiochemistry, Martinos Center for Biomedical Imaging; Associate Neuroscientist; Associate Director, PET Core



TSUNEYA IKEZU, M.D., PH.D.
 Boston University School of Medicine
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TIMOTHY HUANG, PH.D.
 Sanford Burnham Prebys Medical
 Discovery Institute
Research Assistant Professor, Neuroscience Initiative, Neuroscience and Aging Research Center

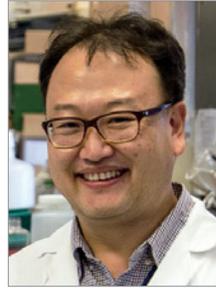


NANCY IP, PH.D.
 Hong Kong University of Science
 and Technology (HKUST)
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Research Leadership Group

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Cecil and Ida Green Distinguished Professor of Biological and Mechanical Engineering



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Research Leadership Group



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Harrison Distinguished Professor, Departments of Pharmacology and Chemistry; Associate Director for Basic Science, UVA Cancer Center

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Instructor in Neurology



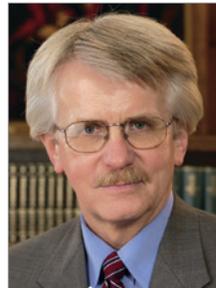
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Executive Director, Charles F. and Joanne Knight
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Former Scientific Director, National Institute
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Robert Allan Finke Professor of Neurology



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 AZTherapies
President and Chief Medical Officer
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 National Institute on Aging
 Division of Neuroscience
Retired Deputy Director
Research Strategy Council



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 at Mount Sinai
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Director, Unit for Neurovisual Disorders



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Associate Professor, Developmental Biology



TONY WYSS-CORAY, PH.D.

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D.H. Chen Endowed Professor; Professor, Neurology and Neurological Sciences



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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

2019 Funded Research

Cure Alzheimer's Fund spent **\$19.9 million to support 72 research projects** across our focus areas. Visit CureAlz.org/the-research to read about all of our current research projects.

| Project/Researcher | Distribution Amount |
|---|---------------------|
| Functional Genomics | |
| Gene Expression Throughout Development of Pathology in APPKI Mice; Effects of Human Tau and Aging Frances Edwards, Ph.D., and John Hardy, Ph.D., University College London | \$195,388 |
| Integrating Functional Maps to Discover MicroRNAs in Alzheimer's Disease Winston Hide, Ph.D., Beth Israel Deaconess Medical Center | \$172,500 |
| Identifying Novel Epigenetic Biomarkers of Human Cognitive Aging Lars Bertram, M.D., University of Lübeck | \$171,875 |
| Impact of Genetic, Epigenetic and Cellular Variants on Alzheimer's Disease Pathology Rudolf Jaenisch, M.D., Massachusetts Institute of Technology, and Joseph R. Ecker, Ph.D., The Salk Institute of Biological Studies | \$287,500 |
| Production Center for Reference and Variation Gene-Regulatory Maps Manolis Kellis, Ph.D., and Li-Huei Tsai, Ph.D., Massachusetts Institute of Technology | \$750,000 |
| Interpreting Alzheimer's Disease-Associated Genetic Variation at Enhancer Regions Andreas Pfenning, Ph.D., Carnegie Mellon University | \$199,013 |
| Genes to Therapies™/Stem Cell Drug Screening Translational studies investigating established and newly confirmed Alzheimer's disease genes | |
| TREM2: Role in Modulating Amyloid Beta and Tau-Related Pathologies and Neurodegeneration Marco Colonna, M.D., and David M. Holtzman, M.D., Washington University School of Medicine in St. Louis | \$345,000 |
| Inhibiting CD33 Function and Modulating Microglial Activation State for Alzheimer's Disease Therapy Ana Griciuc, Ph.D., Massachusetts General Hospital | \$172,500 |
| Therapeutic Modulation of TREM2 Activity Christian Haass, Ph.D., DZNE Munich | \$150,000 |
| High-Throughput Drug Screening for Alzheimer's Disease Using 3D Human Neural Culture Systems Doo Yeon Kim, Ph.D., Massachusetts General Hospital | \$287,500 |
| Single-Cell Analysis of 3D Human Triculture Model of Alzheimer's Disease: The Impact of AD-Associated Genetic Variants Joseph Park, Ph.D., and Rudolph Tanzi, Ph.D., Massachusetts General Hospital | \$172,500 |
| Alzheimer's Disease-Associated Mutations in Protein Kinase C Alexandra Newton, Ph.D., University of California, San Diego | \$287,500 |
| Interactions Among TREM2, APOE and Sex Christian Pike, Ph.D., and Caleb Finch, Ph.D., University of Southern California | \$172,565 |
| Genes to Therapies™ (G2T) Research Models and Materials Taconic Biosciences | \$2,937,502 |
| In Vitro and In Vivo Analysis of Amyloid Precursor Protein Variant Sangram S. Sisodia, Ph.D., University of Chicago | \$200,000 |
| Molecular and Cellular Mechanisms of ACE1 Variant in Alzheimer's Disease Robert Vassar, Ph.D., Northwestern University | \$250,000 |
| Genes to Therapies™ (G2T) Centralized Research Core Wilma Wasco, Ph.D., Massachusetts General Hospital | \$172,500 |
| Uncovering the Molecular Mechanism of Selected Drug Candidates Derived from Systematic Alzheimer's Drug Repositioning Stephen T.C. Wong, Ph.D., Houston Methodist Research Institute | \$287,500 |
| Alzheimer's Disease Pharmacomics in 3D Weiming Xia, Ph.D., Boston University School of Medicine | \$172,500 |
| Genetics | |
| Alzheimer's Genome Project™ Rudolph Tanzi, Ph.D., Massachusetts General Hospital | \$1,475,000 |
| Analytical and Statistical Tools for Sequence Analysis for Alzheimer's Disease Christoph Lange, Ph.D., Harvard T.H. Chan School of Public Health | \$171,523 |

Project/Researcher

Distribution Amount

| Project/Researcher | Distribution Amount |
|--|---------------------|
| Identification | |
| Early detection via biomarkers, imaging, etc. | |
| Understanding Molecular Biomarker Changes in Alzheimer's Disease Using Genetically Defined Mouse Models Mathias Jucker, Ph.D., and Stephan Kaeser, Ph.D., University of Tübingen | \$172,500 |
| Characterization of Alzheimer's Disease Molecular Biomarker Profiles Throughout the Pathobiological Continuum Krista L. Moulder, Ph.D., Washington University School of Medicine in St. Louis | \$103,016 |
| 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 in St. Louis | \$150,000 |
| An Innovative Study of the Pupil Light Reflex in Alzheimer's Disease Shirley H. Wray, M.D., Ph.D., Massachusetts General Hospital | \$108,726 |
| Imaging Microglial Homeostasis and Disruption: P2Y12R Radiotracer Development Jacob M. Hooker, Ph.D., and Michael S. Placzek, Ph.D., Massachusetts General Hospital | \$172,500 |
| Immune System Structures and Processes | |
| Role of inflammation and other responses in Alzheimer's disease | |
| The Role of MGnD-Neurodegenerative Clec7a+ Microglia in an Alzheimer's Disease Mouse Model Oleg Butovsky, Ph.D., Brigham and Women's Hospital | \$172,500 |
| Role of Microglial Matricellular Protein SPARC in Control of Inflammasome Activation Vishwa Deep Dixit, D.V.M., Ph.D., Yale School of Medicine | \$172,500 |
| VGF, a Novel Therapeutic Effector of Alzheimer's Disease Pathogenesis and Progression Michelle E. Ehrlich, M.D., and Stephen R. Salton, M.D., Ph.D., Icahn School of Medicine at Mount Sinai | \$150,000 |
| Targeting Reactive Astrocytes for Therapeutic Intervention in Alzheimer's Disease Gilbert Gallardo, Ph.D., Washington University School of Medicine in St. Louis | \$150,000 |
| Tau and Amyloid Beta are Innate Immune Antimicrobial Peptides in the Brain William Eimer, Ph.D., Deepak Vijaya Kumar, Ph.D., and Rudolph Tanzi, Ph.D., Massachusetts General Hospital | \$350,000 |
| Interpretation of Noncoding Risk Alleles for Alzheimer's Disease Christopher K. Glass, M.D., Ph.D., University of California, San Diego | \$250,000 |
| Assessing the Links Between the Ms4a Risk Genes, Microglia and Alzheimer's Disease Sandeep Robert Datta, M.D., Ph.D., Harvard Medical School | \$250,000 |
| Neuroimmune Molecular Imaging: A Novel Tracer for Imaging Microglia in Alzheimer's Disease Jacob M. Hooker, Ph.D., Massachusetts General Hospital | \$250,000 |
| Neurotoxic Reactive Astrocytes in Alzheimer's Disease Shane A. Liddelow, Ph.D., NYU Grossman School of Medicine | \$250,000 |
| Regulation of Microglial Lysosome Acidification Frederick R. Maxfield, Ph.D., Weill Cornell Medical College | \$150,000 |
| Microglial Heterogeneity and Transcriptional State Changes in Alzheimer's Disease Beth Stevens, Ph.D., Boston Children's Hospital | \$298,115 |
| Interleukin-3 in Alzheimer's Disease Filip Swirski, Ph.D., Massachusetts General Hospital | \$171,914 |
| Human-Specific Evolution of CD33: Evolutionary Relationship to Ancient Host-Pathogen Interactions and Current Implications for Alzheimer's Disease Ajit Varki, M.B.B.S., Pascal Gagneux, Ph.D., and Nissi Varki, M.B.B.S., University of California, San Diego | \$172,500 |
| Rejuvenation of Microglia in Brain Aging and Neurodegeneration Tony Wyss-Coray, Ph.D., Stanford University | \$172,500 |
| Mechanisms for Alzheimer's Disease-Associated SORLA Mutations in Microglia and Neurons in AD Pathogenesis Huaxi Xu, Ph.D., and Timothy Huang, Ph.D., Sanford Burnham Prebys Medical Discovery Institute | \$172,500 |

FUNDED RESEARCH (CONTINUED)

| Project/Researcher | Distribution Amount |
|--|---------------------|
| Microbiome | |
| Interaction of the microbiome with Alzheimer's disease | |
| Gut Microbiome-Mediated Shifts in Amyloid Beta Deposition in a Humanized Alzheimer's Disease Mouse Model Deepak Vijaya Kumar, Ph.D., Massachusetts General Hospital | \$250,000 |
| Targeting the Microbiome and Microglia in Alzheimer's Disease Howard L. Weiner, M.D., and Laura M. Cox, Ph.D., Brigham and Women's Hospital | \$172,500 |
| Other | |
| Novel approaches, targets or therapies aligned with the Cure Alzheimer's Fund mission | |
| Dietary Salt, Tau Phosphorylation and Cognitive Impairment Giuseppe Faraco, M.D., Ph.D., and Costantino Iadecola, M.D., Weill Cornell Medical College | \$172,500 |
| Alzheimer's Risk is Higher in Women: Identification of Female-Specific Brain Bioenergetic Targets Lisa Mosconi, Ph.D., Weill Cornell Medical College/New York-Presbyterian Hospital | \$173,486 |
| Physiological Method for Early Detection of Synaptic Vulnerability in Alzheimer's Disease Model Animals Riqiang Yan, Ph.D., and Srdjan D. Antic, M.D., University of Connecticut Health Center | \$172,500 |
| Modeling Alzheimer's Disease in Specific Subtypes of Human Neurons Through Direct Neuronal Reprogramming of Patient Fibroblasts Andrew Yoo, Ph.D., Washington University School of Medicine in St. Louis | \$172,500 |
| Pathological Pathways and Systems | |
| Human 3D Neurovascular Interaction and Meningeal Lymphatics Models with Application to Alzheimer's Disease Se Hoon Choi, Ph.D., Massachusetts General Hospital, and Roger Kamm, Ph.D., Massachusetts Institute of Technology | \$215,000 |
| Identifying the Blood-Brain Barrier Changes During Alzheimer's Disease Richard Daneman, Ph.D., University of California, San Diego | \$237,500 |
| Assessment of Antibody-Based Drug Trafficking Across the Blood-Brain Barrier Via Skull-Meninges Connections Ali Ertürk, Ph.D., Helmholtz Zentrum München | \$115,000 |
| The Role of Clusterin in Tau Pathology John D. Fryer, Ph.D., Mayo Clinic Arizona | \$172,500 |
| Patient-Based Structural and Functional Biology of Tauopathies Anthony Fitzpatrick, Ph.D., Columbia University, and Leonard Petrucelli, Ph.D., Mayo Clinic Jacksonville | \$255,875 |
| Understanding Human Brain Resilience to Alzheimer's Pathology Teresa Gomez-Isla, M.D., Massachusetts General Hospital | \$300,000 |
| Direct Migration of Myeloid Cells from the Skull Marrow to the Brain Through Anatomical Channels: Adding Fuel to the Fire in Alzheimer's Disease Fanny Herisson, M.D., Ph.D., Massachusetts General Hospital | \$172,443 |
| Evaluation of the Effect of Cell Type-Specific Deletion of ESCRT Genes on the Spread of Tau Pathology Tsuneya Ikezu, M.D., Ph.D., Boston University School of Medicine | \$172,500 |
| Crosstalk of Central Nervous System Barriers and Clearance Routes in Homeostasis and Alzheimer's Disease Jonathan Kipnis, Ph.D., Washington University School of Medicine in St. Louis | \$345,000 |
| Patch-Seq Analysis of the Choroid Plexus Epithelial Cell Barrier in Homeostasis and in Alzheimer's Disease Fernanda Marques, Ph.D., University of Minho | \$115,000 |
| The Circadian Clock Modulates Neurodegeneration in Alzheimer's Disease via REV-ERBa Erik S. Musiek, M.D., Ph.D., Washington University School of Medicine in St. Louis | \$172,497 |
| The Role of Impaired Synaptic Vesicle Machinery Proteostasis in Alzheimer's Disease Pathogenesis Jeffrey Savas, Ph.D., Northwestern University | \$115,000 |
| Central Clock Influence on Alzheimer's Disease Pathogenesis Geraldine Kress, Ph.D., Washington University School of Medicine in St. Louis | \$154,701 |

| Project/Researcher | Distribution Amount |
|---|---------------------|
| Molecular Signatures of APOE-Mediated Blood-Brain Barrier Dysfunction Causing Neuronal and Synaptic Dysfunction Berislav V. Zlokovic, M.D., Ph.D., University of Southern California | \$345,000 |
| Genetic Targets to Block Tau Propagation: Test Knockdown of HSPG Genes <i>In Vivo</i> Marc Diamond, M.D., University of Texas Southwestern Medical Center | \$172,500 |
| Cerebrovascular Dysfunction in Alzheimer's Disease: Targeting the Mechanisms of Vascular Activation Paula Grammas, Ph.D., University of Rhode Island | \$56,404 |
| Stimulating Proteasome Activity for the Treatment of Alzheimer's Disease Hermann Steller, Ph.D., The Rockefeller University | \$150,000 |
| Therapeutic Strategies and Drug Discovery | |
| PEGASUS Clinical Study of AMX0035 in Alzheimer's Disease Amylyx | \$750,000 |
| A Novel APOE Mimetic Therapeutic Peptide CN-105 Attenuates Alzheimer's Disease Pathology and Improves Functional Outcomes in a Murine Model of Alzheimer's Disease Daniel Laskowitz, M.D., M.H.S., Duke University School of Medicine | \$91,687 |
| Harnessing Big Data to Understand Alzheimer's Disease Risk Brad Racette, M.D., Susan Searles Nielsen, Ph.D., and Alejandra Camacho-Soto, M.D., M.P.H.S., Washington University School of Medicine in St. Louis | \$172,500 |
| Treating with Gamma-Secretase Modulators to Prevent Neurodegeneration in Mouse Models of Down Syndrome and Alzheimer's Disease William C. Mobley, M.D., Ph.D., and Steven L. Wagner, Ph.D., University of California, San Diego | \$150,000 |
| Activation of the 26S Proteasome for the Treatment of Alzheimer's Disease Alfred L. Goldberg, Ph.D., Harvard Medical School | \$172,500 |
| Discovery of Chemical Compounds That Induce Degradation of Amyloid Precursor Protein-Beta-C-Terminal Fragment in Cells Subhash Sinha, Ph.D., and Victor Bustos, Ph.D., The Rockefeller University | \$172,500 |
| 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, and Yueming Li, Ph.D., Memorial Sloan Kettering Cancer Center | \$300,000 |
| The Effect of Chronic Gamma-Secretase Modulation on the Prevention of Traumatic Brain Injury-Provoked and Alzheimer's Disease-Relevant Biochemical, Pathological and Behavioral Alterations Steven L. Wagner, Ph.D., and Brian Head, Ph.D., University of California, San Diego | \$230,000 |

Functional Genomics

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

FRANCES EDWARDS, PH.D., University College London

JOHN HARDY, PH.D., University College London

Recent advances in technology have allowed the development of improved animal models for Alzheimer's disease. This has required optimization of protein levels for the factors that influence progression of the disease, which has been done by replacing mouse proteins with humanized amyloid precursor protein that include disease-causing mutations and normal human tau. The amyloid precursor protein that contains mutations induces the early stages of Alzheimer's disease. By adding normal human tau into the mice, this research will investigate how human tau influences disease

progression. All effects will be evaluated in both male and female mice to help provide insights into why women are more prone to disease than men. The mice will be evaluated at early stages of disease progression to determine the influence of the plaques on the immune system and the activity of synapses. This project seeks to find molecular targets that could prevent the progression of Alzheimer's disease at the early stages, as plaques develop, but before the symptoms of dementia begin.

Integrating Functional Maps to Discover MicroRNAs in Alzheimer's Disease

WINSTON HIDE, PH.D., Beth Israel Deaconess Medical Center

Alzheimer's disease is the most common form of dementia. To date, no treatments successfully altering the progression of Alzheimer's disease have been discovered. Although some genes play a role, the underlying cause of AD is unknown. People with AD have amyloid beta plaques and neurofibrillary tangles in their brains. This study finds and organizes genes, and the pathways they contribute to, associated with the underlying pathologies of AD. MicroRNAs target and regulate genes and biological processes in AD, but have

not yet been systematically organized according to their relationships with AD-associated genes and pathways. This study uses associated genes and pathways to rigorously and systematically predict the miRNAs that may be regulating them. These miRNAs often are found in the blood of patients with AD. If we are confident of miRNAs' involvement, it will be possible to develop powerful miRNA biomarkers that may classify Alzheimer's disease.

Identifying Novel Epigenetic Biomarkers of Human Cognitive Aging

LARS BERTRAM, M.D., University of Lübeck

Cognitive decline and the development of such age-related conditions as Alzheimer's disease are determined by the concerted action of genetic, epigenetic and nongenetic factors. Over the last decade, genetics research in AD has progressed at unprecedented pace owing to the application of high-throughput genotyping technologies in the context of genome-wide association studies (GWAS). However, it is becoming increasingly evident that variants of the DNA sequence themselves do not fully explain AD's phenotypic picture, and that other mechanisms, such as those related to epigenetics, must make substantial contributions to disease development and progression. To this end, in the first phase of the CIRCUITS consortium, we had proposed to study the impact of epigenetics on two important domains. First, to decipher the correlation of DNA methylation (DNAm) patterns in brains and

buccal swabs from the same individuals examined neuropathologically at the Massachusetts Alzheimer's Disease Research Center, and second, to perform one of the largest epigenome-wide association studies (EWAS) to date on AD-relevant neuropsychiatric phenotypes in an extremely well and deeply characterized cohort of healthy at-risk individuals from Berlin, Germany. In this second phase of our CIRCUITS consortium contribution, we propose to extend this work in scope, both by increasing sample size and extending our analyses to other epigenetic domains and tissue compartments. Together, the combination of experimental data derived from this and the previous phase of our project will help to elucidate novel molecular mechanisms underlying cognitive decline and the onset of dementia, and improve our ability to develop and apply novel genetic and epigenetic biomarkers of cognitive aging.

Impact of Genetic, Epigenetic and Cellular Variants on Alzheimer's Disease Pathology

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

JOSEPH R. ECKER, PH.D., The Salk Institute of Biological Studies

Alzheimer's disease is the most common form of dementia, affecting approximately 50 million people worldwide. With prevalence expected to double every 20 years, AD is a global health crisis requiring urgent action. Unfortunately, despite years of basic and clinical research, no treatments to prevent, slow down or reverse the disease have been found, and the underlying causes of the most common form of the disease (sporadic AD) remain poorly understood. While aging is the major risk factor for developing AD, numerous genetic and

epigenetic variants have been found to be significantly associated with AD risk and disease status, but the biological impact of these variants remains unclear. In our proposed work, we will address this issue by profiling epigenetic (DNA methylation) changes in AD brains, validating the role of these changes in induced pluripotent stem cell-derived neuronal cells, and investigating the role of microglia—the immune cells of the brain—on AD initiation and progression.

Production Center for Reference and Variation Gene-Regulatory Maps

MANOLIS KELLIS, PH.D., Massachusetts Institute of Technology

LI-HUEI TSAI, PH.D., Massachusetts Institute of Technology

Alzheimer's disease is a devastating neurodegenerative disorder affecting 1 in 3 dying seniors and costing \$236 billion annually in the United States alone. Its prevalence is increasing rapidly in an aging population, and there currently is no cure. Recent genetic studies provide new hope for therapeutic avenues, but translating genetic results into therapeutics has been remarkably difficult, due primarily to the fact that most genetic mutations do not alter protein function directly, but instead affect the expression of nearby genes in subtle ways.

Here, we seek to overcome this limitation by directly profiling changes in the circuitry of neurons and other brain cell types during Alzheimer's disease, and how genetic variants are affecting that circuitry. In our initial efforts, we generated thousands of transcriptional and

epigenomic maps of gene expression and control region activity by profiling post-mortem brains and *in vitro* differentiated brain cells from induced pluripotent cells across individuals at the tissue level, cell-type level and single-cell level.

We integrate the resulting datasets to decipher the mechanistic basis of genetic variants associated with disease, and to discover new therapeutic targets, and the pathways and cell types where they act. The resulting datasets and predictions will be disseminated broadly to the scientific community, and form the foundation for computational and experimental work by the broader Cure Alzheimer's Fund CIRCUITS consortium, in order to translate our datasets and predictions into mechanistic insights and new therapeutic avenues for Alzheimer's disease.

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

ANDREAS PFENNING, PH.D., Carnegie Mellon University

Treating Alzheimer's disease is one of the greatest challenges we face in the coming years; the disease has the potential to have an enormous impact on human health. Despite its importance, there still are no highly effective treatments for AD, 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.

Genes to Therapies™/Stem Cell Drug Screening

Translational studies investigating established and newly confirmed Alzheimer's disease genes

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

MARCO COLONNA, M.D., Washington University School of Medicine in St. Louis

DAVID M. HOLTZMAN, M.D., Washington University School of Medicine in St. Louis

The TREM2 gene provides instructions for making a protein called triggering receptor expressed on myeloid cells 2; the gene first was identified to be involved in the immune system. The role of TREM2 in the body has expanded to involve facilitating the activation of microglia in response to amyloid plaque accumulation in Alzheimer's disease. TREM2 regulates microglia metabolism and production of the energy currency of the cell, ATP.

The brains of mice that have been genetically modified to have TREM2 knocked out exhibit something called neuritic dystrophy, suggesting that TREM2 plays a neuroprotective role when it comes to preventing amyloidosis. On the other hand, a deficiency in TREM2 in a mouse model for tau accumulation, the P301S mouse model, led to a decrease in microglial activation, but less brain atrophy. This result suggested that TREM2-dependent microglial activation in a tau model for Alzheimer's disease could be toxic to neurons. Given that loss of function mutations in TREM2 strongly increase the risk of developing Alzheimer's disease, we sought to investigate the effect of TREM2 on amyloid-dependent tau accumulation. This research project will

take advantage of a newly developed technology called the pathological tau seeding model. Our findings indicate that microglia activation around amyloid plaques may serve a protective role by impeding the development of tau-induced neuritic plaques by a mechanism that involves TREM2.

To further examine the impact of TREM2 in neuronal pathology, we have developed a novel technology in which we obtain whole gene expression data from single cells in the brain. This technology enables identification of every cell population in the brain, such as neurons, microglia, astrocytes and oligodendrocytes, based on common gene expression profiles. Moreover, we can identify the presence of altered cell populations. By using this technology, we have demonstrated that accumulation of amyloid beta plaques in mice lacking TREM2 results in the appearance of a new neuronal population indicative of damaged neurons. We now have treated the same mice with a drug, cyclocreatine, that increases the energetic metabolism of microglia. We anticipate this treatment will reduce the population of damaged neurons by restoring microglial functions.

Inhibiting CD33 Function and Modulating Microglial Activation State for Alzheimer's Disease Therapy

ANA GRICIUC, PH.D., Massachusetts General Hospital

The microglial regulator CD33 controls brain amyloid beta clearance in Alzheimer's disease. Through an unbiased high-throughput screen, we identified medications that increased amyloid beta uptake and maintained microglia in an anti-inflammatory activation state. CD33-specific antibodies that dramatically reduced CD33 levels also were identified. This project will investigate the mechanism of action of four FDA-approved medications that were highly effective at increasing amyloid beta uptake and reducing

inflammation in microglia. We also will screen a natural product library for modulation of amyloid beta uptake and inflammation in microglia. We will investigate the effects of two CD33-specific antibodies on CD33 activity, inflammation and CD33-mediated signaling. To identify CD33 inhibitors, we also will screen anti-sense RNA targeting CD33 in microglia. Effective anti-inflammatory medications and CD33 inhibitors have the potential to provide a novel therapeutic approach for this devastating disease.

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; understanding this process can help us to design new therapeutic approaches. TREM2 is a protein directly involved in the inflammation process that occurs in the brains of patients with Alzheimer's disease. Mutations in the TREM2 protein increase the risk of developing Alzheimer's disease up to threefold. A fragment of this protein, called soluble TREM2 (sTREM2), increases at the earliest stages of Alzheimer's disease. This sTREM2 increase occurs in parallel to an increase in biomarkers signaling cell death in neurons. Our research demonstrates that increased sTREM2 indicates a protective response. The goal of this research is to maintain this protective response in later

stages of Alzheimer's disease by enhancing TREM2 activity. To accomplish this, we will look for a way to prevent the cleavage of TREM2, which would result in an increase in TREM2 levels on the surface of brain cells. The downstream effect of this increase will be to increase the clearance of amyloid beta plaques and cellular debris. Our research has identified the exact spot where this protein is cleaved. Of interest, there is a disease-causing mutation exactly at this site that occurs in Alzheimer's disease patients. This mutation increases the cleavage of TREM2 and, as a consequence, reduces its function. Successful identification of the cleavage site will enable us to generate therapeutic antibodies to block the access of the enzyme that cleaves TREM2.

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

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

Alzheimer's disease has become a major public health problem—and there is no cure for the disease. Previously, we have developed a novel three-dimensional human neural cell culture model of AD (Alzheimer's in a Dish), which recapitulates key pathological events in AD in human brain-like environment. In this ongoing project, we have been using our 3D AD cellular model as a platform to screen novel AD drug candidates and identify druggable cellular pathways that can reduce AD pathogenesis. The current research will validate and

test the efficacy of lead AD drug candidates in more physiologically relevant 3D cellular models, including 3D cell models from female and male patient-derived AD neurons, and explore their impacts on human AD neurons. The project includes a new pilot drug library screening project from a natural compound library. Overarching goals are to provide novel mechanistic insights how to block the pathological cascade of AD in human neural cells and to find novel AD drug candidates that can be directly applicable in human clinical trials.

Single-Cell Analysis of 3D Human Triculture Model of Alzheimer's Disease: The Impact of AD-Associated Genetic Variants

JOSEPH PARK, PH.D., Massachusetts General Hospital

RUDOLPH TANZI, PH.D., Massachusetts General Hospital

A growing number of Alzheimer's disease genes are linked to innate immunity and neuroinflammatory pathways. AD mouse models have been used to test the effects of these microglial genes on AD pathogenesis. However, it has not been possible to precisely test the impact of AD-associated microglial genetic variant due to fundamental differences in gene structures between human and mouse. Recently, we developed a three-dimensional human neuron-astrocyte-microglia triculture AD model, which recapitulates neuroinflammation in a human AD brain-like environment (Park et al., *Nat. Neurosci.* 2018). We demonstrate that human microglial cells are recruited toward 3D AD (amyloid beta-producing) neuron-astrocyte cultures via microglia-specific migration channels, in a chemokine-dependent manner, leading to neuroinflammation

and neurodegeneration. In this project, we will explore the molecular mechanism underlining AD-associated neuroinflammation/neurodegeneration and the impact of AD-associated microglial genetic variants on AD pathology in the single cellular level by using single-cell RNAseq. In the previous period, we focused on developing a novel 3D-3D triculture model that does not require microfluidic devices. Compared with the published microfluidic semi 2D-3D triculture models, the 3D-3D model is advantageous for single-cell analysis and high-throughput drug screening. The new 3D-3D triculture models also provide a valid platform for studying human-induced pluripotent stem cell-derived microglial cells—male and female—with or without AD-associated genetic variants.

Alzheimer's Disease-Associated Mutations in Protein Kinase C

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. When this mutation is introduced into mice, they have behavioral deficits associated with Alzheimer's disease. This work identifies protein kinase C as a promising therapeutic target in Alzheimer's disease.

Interactions Among TREM2, APOE and Sex

CHRISTIAN PIKE, PH.D., University of Southern California

CALEB FINCH, PH.D., University of Southern California

Men and women differ in their vulnerability, clinical manifestations and neuropathological progression of Alzheimer's disease. Women typically exhibit worse outcomes. In this project, we investigate how sex modulates interactions between two significant genetic risk factors for Alzheimer's disease that regulate the immune system: APOE4 and TREM2. The immune system is increasingly recognized as an important player in Alzheimer's disease pathogenesis and is under investigation for its potential as a therapeutic target. The strategy for this project was to examine how female sex and the presence of APOE4 (versus the more common and comparatively benign APOE3 gene) affect disease pathology and immune activation in the brains of mice genetically engineered to develop Alzheimer's pathology. This project employs high-resolution microscopy to

study how the brain's primary immune-like cell, microglia, interact with amyloid plaques—an interaction known to be dependent on TREM2. This experiment enables the understanding of how sex and APOE genotype (APOE3 versus APOE4) independently and cooperatively affect TREM2 actions in the context of Alzheimer's disease. Protective TREM2-dependent interactions of microglia with plaques was strongest in both males and APOE3 mice. The poorest outcome was found in female APOE4 mice. This same pattern of sex and APOE genotype differences was observed in overall levels of Alzheimer's pathology—male APOE3 mice had the best outcomes. Further understanding of how sex and APOE genotype interact to regulate protective microglial actions holds significant promise for developing therapeutics for Alzheimer's disease.

Genes to Therapies™ (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.

In Vitro and In Vivo Analysis of Amyloid Precursor Protein Variant

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

Early-onset, familial forms of Alzheimer's disease are caused by the inheritance of mutations in genes that code for amyloid precursor protein (APP) or presenilins (PS1 and PS2). The main pathological hallmark of Alzheimer's disease is the presence of senile plaques composed of amyloid beta plaques that arise from the cleavage of amyloid precursor protein. Mutations in the amyloid precursor protein gene are located within or close to the sequence that codes for the amyloid beta peptide. Recently, Dr. Rudy Tanzi and colleagues have identified an additional mutation in the APP gene that

causes familial Alzheimer's disease. Of interest, this mutation is located far away from the other mutations typically seen next to the amyloid beta domain. We have examined the impact of this mutation on the production of amyloid beta plaques and have demonstrated, using two methods (cultured mammalian cells and mouse models of Alzheimer's disease that carry this mutation), that levels of amyloid beta are increased. This proposal seeks to clarify the mechanism by which this mutation in amyloid precursor protein enhances amyloid beta production.

Molecular and Cellular Mechanisms of ACE1 Variant in Alzheimer's Disease

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 Alzheimer's disease. How the ACE1 gene causes Alzheimer's disease is completely unknown. The overarching goal of this

project is to understand the role of the ACE1 gene in Alzheimer's disease using cell-based models and genetically engineered mice. The information gathered from this study is expected to provide greater insight into the causes of Alzheimer's disease, with the hope of identifying new therapeutic approaches.

Genes to Therapies™ (G2T) Centralized Research Core

WILMA WASCO, PH.D., Massachusetts General Hospital

The Cure Alzheimer's Fund Genes to Therapies™ program works in concert with the Alzheimer's Genome Project™ and in partnership with Taconic Biosciences to create new Alzheimer's disease mouse models. While the models are being validated, they are available to Cure Alzheimer's Fund grantees. Ultimately, all models will be made available to the scientific community in general.

Providing these mouse models and other appropriate reagents to investigators not only will obviate the time and effort necessary for each investigator to generate their 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.

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

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

This project recently established a more accurate and efficient model to identify fluorescent images generated by treating the Alzheimer's in a Dish model with compounds that can clear accumulated phosphorylated tau. Meanwhile, 29 new candidate compounds recently going through clinical trials for various diseases were generated by *in silico* prediction and validated using the ADiD model. Some 23 of these 29 validated predictions cleared p-tau by more than 95%. These validated

predictions include compounds originally designed for treating cancer, autoimmune diseases or metabolic diseases; we now are working to determine why these compounds can clear p-tau and how these candidates can lead us to novel therapeutic options for AD. Our mechanism study allows us to identify subgroups among known screening hits that may share similar ways of clearing p-tau.

Alzheimer's Disease Pharmacomics in 3D

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

Our goal of characterizing potential Alzheimer's therapeutics is based on our success in identifying compounds from the original screening of drugs previously approved by the U.S. Food and Drug Administration for the treatment of other diseases. We will study the changes in pathological proteins that

are affected by candidate Alzheimer's therapeutics in cultured cells, and establish new methods to measure these proteins in blood samples. The significance of this project is illustrated by our progress in exploring candidate proteins as biomarkers potentially acceptable for efficacy readout in future human clinical trials.

Genetics

Alzheimer's Genome Project™

RUDOLPH TANZI, PH.D., Massachusetts General Hospital

The overarching goal of the Alzheimer's Genome Project™ (AGP) is two-pronged; first, to analyze an extensive Alzheimer's disease genetics database consisting of approximately 1.5 petabytes of whole genome sequence (WGS) and whole exome (WES) data from family-based samples and other currently available AD samples to identify and functionally validate novel AD genes and AD-associated functional mutations and single nucleotide variants (SNVs) that are either common or rare; and second, to functionally validate and characterize their effects on multiple aspects of AD pathology in our 3D stem cell-derived neural glial culture models as well as AD mouse models, either in the Tanzi lab or other Cure Alzheimer's Fund (CureAlz)-funded labs participating in the Genes to Therapies™ program. Induced pluripotent stem cell (iPSC) progenitors of either neurons or glia are generated, using CRISPR-Cas9 gene editing, that carry the identified potentially detrimental and protective mutations and SNV in AD-associated genes, which allows the observation and analysis of any differences in amyloid beta production, oligomerization and deposition, tau and neurofibrillary tangle formation, neuroinflammation (microglial activation and astrogliosis), and blood-brain barrier integrity from control iPSC-derived neurons or glia. These experiments employ the original 3D neural culture model (Choi et al., 2014), 3D neural-glial triculture system (Park et al., 2018) and new combined 3D neural-glial/blood-brain barrier model (Shin et al., 2019) developed in past years of this grant and in the CureAlz 3D Drug Screening Consortium's efforts. We also test for effects on neural/synaptic activity using calcium imaging with GCaMP6 (courtesy of Dr. Clifford Wolfe, Harvard University). High priority will be given to gene variants identified through

prior sex-specific genome-wide association studies investigation.

We now will focus on a major new effort of the AGP, testing and functionally validating potentially detrimental or protective mutations/SNVs in the 30 known AD-associated GWAS genes. The extensive collection of AD WGS and WES datasets, together with the 3D human triculture AD model, will be used to evaluate the pathogenic effects of functional variants in AD-associated innate immune genes linked to neuroinflammation. Notably, the Alzheimer's in a Dish model and each of its more sophisticated iterations now are used in iPSC-derived neurons and glia from both male and female control and AD donors; this is always important, but particularly so given observed and as-yet unexplained sex-based differences in microglial behavior. The overarching goal is to comprehensively assess the pathogenic effects of functional variants in innate immune AD-risk genes on AD pathogenesis and explore underlying molecular networks in order to identify novel therapeutic targets. The Tanzi lab thus will test its hypothesis that microglia-related AD functional variants lead to reduced levels of microglial recruitment to AD pathology, that other AD functional variants reduce amyloid beta clearance and amyloid beta-reactive microgliosis that should cause microglial clustering around plaques and amyloid beta removal, and that microglial triggering of astrocyte transformation into "A1" states lead to chemical signaling that then leads to neuronal death. Pursuing these hypotheses will involve collaborations with other CureAlz-funded labs, particularly members of the 3DDS, CIRCUITS and Gifford Neuroinflammation Consortia.

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

CHRISTOPH LANGE, PH.D., Harvard T.H. Chan School of Public Health

We are seeking to develop new analysis tools for the Cure Alzheimer's Fund whole genome sequencing (WGS) data of the National Institute of Mental Health family sample, as recent developments in statistics have provided new theoretical insights that enable the construction of much more powerful analysis approaches. The re-analysis of our existing dataset with the new approaches will provide important additional insights into the genetic architecture of Alzheimer's disease. We will continue our work on the sex-specific

analysis of the WGS data, which already has identified new disease loci that differentiate the disease risk for Alzheimer's by sex. Our findings are currently under review by the journal Nature. We now will focus on decline phenotypes, analysis tools for such analyses and the influence of rare variants on the sex-specific genetic risk of Alzheimer's disease. Furthermore, as now numerous AD loci are known, we will develop a polygenic risk model for AD that will allow us to identify patients at high risk of developing AD.

2019 FUNDED RESEARCH

Identification

Early detection via biomarkers, imaging, etc.

Understanding Molecular Biomarker Changes in Alzheimer's Disease Using Genetically Defined Mouse Models

MATHIAS JUCKER, PH.D., University of Tübingen

STEPHAN KAESER, PH.D., University of Tübingen

The measurements of key proteins, also known as biomarkers, in cerebrospinal fluid and blood have become important diagnostic tools for Alzheimer's disease and other neurodegenerative disorders. However, the mechanisms behind these protein changes are poorly understood. The large heterogeneity of disease patterns among patients and possible co-morbidities are challenging obstacles to biomarker research in humans.

Transgenic mouse models recapitulate pathological disease hallmarks and can help bridge the gap between biomarker findings and mechanistic readout. Moreover, novel highly sensitive technologies allow the measurement of biomarkers in very small volumes. Thus, we aim at using mouse models to find and understand novel fluid biomarkers and validate them in human samples and clinical cohorts.

Characterization of Alzheimer's Disease Molecular Biomarker Profiles Throughout the Pathobiological Continuum

KRISTA L. MOULDER, PH.D., Washington University School of Medicine in St. Louis

Recent evidence suggests that molecular markers of Alzheimer's disease may differ by race, but existing studies have been limited by small sample sizes. The Alzheimer's Disease Research Centers at Washington University School of Medicine in St. Louis and Emory University have embarked on a collaboration to share spinal fluid and plasma samples from well-characterized African American and non-Hispanic white research participants between their two centers. Such sharing will allow for combined larger sample sizes, and hence the ability to ask more detailed scientific questions.

Washington University School of Medicine in St. Louis will focus on the ability of spinal fluid and plasma markers to predict the transition from normal memory and thinking to symptomatic disease. Emory University will focus on characterizing the pattern of protein expression in spinal fluid and plasma samples from individuals across a range of disease severity. These complementary approaches will help to provide insight into whether racial factors could impact treatment and prevention strategies for Alzheimer's disease.

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 in St. Louis

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 that 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. The outcomes will provide new insights 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 such other devastating neurodegenerative diseases as Parkinson's disease, frontal-temporal dementia and amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease).

An Innovative Study of the Pupil Light Reflex in Alzheimer's Disease

SHIRLEY H. WRAY, M.D., PH.D., Massachusetts General Hospital

In healthy people, the pupil constricts in response to light. This reflex, referred to as the pupil light reflex (PLR), is simple to study with a device called a pupillometer, which both illuminates the eye and measures the extent and speed of the resulting pupillary constriction. Pupillometry provides objective information regarding the integrity of the structures in the eye and brain that mediate the PLR (the retina, optic nerve, midbrain, oculomotor nerve and iris). In people who have

Alzheimer's disease, the same characteristic protein deposits that accumulate in the brain are found in the retina. This is associated with loss of one class of retinal neuron that mediates part of the PLR. Thus, the PLR may be abnormal in patients with AD. Definition of the specific pupillary abnormalities in AD may allow pupillometry to be used as a rapid, objective, inexpensive and noninvasive measure of AD, improving AD diagnosis, monitoring and research.

Imaging Microglial Homeostasis and Disruption: P2Y12R Radiotracer Development

JACOB M. HOOKER, PH.D., Massachusetts General Hospital
MICHAEL S. PLACZEK, PH.D., Massachusetts General Hospital

Inflammation is prominent in several neurodegenerative diseases, including Alzheimer's disease, and microglial cells are known to play a key role in the inflammatory process. Emerging evidence suggests that dysregulated microglia may influence the onset and progression of disease, but there remains a critical need to visualize these early-stage molecular changes in the living brain. The development of a P2Y12R-selective radiotracer for use in *in vivo* imaging will provide a novel cell-specific biomarker to visualize homeostatic and dysregulated microglial phenotypes in the living brain.

The cause of Alzheimer's disease remains unknown despite convincing evidence for the involvement of amyloid beta accumulation, tau tangles, chronic neuroinflammation and oxidative stress. There is a biological process that has a hand in regulating all of these processes. That cellular process is called purinergic signaling, which refers to cellular pathways that are activated by nucleotides such as ATP (the energy currency of the cell) and regulate cell signaling

pathways involved in inflammation, cell growth, repair and neuronal survival. Studies examining the brains of individuals with Alzheimer's disease have found there is a protein that is uniquely altered both during the onset of Alzheimer's disease and in the cells surrounding the amyloid plaques in the brains. This protein belongs to the purinergic signaling family and is called P2Y12R. For therapeutic interventions to start as early as possible, it is necessary to identify biomarkers that serve as an alarm bell that a shift in the brain is occurring from presymptomatic to a symptomatic Alzheimer's state. Cerebrospinal fluid collection is invasive and brain imaging currently monitors amyloid plaque and tau accumulation—and accumulation of these proteins often occurs after a patient already has developed memory impairments. Identifying a protein that signaled Alzheimer's disease before the accumulation of plaques and tangles would help to identify individuals with the greatest risk of developing Alzheimer's disease for the purposes of early therapeutic intervention.

Immune System Structures and Processes

Role of inflammation and other responses in Alzheimer's disease

The Role of MGnD-Neurodegenerative Clec7a+ Microglia in an Alzheimer's Disease Mouse Model

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

Microglia are the primary immune cells and surveillance sensors of the brain. These cells play a vital role in the maintenance of brain health by "pruning" areas of injury. When microglia lose their function, they can exacerbate conditions during the course of aging that lead to neurodegenerative diseases. There is a gap in our knowledge about how microglial function is maintained in the healthy brain, and how it is prone to dysregulation in Alzheimer's disease. Alzheimer's is the most prevalent form of senile dementia, accounting for up to 80% of all dementias. Although recent studies have distinguished and described characteristics of microglia in neurodegenerative diseases, the signatures

necessary to determine their exact functions and whether they are protective or destructive are not well understood. This project seeks to investigate the role of neurodegenerative microglia as a potential therapeutic target in Alzheimer's disease. The role of disease-associated microglia will be studied using an Alzheimer's disease mouse model created by Cure Alzheimer's Fund. This mouse model enables the specific targeting of microglia, with the goal of restoring proper function in the mouse brain. The aim of this project is to create a basis for new approaches for immune-based therapies for Alzheimer's disease.

Role of Microglial Matricellular Protein SPARC in Control of Inflammasome Activation

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

SPARC, secreted protein acidic and rich in cysteine, is a 32kDa calcium-binding matricellular protein. The matricellular proteins (thrombospondin-1, tenascin-C and SPARC) are extracellular matrix proteins that antagonize cell adhesions when presented to cells as soluble molecules. This proposal is based on our findings from CALERIE-II (Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy) a National Institute on Aging-sponsored randomized control trial in which healthy humans underwent 15%

caloric restriction for a period of two years. The RNA sequencing analysis of adipose tissue derived from humans post-caloric restriction identified SPARC as the most highly expressed and most significantly downregulated gene. The proposal tests the hypothesis that microglial-specific SPARC downregulation will protect against age-related central nervous system inflammation, inflammasome activation, and decline of memory and cognition.

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 recently have converged on VGF as a critical

regulator in the signaling networks that underlie AD pathogenesis and progression in human patients.

With funds generously provided by Cure Alzheimer's Fund, we have completed studies demonstrating that VGF overexpression or administration of the VGF-derived peptide TLQP-21 to a mouse model of AD reduce brain amyloid plaque load, microgliosis and astrogliosis in a region-specific manner. We have further demonstrated that TLQP-21 activates microglia via interaction with the complement C3a receptor (C3aR1). Continuing our analysis of how TLQP-21 modulates amyloidosis and whether it also modulates tauopathy will help to validate a novel AD target, and will test new approaches to reduce neuroinflammation in neurodegenerative disease.

Targeting Reactive Astrocytes for Therapeutic Intervention in Alzheimer's Disease

GILBERT GALLARDO, PH.D., Washington University School of Medicine in St. Louis

Reactive astrocytes and neuroinflammation are well-known features of Alzheimer's disease that are associated with disease manifestation, pathology and brain atrophy. Despite a compelling association with Alzheimer's disease, the impact of reactive astrocytes on disease progression or their therapeutic potential remains unknown. The goal of this project is to clarify the contribution of reactive astrocytes to the pathogenesis of Alzheimer's disease. Knowledge of the involvement of astrocytes may be the key to delaying

or preventing neuronal cell death. This research team previously discovered a complex composed of two players—the ion pump Alpha2-Na/K ATPase and the protein Alpha-Adducin—that promote a neurotoxic response and are present in reactive astrocytes. In the proposed study, we will investigate the role of the Alpha2-Na/K ATPase and Alpha-Adducin complex in Alzheimer's disease. The underlying goal will be to determine whether pharmacological inhibition of this complex is beneficial in Alzheimer's disease.

Tau and Amyloid Beta are Innate Immune Antimicrobial Peptides in the Brain

WILLIAM EIMER, PH.D., Massachusetts General Hospital
DEEPAK VIJAYA KUMAR, PH.D., Massachusetts General Hospital
RUDOLPH TANZI, PH.D., Massachusetts General Hospital

Alzheimer's disease therapeutic trials recently have been dominated with targeting the prevention or removal of the amyloid beta peptide. This has been predicated on the hypothesis that amyloid beta is a useless byproduct of metabolism that abnormally aggregates, driving AD pathology. Our recent research demonstrated that the amyloid beta peptide's previously perceived abnormal properties are indicative of antimicrobial peptides (AMPs). AMPs are a family of important peptides and proteins that serve as the first line of defense against bacteria, yeast, fungi and viruses. 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 suggest that an immune response to pathogens may be initiating or accelerating AD pathology. Our planned studies will characterize amyloid beta's role as an AMP by examining its function at physiological levels in both mouse and a three-dimensional human neural progenitor cell culture system. In addition, we will explore amyloid beta's destructive properties, selectively targeting neurons that already are infected. Finally, we will expand our antimicrobial hypothesis by demonstrating that tau, the second important peptide in AD, is also an AMP. Our preliminary data already suggests tau is a potent antibacterial. We think our proposed study will contribute significantly to the shifting of hypotheses surrounding AD etiology and pathology toward immune responses and inflammation. These findings will provide important information for current and future AD prevention and treatment therapies.

Interpretation of Noncoding Risk Alleles for Alzheimer's Disease

CHRISTOPHER K. GLASS, M.D., PH.D., University of California, San Diego

Genetic studies have identified dozens of changes in DNA that are associated with the risk of Alzheimer's disease. Most of these changes do not occur in the regions of DNA that code for proteins, making it difficult to understand their relationship to disease risk. In the proposed study, we will investigate the possibility that such "noncoding" changes in DNA affect the amounts of specific proteins that are made within neurons and other cell types in the brain. Remarkably, most of the noncoding changes in DNA associated with risk of Alzheimer's disease have been suggested to affect the amounts of proteins made by microglia, which are the

main immune cells of the brain. These observations suggest that alterations in the functions of microglia contribute to the development of the most common forms of Alzheimer's disease. This investigation will use powerful new experimental and computational approaches to directly examine whether DNA sequences associated with risk of Alzheimer's disease control the production of proteins that are made by neurons and microglia. Results from these studies will enable better understanding of how noncoding changes in DNA influence the risk of Alzheimer's disease, and may lead to the identification of new therapeutic targets.

Assessing the Links Between the Ms4a Risk Genes, Microglia and Alzheimer's Disease

SANDEEP ROBERT DATTA, M.D., PH.D., Harvard Medical School

Alzheimer's disease is caused by progressive changes in brain cells that culminate in memory loss, confusion, difficulty completing tasks, withdrawal, mood changes and, ultimately, death. The main cell type affected in the brain by Alzheimer's disease is called the neuron, which primarily is responsible for processing information and generating action. Alzheimer's disease damages neurons and the connections between neurons required to pass information along; as the ability of the brain to process information declines, so does the ability to care for one's self and to interact with loved ones. Although the ultimate target of Alzheimer's disease is the neuron, recent advances in genetics have suggested that a different type of cell might be the cause. These cells are called glia, which for many years were thought to be merely the "glue" that holds the brain together. It is now thought that glia may act to protect or harm neurons, and in doing so may influence the likelihood of getting Alzheimer's disease and the progression of

the disease. Here we focus on a set of genes, called the Ms4as, that seem to have a surprising degree of influence on an individual's risk of developing sporadic (late in life) Alzheimer's. Interestingly, these genes seem to act in a subset of glial cells called microglia, rather than in neurons, consistent with microglia playing an important role in disease initiation and/or progression. To assess the link between the Ms4as and Alzheimer's disease, we propose mouse experiments to explore how the Ms4a genes influence both the normal function of microglia and the function of microglia in the context of Alzheimer's disease. Further, we propose to build tools allowing us to better understand disease-associated human Ms4a genes. Results from these studies will teach us how a gene family that acts in microglia might influence the risk that a person will get Alzheimer's disease. Our experiments also may identify a new set of promising targets that could be the substrate for future drug development.

Neuroimmune Molecular Imaging: A Novel Tracer for Imaging Microglia in Alzheimer's Disease

JACOB M. HOOKER, PH.D., Massachusetts General Hospital

Alzheimer's genome-wide association studies (GWAS) that compare the genetic material from individuals with Alzheimer's with that of healthy individuals have implicated genes involved in regulating the immune system as a risk factor for neurodegeneration. Emerging evidence shows that dysregulation of the brain's immune system, and its microglial cells, plays an important role in the onset and progression of Alzheimer's disease. Studies have shown that activated microglia surround amyloid plaques, the classic pathology associated with Alzheimer's disease, and implicate inflammatory pathways in disease progression. Investigations of the role glial cells play in Alzheimer's disease have been hampered by an inability to image these cells

in the brains of living patients. Imaging microglia-specific molecules has a key role to play in defining neuroinflammation as it relates to glial function, and the consequence of glial activation in the living human brain. The goal of this project is to develop a Positron Emission Tomography (PET) radiotracer to quantify changes in microglia molecular activity in the living brain as a reflection of the pathophysiological changes associated with Alzheimer's disease. Our research has identified a new molecular target for PET imaging—the activation of microglia called SH2 Domain-containing Inositol Phosphatase 1 (SHIP1). Developing a SHIP1-specific PET radiotracer will pave the way for imaging microglial dynamics associated with Alzheimer's disease.

Neurotoxic Reactive Astrocytes in Alzheimer's Disease

SHANE A. LIDDELOW, PH.D., NYU Grossman School of Medicine

The brain is composed of neurons that transmit signals to enable thought, memory and motion. The brain also contains a type of cell that outnumbers neurons 2-to-1 called glial cells, which provide support to neurons. Recent genetic association studies have implicated many disease-associated genes in patients with Alzheimer's disease that almost exclusively are associated with glial cells. Astrocytes, a specific type of glial cell involved in nutrient delivery to neurons, are the most abundant cells in the brain. Astrocytes provide the environment necessary for neurons to correctly wire together and transmit signals. During diseases like Alzheimer's disease, astrocytes can become reactive—switching from a supportive state to a diseased state, in which neuron-killing toxins are

secreted. In both animal models of AD and in human patients, our research recently has localized the toxic reactive state of astrocytes to regions of dead and dying neurons. This research will employ a powerful technique called single-cell sequencing technology to increase the resolution at which changes in gene expression are observed at the cellular level. This technology will be used to determine how many populations of reactive astrocytes exist in the human brain, and how this cell plays a role in the initiation and progression of Alzheimer's disease by becoming neurotoxic. Results of this study will provide much-needed insights into basic astrocyte biology in the context of AD, as well as the identification of new targets for development of future therapies.

Regulation of Microglial Lysosome Acidification

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

Microglial cells are the scavenger cells of the brain 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—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 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*. 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 deep in a mouse brain. 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.

Microglial Heterogeneity and Transcriptional State Changes in Alzheimer's Disease

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

Alzheimer's disease is the health challenge of our generation. The majority of AD cases are late onset and result from the interaction of multiple genetic and nongenetic risk factors, of which the most important is aging. Genetic studies implicate the brain's resident immune cells, microglia, in the pathogenesis of late-onset AD, while other evidence ties immune mechanisms not only to AD, but also to other neurodegenerative disorders. In fact, more than half the risk genes associated with late-onset AD are selectively expressed in microglia, yet we know shockingly little about their biology or how they contribute to AD pathogenesis. Under normal conditions, microglia actively survey the brain; they are highly sensitive to changes caused by injury, infection or other abnormalities. In this role they can be beneficial by removing toxic proteins and cellular debris, but in disease they also can promote detrimental neuroinflammation leading to inappropriate synapse loss—one of the earliest changes in the AD brain, and the strongest correlate of cognitive decline.

Given the complexity and diversity of microglia in health and disease, there is a critical need for biomarkers that distinguish "beneficial" from "detrimental" microglial states over the course of AD. For the first time, it is possible to isolate individual cells from banked postmortem brains and analyze changes in gene expression and cell state at single cell resolution. Using these and other emerging technologies, we will help build the first comprehensive map of immune and neural cell state changes in AD and normal aging. We will examine the microglial response in the human AD brain at the single-cell level and ask how microglia transcriptional changes relate to other neural cells (neurons, astrocytes) in vulnerable brain regions. In parallel, we will profile the glial response in an established mouse model of AD and test whether inhibition of the classical complement cascade, a pathway that mediates synaptic loss and glial activation, ameliorates pathogenic inflammation and neuropathology. Results from these studies will further our knowledge of the neuroinflammatory response in AD and may lead to the identification of new biomarkers and therapeutic targets or pathways.

Interleukin-3 in Alzheimer's Disease

FILIP SWIRSKI, PH.D., Massachusetts General Hospital

Alzheimer's disease is a chronic neurodegenerative disease and a major cause of dementia. Early symptoms include short-term memory loss; as the disease advances, symptoms progressively worsen and include cognitive decline, disorientation, and ultimately loss of body function and death. The disease involves accumulation of plaques in the brain, which are characterized by the deposition of a protein called amyloid beta. Relatively recent research has shown the immune system—specifically microglia—is an important component of AD. These are immune cells interspersed throughout the brain throughout the lifetime among and between the neurons. Microglia participate in many normal functions, but also can be critical in

AD. Understanding microglia in AD is necessary and may uncover previously unknown pathways by which the immune system promotes or protects against AD. A powerful strategy to delve into microglial function involves identifying the key molecules that control microglial development, survival and behavior. Preliminary data suggest a specific molecule, a growth factor and cytokine called IL-3, activates microglial cells, instructing them to remove harmful amyloid beta plaques. In the absence of IL-3, however, microglia are unable to find such plaques, which worsens disease. IL-3, therefore, might be an important therapeutic target in AD, and this research seeks to elucidate IL-3's role in animal models of AD.

Human-Specific Evolution of CD33: Evolutionary Relationship to Ancient Host-Pathogen Interactions and Current Implications for Alzheimer's Disease

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We humans are very unusual in being capable of a prolonged post-reproductive life span, a life period associated with susceptibility to late-onset Alzheimer's disease. Human brains are rich in molecules called sialic acids, which are recognized by certain receptors (called "Siglecs") on brain immune cells (microglia). Such recognition by a Siglec called CD33 already is known to regulate immune reactions that are important in disease risk and progression, and we have shown that humans have newly evolved a protective form of this receptor.

The same receptor also is exploited by important human pathogens that affect younger humans and may have resulted in wide variations in human CD33 function. This, in turn, could have affected changes in neuroinflammation in late-onset AD. We are working on a detailed structural and functional exploration of the many human variations in CD33, which may reveal other protective forms—perhaps suggesting novel therapeutic approaches.

Rejuvenation of Microglia in Brain Aging and Neurodegeneration

TONY WYSS-CORAY, PH.D., Stanford University

Aging impacts nearly every tissue and function in an organism, and the associated deterioration is the primary risk factor for major human diseases, including cancer, cardiac disease and such neurodegenerative diseases as Alzheimer's. The underlying cause of aging is likely a multifaceted yet interconnected tangle of processes, and accumulating evidence suggests that in the brain, microglia—the resident immune cells—play

a major role. We discovered that these cells show profound changes with aging, and that soluble factors in the blood of young mice can rejuvenate these cells. We propose here to study how microglia age and determine the mechanism of rejuvenation. Our studies will help characterize the role of microglia in brain aging and may uncover new ways to rejuvenate these cells to slow brain aging and neurodegeneration.

Mechanisms for Alzheimer's Disease-Associated SORLA Mutations in Microglia and Neurons in AD Pathogenesis

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

Memory loss and mental decline associated with Alzheimer's disease arise from neuronal impairment. Many genes associated with Alzheimer's disease that were identified through genome-wide analysis represent genes that are mostly active in microglia, the innate immune cells in the brain. One Alzheimer's disease risk gene, SORLA, is expressed in both neurons and microglia. This gene previously has been shown to reduce levels of the toxic amyloid beta peptide in cultured cells and mouse models of Alzheimer's disease. SORLA can protect neurons from pathways that disrupt neuronal communication in the presence of amyloid beta. How SORLA influences neuronal protection in microglia remains unexplored. Various mutations

within the SORLA gene have been identified in human Alzheimer's patients. Studying these mutations has the potential to determine how altering SORLA function can disrupt neuronal communication. This research project will develop a model for mutant SORLA in neurons and microglia by integrating Alzheimer's disease-associated SORLA mutations in embryonic human stem cells that will be differentiated into neurons and microglia. By analyzing how SORLA mutations can alter global gene activity, cellular function, and the cell's response to amyloid beta in neurons and microglia, this research may be able to understand how alterations in SORLA can enhance Alzheimer's disease risk.

Microbiome

Interaction of the microbiome with Alzheimer's disease

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

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

Evidence is accumulating of an extensive bidirectional relationship between the gut microbiome and the brain. This interaction has important implications for brain health. The gut and microbiota modulate brain pathways that, in turn, influence gastrointestinal functioning, as well as the composition and functioning

of the enteric microbiome. This complex interaction is referred to as the microbiota-gut-brain axis. Our study aims to investigate whether deposition of amyloid beta plaques in the brain can be modulated by changing the microbiota-gut-brain axis.

Targeting the Microbiome and Microglia in Alzheimer's Disease

HOWARD L. WEINER, M.D., Brigham and Women's Hospital

LAURA M. COX, PH.D., Brigham and Women's Hospital

Alzheimer's disease affects 5.5 million Americans and leads to progressive memory loss. Currently, there are few treatments to help prevent or slow this disease. Recently, the gut microbiota—essential for maintaining health—has emerged as a potential therapeutic target for AD. As we age, the gut microbiota becomes less stable and can drive disease. We think slowing the aging process in the microbiome could be used to help prevent or treat AD. While it has been shown that the human gut microbiota contributes to other neurologic diseases, no study has proven contribution of the microbiota to AD. In this proposal, we will colonize mice with microbiota from AD patients to determine whether the AD microbiota results in worse disease. We will identify

key bacteria and metabolites associated with protection from healthy control patients that may be developed into new therapies for AD. The immune system plays an important role in AD, and specialized cells in the brain called microglia help clear up amyloid beta plaques in early disease but can lead to toxicity in late-stage disease. It recently has been shown that the microbiota can alter microglia immune function. In this proposal, we also will test whether the human AD microbiota alters microglia in an animal model of AD. Altering the microbiota and microglia function could serve as a novel therapeutic modality, in addition to providing unique characterization of an "AD phenotype" in the gut.

2019 FUNDED RESEARCH

Other

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

Dietary Salt, Tau Phosphorylation and Cognitive Impairment

GIUSEPPE FARACO, M.D., PH.D., Weill Cornell Medical College
COSTANTINO IADECOLA, M.D., Weill Cornell Medical College

Vascular factors contribute to Alzheimer's disease, the most common cause of dementia in the elderly. It is characterized by accumulation of amyloid beta in amyloid plaques and hyperphosphorylated tau in neurofibrillary tangles. Dietary salt has emerged as a risk factor for stroke, white matter disease and cognitive impairment, independent of hypertension. A high-salt diet (HSD) leads to a selective reduction in endothelial nitric oxide, a key mediator of vascular tone in the brain, and is associated with profound cognitive impairment in mice. However, how HSD-induced endothelial dysfunction affects cognitive function is

not clear. In particular, considering the potential link between a deficit in endothelial nitric oxide and tau phosphorylation, it is conceivable that HSD may promote cognitive impairment through tau phosphorylation. This research examines the hypothesis that a high-salt diet-caused endothelial dysfunction induces cognitive impairment by suppressing endothelial nitric oxide production. Elucidating how endothelial dysfunction induces cognitive impairment may provide a previously unrecognized mechanism linking vascular health to tau pathology and subsequent cognitive impairment.

Alzheimer's Risk is Higher in Women: Identification of Female-Specific Brain Bioenergetic Targets

LISA MOSCONI, PH.D., Weill Cornell Medical College/New York-Presbyterian Hospital

After advanced age, female sex is the major risk factor for Alzheimer's disease, the most common form of dementia affecting 5 million patients in the United States alone. For every three patients with AD, two are women. Brain imaging studies implicate the menopause transition in the increased AD risk in women by showing that perimenopausal and postmenopausal women exhibit altered brain bioenergetics as compared with age-matched men and premenopausal women. There is evidence that the ebb in estrogen heralding the onset

of menopause causes the loss of a key neuroprotective element in the female brain, with an aggressively higher vulnerability to brain aging and Alzheimer's disease. In this project, we will perform *in vivo* imaging of brain mitochondrial function to determine how bioenergetic systems might be compromised in postmenopausal women. This project seeks to unravel the biological mechanism that increases AD vulnerability in women by using novel brain imaging techniques that allow quantification of energy production in the brain.

Physiological Method for Early Detection of Synaptic Vulnerability in Alzheimer's Disease Model Animals

RIQIANG YAN, PH.D., University of Connecticut Health Center
SRDJAN D. ANTIC, M.D., University of Connecticut Health Center

Alzheimer's disease is the third most common disease affecting the U.S. population. AD is an age-dependent chronic neurodegenerative disease, characterized by the accumulation of protein plaques in the brain, and loss of memory and cognitive capacity. Prior to the detection of brain plaques and behavioral changes, synaptic dysfunction begins to emerge and appears to

lead to cognitive deterioration in AD patients in a vicious downward cycle. Hence, AD is recognized as a disease of synaptic failure. This project seeks to develop an optical imaging method for detecting early changes in synaptic function occurring in animal models of Alzheimer's disease.

Modeling Alzheimer's Disease in Specific Subtypes of Human Neurons Through Direct Neuronal Reprogramming of Patient Fibroblasts

ANDREW YOO, PH.D., Washington University School of Medicine in St. Louis

The risk of developing Alzheimer's disease increases with age, and identifying the cellular processes that occur during brain aging will provide fundamental insights into the pathogenesis of AD. The ability to derive and grow human neurons that mimic neurons of elderly individuals will offer experimental tools to investigate cellular properties in aged human neurons and their relation to the increased risk for Alzheimer's disease. We previously have demonstrated the feasibility of generating human neurons by expressing small RNA molecules termed microRNAs in an abnormal place—in this case, dermal fibroblasts. This change in the location alters the "fate" of cells as they are converted directly to neurons. The overall goal of the Cure Alzheimer's Fund grant was to examine age-associated cellular properties in human neurons generated by the microRNA-mediated direct conversion of adult

fibroblasts to neurons, and further develop cellular reprogramming approaches for producing the type of human neurons affected in AD. From this project, we learned that human neurons generated through direct neuronal conversion retained the age information stored in the starting fibroblasts, resulting in the generation of human neurons that reflect the age of fibroblast donors. This maintenance of age in converted neurons was found to be an integral component of recapitulating cellular phenotypes associated with adult-onset neurodegenerative disorders. Also, the Cure Alzheimer's Fund grant offered opportunities to refine the cellular reprogramming approaches to generate different types of human neurons affected in AD. Our current research goal is to use defined subtype-specific reprogramming approaches to model AD from the patient samples and investigate the pathogenesis of AD.

Pathological Pathways and Systems

Human 3D Neurovascular Interaction and Meningeal Lymphatics Models with Application to Alzheimer's Disease

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

Alzheimer's disease is the most common form of dementia among older people. The blood-brain barrier (BBB) is a highly selective permeable barrier that separates the brain from circulating blood. It is formed by brain endothelial cells and prevents harmful materials from the blood from entering the brain. The BBB also plays critical roles in removing toxic molecules, such as amyloid beta that causes AD, from the brain. The meningeal lymphatic vessels (meningeal lymphatics) are a network of conventional lymphatic vessels located parallel to the dural venous sinuses and middle meningeal arteries of the mammalian brain. Recently, it has been shown that the meningeal lymphatics have an important role in maintaining a healthy balance in the brain by draining it of toxic proteins, including amyloid

beta. Although disruptions of the blood-brain barrier and meningeal lymphatic vessels occurs in various neurological disorders including Alzheimer's disease, their contributions to the onset and progression of AD have not been elucidated fully. This is due, in part, to the lack of an effective model to capture the complex interactions between the various fluid compartments in the brain. Drawing upon our considerable experience in models for the BBB, and neurovascular units, and in combination with our collaborators in AD neurobiology, we propose to create new and more realistic models to capture the key interactions between the vascular, neural and meningeal compartments, and use these models to explore the process of disease and potentially identify new cures.

Identifying the Blood-Brain Barrier Changes During Alzheimer's Disease

RICHARD DANEMAN, PH.D., University of California, San Diego

Alzheimer's disease is a debilitating chronic neurodegenerative disease that is the leading cause of dementia and involves memory loss, disorientation, language issues, mood swings and many other behavioral abnormalities. Recently, it has been suggested that dysfunction of the blood-brain barrier may be an important component of the pathogenesis of Alzheimer's disease; however, very little is known about how the BBB may change in patients with AD. In this proposal, we aim to determine the molecular changes

to the BBB in patients with AD, by using mouse models to determine how these changes affect the function of the BBB and the progression of AD models. In particular, our lab has identified that there may be changes to the vascular circadian clock in patients with Alzheimer's that affect the removal of waste products, including amyloid. This project intends to determine how loss of the vascular clock affects BBB function, the buildup of amyloid, brain entry and exit routes, and the progression of AD models.

Assessment of Antibody-Based Drug Trafficking Across the Blood-Brain Barrier Via Skull-Meninges Connections

ALI ERTÜRK, PH.D., Helmholtz Zentrum München

The central nervous system is separated from the rest of the body by various barriers, including the blood-brain barrier, which maintains the highly controlled environment needed for proper CNS function. The BBB can be impaired in Alzheimer's disease. It is a challenge to deliver medical compounds across the blood-brain barrier. Therapies relying on antibody engagement with a target of interest are a novel class of drugs that is promising. These antibodies belong to the adaptive immune system and can be tailored to act on proteins involved in the progression of Alzheimer's disease.

Large molecules, like antibodies, largely are excluded from entering the brain under normal conditions. This research team specializes in tissue-clearing methods that render the entire body of a mouse transparent. This system allows visualization of the brain inside the intact skull without disrupting the fine structures that surround and separate the brain from the rest of the body. This project will investigate the distribution of antibodies in a mouse model of AD to find improved ways to deliver these promising new drugs across the blood-brain barrier to the brain.

The Role of Clusterin in Tau Pathology

JOHN D. FRYER, PH.D., Mayo Clinic Arizona

Alzheimer's disease is caused by the accumulation of toxic protein aggregates in the form of extracellular amyloid plaques and intracellular tangles composed of the tau protein. In the current genomic era, several genes have been discovered that are associated with Alzheimer's disease risk. However, for most of these risk genes, we do not know in any detail how they are playing a role in the development of Alzheimer's disease. One of the top genes to emerge from these genetic studies is the Clusterin (CLU) gene. Our lab recently has published that CLU plays a critical role in the formation of the extracellular amyloid plaques that form near neurons and also the blood vessels of the brain. We now

have new evidence that CLU also might play a role in the formation of the other major pathological hallmark of Alzheimer's disease, the neurofibrillary tau tangles. In this proposal, we will directly test whether CLU influences the ability of the tau protein to accumulate and cause toxicity and behavioral impairments using novel mouse models developed in our lab. We also will employ new cutting-edge technologies to determine how CLU influences tau pathology. The completion of these studies could firmly establish that CLU is an important therapeutic target for the development of both major Alzheimer's disease pathologies.

Patient-Based Structural and Functional Biology of Tauopathies

ANTHONY FITZPATRICK, PH.D., Columbia University
LEONARD PETRUCELLI, PH.D., Mayo Clinic Jacksonville

Using a technique called cryo-electron microscopy (cryo-EM), this research will focus on understanding the clumps of misfolded tau protein that are associated with a diversity of neurodegenerative diseases, most notably Alzheimer's and chronic traumatic encephalopathy. Cryo-EM is a revolutionary imaging technique that fires beams of electrons at protein molecules that have been

frozen in solution to deduce the protein's structure. By reconstructing the structure of tau tangles in disease, this research hopes to gain new insights into how tangles form and drive disease progression. These findings will enable researchers to design drug molecules aimed at preventing tangle buildup and identifying biomarkers that detect the disease before symptoms arise.

Understanding Human Brain Resilience to Alzheimer's Pathology

TERESA GOMEZ-ISLA, M.D., Massachusetts General Hospital

Not everyone with a significant burden of classic Alzheimer's disease neuropathological changes (e.g., plaques and tangles) experiences comparable cognitive decline or has the typical tissue responses of neuronal and synaptic derangement. Identifying predictive markers of such natural protection and understanding the underlying mechanisms involved may hold key clues to developing novel cognitive-sparing therapies for the elderly. This project will perform detailed quantitative pathologic and biochemical studies in a large series of human post-mortem tissue samples to define these mechanisms, through comparisons between individuals cognitively intact at the time of death, whose brains were free of substantial AD pathology at post-mortem; cognitively intact individuals whose post-mortem exam demonstrated significant amounts of AD changes ("resilient"); and typical demented AD patients. The vast majority of these cases were followed prospectively for years, with extensive clinical information available and a short interval between the last detailed cognitive assessment and death, making this large set of brains unique and particularly informative. Our previous work

has allowed us to rigorously demonstrate that plaques and tangles do not inevitably result in neuronal and synaptic derangement and impaired cognition in all cases (Perez-Nievas et al., 2013). We also have gained significant insight into the events that appear to be more proximate correlates to neuronal changes and cognitive impairment than just the presence of plaques and tangles, including activation of GSK-beta enzyme and soluble phosphotau accrual in synapses, and neuroinflammation. The identification of a histologic and biochemical "signature" characteristic of human brain resilience to AD pathology will be used to understand the hierarchy of events that result in cognitive impairment in the presence of plaques and tangles. The ultimate goal is to identify druggable pathways and molecular targets linked to brain resilience to AD pathology, and eventually to test novel meaningful interventions. We seek to provide valuable hints to identify novel targets and better disease-modifying treatments for AD. Given the evidence for neuroinflammation as a critical mediator in other neurodegenerative disorders, such therapies may have wide potential benefits.

Direct Migration of Myeloid Cells from the Skull Marrow to the Brain Through Anatomical Channels: Adding Fuel to the Fire in Alzheimer's Disease

FANNY HERISSON, M.D., PH.D., Massachusetts General Hospital

There are critical unmet needs for early diagnosis, prevention and cure in Alzheimer's disease. After decades of efforts focused on reducing abnormally aggregated amyloid and tau proteins that accumulate in the brains of patients with AD, recent research now is directed at understanding the inflammation surrounding these aggregates and leading to novel hypotheses. Inflammation not only relies on the defense cells that permanently reside in the brain, but also on the circulating white blood cells that are produced and stored in the bone marrow. Under specific circumstances, circulating white blood cells can enter the brain and promote inflammation. Several routes are available for these cells to enter the brain. We recently

discovered that one of these routes is a network of channels connecting the marrow located in the skull bone and the brain. This route provides a direct supply of white blood cells from the skull marrow to the brain. Even though this may promote inflammation in chronic cerebral diseases, it has not been explored yet in this context. Here we propose to use new technologies to investigate the relevance of the skull marrow-brain connections in AD. This includes not only methods optimized in our laboratory, but also techniques developed by other researchers gathered in this consortium. Through this work, we aim to identify novel modalities for Alzheimer's patients' care.

Evaluation of the Effect of Cell Type-Specific Deletion of ESCRT Genes on the Spread of Tau Pathology

TSUNEYA IKEZU, M.D., PH.D., Boston University School of Medicine

We propose to comprehensively examine the molecular machinery of biogenesis of extracellular vesicles such as exosomes and microvesicles among different brain cell types (neurons, microglia) in mouse models. Extracellular vesicles are membranous vesicles enclosed by a lipid bilayer and containing the cytosol of their cell of origin. There is a positive correlation between disease progression and neuron-derived exosomal amyloid beta peptide and tau protein in plasma from Alzheimer's disease and prodromal AD patients. However, little is known about how exactly exosomes package and spread pathogenic tau in which neuronal cell types in the central nervous system. Our preliminary study suggests that two components of the canonical exosomal pathway—the ESCRT (Endosomal Sorting Complexes Required for Transport) pathway—are critical for neuronal exosome synthesis. We hypothesize that cell type-specific targeting of the ESCRT pathway will suppress the spread of tau pathology in the brain. We will create a novel

mouse model to examine whether neuron and microglia-specific targeting of ESCRT-0 (Hgs) and ESCRT-1 (Tsg101) will halt tau propagation *in vivo*.

The project's first efforts will test whether microglia and neuron-specific silencing of the ESCRT-0 or ESCRT-1 gene suppresses the spread of tau pathology in the mouse brain. Hgs and Tsg101 will be targeted specifically by Cre-mediated gene disruption *in vivo*.

The second efforts will evaluate the effect of cell type-specific suppression of ESCRT-0 and ESCRT-1 on exosome synthesis using human-induced pluripotent stem cell-derived neurons and microglia on the spread of tau *in vitro*.

The newly gained mechanistic and functional knowledge of exosomal pathways that may contribute to AD pathogenesis can help on the road to a cure.

Crosstalk of Central Nervous System Barriers and Clearance Routes in Homeostasis and Alzheimer's Disease

JONATHAN KIPNIS, PH.D., Washington University School of Medicine in St. Louis

The brain is a remarkably fragile organ with limited self-renewal capacity after insults. Consequently, it has developed a complex system of barriers to limit the access of unwanted matter, thus protecting itself from detrimental peripheral factors. As the brain is a highly metabolic organ, it also has developed a series of nonconventional clearance routes to drain tissue waste products. Correct functioning of these brain barriers and clearance routes is critical to appropriate entrance and exit of desired matter during homeostasis. However, dysfunction in these pathways has been observed in numerous neurological conditions, including Alzheimer's disease. Despite these initial observations, the consequences of individual barrier/clearance route dysfunction on one another is unclear, but will be critical for a holistic understanding of these

devastating conditions. We propose that these barriers and clearance routes form an interconnected system, and that dysfunction of one will precipitate deterioration in additional routes, ultimately worsening disease progression. Thus, restoration of a single disrupted pathway may be sufficient to rescue detrimental aspects of numerous routes, offering an attractive therapeutic intervention to prevent widespread impairments. We propose to explore a largely understudied barrier between the brain and surrounding membranes termed the meninges, which may offer a novel therapeutic delivery route to the brain. Additionally, we will examine the functional consequences of brain barrier impairments on clearance pathways, and vice versa, in the healthy and AD brain.

Patch-Seq Analysis of the Choroid Plexus Epithelial Cell Barrier in Homeostasis and in Alzheimer's Disease

FERNANDA MARQUES, PH.D., University of Minho

Blood-brain barriers act as strict control points for what can and cannot enter the brain. Three main barriers exist to protect the brain from the free exchange of substances that are traveling in the bloodstream, making the brain unique compared with other organs of the body. Three main barriers protect the brain: the blood-brain barrier, the blood-cerebrospinal fluid barrier, and the blood-meningeal barrier. The cerebrospinal fluid is the clear, colorless fluid that surrounds the brain and spinal cord. The main function is to supply nutrients to the central nervous system, to protect against trauma and remove waste products. All of these barriers allow the brain to exist in a stable equilibrium. This project intends to study the blood-CSF barrier, which is located in the brain's ventricles—a network of cavities filled with

cerebrospinal fluid. Key cells involved in this system include the choroid plexus epithelial cells, which are cells that produce CSF. Importantly, the blood-CSF barrier is a clearance route that rids the brain of unwanted waste products. Dysfunction in brain barriers has been observed during aging and in neurological conditions such as Alzheimer's disease. The aim of this proposal is to gain a better understanding of how CSF production impacts the barrier and clearance systems of the brain by studying the blood-CSF barrier at the single-cell level. This study will help understand how choroid plexus cells change during aging and Alzheimer's disease, and how these changes impact the delivery of producing and delivering CSF to the brain.

The Circadian Clock Modulates Neurodegeneration in Alzheimer's Disease via REV-ERBa

ERIK S. MUSIEK, M.D., PH.D., Washington University School of Medicine in St. Louis

The circadian clock controls 24-hour rhythms in the body and serves as an important regulator of brain function. Recent evidence suggests that disturbances in circadian function, which are common in our modern society, can promote Alzheimer's disease. People with AD often exhibit symptoms of circadian dysfunction, such as disrupted sleep at night and excessive daytime napping—and subtle circadian changes can be detected in people with AD-related changes in the brain years before the onset of memory symptoms. Circadian rhythms are generated by the function of specific circadian clock genes, which are expressed in most

cells of the body. Disrupting these clock genes can cause inflammation or damage in the brain of mice. A specific clock gene, REV-ERBa, seems to regulate brain inflammation. This research will investigate the functions of REV-ERBa in the brain, and determine molecular mechanisms by which it may influence neurodegeneration. Novel drugs that activate REV-ERBa will be used to see whether this might have protective effects in a mouse model of AD. The research goal is to understand exactly how circadian dysfunction promotes AD, and to use novel therapies to directly activate certain clock genes to prevent neurodegeneration.

The Role of Impaired Synaptic Vesicle Machinery Proteostasis in Alzheimer's Disease Pathogenesis

JEFFREY SAVAS, PH.D., Northwestern University

Despite the tremendous biomedical research efforts of the past century, Alzheimer's disease remains an incurable form of dementia that affects more than 44 million people worldwide. While it is known that the most prevalent early symptom of AD is memory impairment, a precise understanding of the molecules and mechanisms that underlie memory loss remain unknown. This project investigates the possibility that

synapse malfunction and memory failure in AD may be caused, in part, by impaired degradation of the synaptic vesicle (SV) machinery. Lack of properly functioning SV machinery over months and years leads to an eventual halt in synaptic communication, contributing to progressive cognitive decline. This research proposes to provide a new understanding of synaptic dysfunction in AD and identify potential therapeutic targets.

Central Clock Influence on Alzheimer's Disease Pathogenesis

GERALDINE KRESS, PH.D., Washington University School of Medicine in St. Louis

The circadian timing system regulates daily oscillations in behavior and physiologic functions. There is a growing realization that long-term circadian timing system dysfunction has serious health consequences and may directly influence various disease pathologies. This project will test the

hypothesis that poor circadian rhythms mediated by a dysfunctional hypothalamic central circadian clock directly influence Alzheimer's disease pathogenesis. The long-term goal of this research is to identify possible therapeutic strategies to ameliorate the progression of Alzheimer's disease.

Molecular Signatures of APOE-Mediated Blood-Brain Barrier Dysfunction Causing Neuronal and Synaptic Dysfunction

BERISLAV V. ZLOKOVIC, M.D., PH.D., University of Southern California

Vascular contributions to dementia and Alzheimer's disease increasingly are being recognized. Recent studies have shown that blood-brain barrier (BBB) breakdown is an early independent biomarker of human cognitive dysfunction, including the early clinical stages of AD. Apolipoprotein E4 (APOE4), the major AD susceptibility gene, exerts strong cerebrovascular toxic effects, including accelerated BBB breakdown and degeneration of BBB-associated cells such as pericytes that maintain BBB integrity. Our recent neuroimaging and biomarker data show that APOE4 leads to early BBB dysfunction predicting human cognitive decline, and to neuronal and synaptic dysfunction in humanized APOE4 transgenic mice, and does so independently of the classical Alzheimer's amyloid beta and tau pathways. However, how APOE's effects on BBB and BBB-associated cells contribute to vascular and brain dysfunction remains largely unknown. We also do not have an effective APOE-based therapy for AD targeting the cerebrovascular system. To begin addressing these questions, we propose to use stem cell technology to generate new human BBB models with neurons (BBB on a chip) from APOE4 and APOE3 living donors clinically characterized by cognitive, neuroimaging and biomarker studies. We also will use new APOE4 and APOE3 mouse

models generated by Cure Alzheimer's Fund that allow cell-specific deletion of APOE from BBB-associated cells. We will use molecular (single cell, nuclear RNAseq, proteomics) analyses of different vascular and neuronal cell types to understand at the cellular and molecular level how APOE4 effects lead to BBB dysfunction, causing brain dysfunction. We will use bioinformatics tools to establish molecular signatures of each studied cell type; compare BBB with neuronal transcriptomes and BBB with synaptic protein interaction networks; relate molecular to functional findings; and predict candidate master regulators for targeting. We expect to identify and validate key new genes, proteins and pathways at the BBB (and the BBB-associated cell types) to slow down vascular and brain disorders caused by APOE4. Future studies will examine how the APOE4 BBB pathway(s) interact with Alzheimer's amyloid beta and tau pathways to influence AD pathogenesis, and potentially will develop new therapeutic approaches for dementia and AD based on DNA designer strategies, gene and cell therapy, and/or pharmacologic approaches targeting key pathogenic and protective genes, proteins and pathways at the BBB and the cerebrovascular system to control brain functions.

Genetic Targets to Block Tau Propagation: Test Knockdown of HSPG Genes *In Vivo*

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

Neuritic plaques surround amyloid deposits and are made up of swollen, dystrophic neural processes that contain aggregated phosphorylated tau. Neurofibrillary tangles are made up of phosphorylated tau that has abnormally been aggregated in Alzheimer's disease. Tau normally is a microtubule adaptor protein involved in the highways of neurons that allow for trafficking. Significant preliminary data (published and unpublished), as well as reports from other groups, indicate that tau aggregate

binding to heparan sulfate proteoglycans (HSPGs) on the cell surface mediates cell uptake and intracellular seeding by pathogenic aggregates. However, the precise mechanisms that could mediate progression or propagation of tau pathology in the brain have not been explicitly tested. Nor do we know the cellular mechanisms that facilitate tau uptake into the cell after initial binding to the cell surface. This proposal seeks to answer these questions.

Cerebrovascular Dysfunction in Alzheimer's Disease: 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. 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—caused by the accumulation of toxic proteins that impair cell function and lead to neuronal death—poses a major unmet health need, since neither cures nor treatments that address the root cause of the disease exist. All cells have the capacity to clear out and degrade unwanted and potentially dangerous protein buildup. Unfortunately, this “trash removal” process becomes less efficient with age. The lab recently discovered a novel mechanism that stimulates the activity of “proteasomes,” the nano-machines responsible for the removal of unwanted

proteins. We have found this mechanism is essential for the maintenance of neuronal health and brain function. Mutations in this pathway are found in human patients suffering from age-related neurological diseases. Stimulating the activity of this protein clearance pathway can prevent neuronal degeneration and extend life span in animal models. We identified an inhibitor of this pathway that represents a promising drug target for the treatment of Alzheimer's disease. This research has the potential to radically transform the field and yield a novel class of drugs that promote clearance of toxic proteins.

Therapeutic Strategies and Drug Discovery

PEGASUS Clinical Study of AMX0035 in Alzheimer's Disease

AMYLYX

The Amylyx PEGASUS Alzheimer's disease Phase 2 clinical trial will enroll 100 patients in sites across the country in a double-blind protocol to test a combination therapy. AMX0035 is composed of two known compounds that together address endoplasmic

reticulum and mitochondrial stress, both of which have been implicated in neuronal death and degradation. The trial is enrolling patients who already are experiencing mild cognitive impairment or early dementia. Readout is anticipated in 2020.

A Novel APOE Mimetic Therapeutic Peptide CN-105 Attenuates Alzheimer's Disease Pathology and Improves Functional Outcomes in a Murine Model of Alzheimer's Disease

DANIEL LASKOWITZ, M.D., M.H.S., Duke University School of Medicine

Inflammation plays an important role in the progression of Alzheimer's disease. Several genetic factors modulate inflammation and have the potential to provide insight into novel treatment strategies. Modifying brain inflammatory responses is one important mechanism by which apolipoprotein E protein isoforms may modify susceptibility and progression of AD. The APOE gene provides instructions for making apolipoprotein E, which combines with fats or lipids in the body to form molecules called lipoproteins responsible for packaging cholesterol and other fats and carrying them through the bloodstream. There are different versions or alleles of the APOE gene, and the APOE4 allele is associated with increased risk of Alzheimer's disease. In this project, there has been the development of a therapeutic peptide, CN-105, that mimics the adaptive, anti-inflammatory and

neuroprotective function of the protein. This therapeutic peptide was chosen from a library of APOE mimetic compounds based on its safety, efficacy in preclinical models, penetration of the central nervous system and ability to hit the target. Chronically administering CN-105 in a mouse model of AD that included the APOE4 allele improved brain pathology and learning and memory performance. The researchers observed a strong sex effect—female animals had significantly more advanced pathology. The next phase of this project will focus on sex differences in order to understand the factors that might inform early clinical trials. CN-105 has received investigational new drug approval, and it has completed Phase 1 clinical studies in which it demonstrated linear pharmacokinetics and safety. This therapeutic intervention has the potential for clinical translation in AD.

Harnessing Big Data to Understand Alzheimer's Disease Risk

BRAD RACETTE, M.D., Washington University School of Medicine in St. Louis

SUSAN SEARLES NIELSEN, PH.D., Washington University School of Medicine in St. Louis

ALEJANDRA CAMACHO-SOTO, M.D., M.P.H.S., Washington University School of Medicine in St. Louis

We propose to take a unique, big data approach to understanding risks factors for Alzheimer's disease using medical claims obtained from Medicare. Medicare provides insurance coverage for more than 95% of adults ages 65 and older in the United States, corresponding to the age at which AD is most common. These Medicare data contain nearly 100,000 diagnoses codes, procedures and medications that can be investigated to determine which are associated with either a lower or a higher risk of AD. In our preliminary studies, we found that those with a prior history of meningitis had a higher risk of developing AD. In addition, we identified 41 medications, most notably medications used to

treat gout, which were associated with a lower risk of developing AD. In the current application, we will build on our preliminary studies by creating the largest Medicare study of AD risk ever performed. In this study, we will evaluate the relationship between meningitis and the risk of AD in order to provide evidence from clinical data to confirm results from nonhuman AD model systems. We will use the entire Medicare medication formulary to identify medications associated with a lower risk of developing AD. If successful, we will provide unique insight into causes of AD and identify novel, potential disease-modifying therapies for AD from drugs that easily could be repurposed to treat those with AD.

Treating with Gamma-Secretase Modulators to Prevent Neurodegeneration in Mouse Models of Down Syndrome and Alzheimer's Disease

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

STEVEN L. WAGNER, PH.D., University of California, San Diego

There is much data that continue to point to accumulation of amyloid beta as a contributor to the pathogenesis of Alzheimer's disease—particularly in early-onset versions of the disease. In Down syndrome, for example, a triplication of the number of inherited copies of chromosome 21 increases the gene dosage of the amyloid precursor protein that is localized to that chromosome. As a result, patients with Down syndrome develop the neuropathology associated with Alzheimer's disease, plaques and tangles, at an accelerated rate. This research product aims to mitigate neurodegeneration in Down syndrome patients with Alzheimer's disease (AD-DS) as well as in other

types of Alzheimer's disease using small molecules called gamma-secretase modulators (GSMs). The researchers have found that GSMs can reduce the levels of the toxic products of APP. This project will validate the effects of a GSM, UCSD776890, in a mouse model of AD-DS to determine whether AD-related neurodegeneration and pathology can be ameliorated. UCSD776890 has excellent pharmacological characteristics and is poised to be effective in clinical trials. This research will provide insights into the efficacy of this GSM in order to support its filing as an investigational new drug, as well as the design of future clinical trials for AD-DS.

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

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

Alzheimer's disease and several other neurodegenerative diseases are associated with the accumulation in neurons of misfolded aggregation-prone proteins (e.g., tau and amyloid beta). Presently, no treatment is available to slow the steady accumulation of such toxic proteins. Such misfolded proteins in cells typically are selectively destroyed by the proteasome (the primary site of protein breakdown in our cells). There is growing evidence that this enzymatic system becomes defective in these diseases, apparently because protein aggregates can disrupt proteasome functioning. This research seeks to identify novel pharmacological agents that activate the 26S proteasome and stimulate the degradation of such misfolded, toxic proteins.

Our lab has identified three cellular signaling systems that can be activated by drugs and that can stimulate the cell's capacity to destroy misfolded proteins. We had found previously that agents that raise the level of the signaling molecule cyclic adenosine monophosphate (cAMP) cause a chemical modification of the

proteasome that enhances its activity. Moreover, such agents could restore proteasome activity and stimulate the clearance of tau in brains of a mouse model of Alzheimer's disease. We recently demonstrated that another important cellular signaling molecule, cyclic GMP, also can stimulate protein breakdown by modifying the proteasome in distinct ways from cAMP. We have focused on the promising effects of cGMP because drugs that raise cGMP are widely used in medicine. Furthermore, in zebrafish models of Alzheimer's and Huntington's diseases and in a mouse model of a human peripheral neuropathy (Charcot-Marie-Tooth Disease 1b), drugs that raise cGMP stimulated proteasome activity, decreased the levels of the disease-causing mutant proteins, and reduced neuronal death and the associated pathology. We now hope to further clarify the mechanisms for these promising drug actions and to test whether other agents that raise cGMP or activate protein kinase C also enhance the clearance of pathogenic proteins and therefore may be useful therapies for these diseases.

Discovery of Chemical Compounds That Induce Degradation of Amyloid Precursor Protein-Beta-C-Terminal Fragment in Cells

SUBHASH SINHA, PH.D., The Rockefeller University
VICTOR BUSTOS, PH.D., The Rockefeller University

Alzheimer's disease is a neurodegenerative disorder that affects more than 5 million people in the United States. One of the hallmarks of Alzheimer's disease is the accumulation of amyloid plaques in the brain of patients. Recent findings from our lab indicate that C99, the direct precursor of amyloid beta, could have a

role in the initiation of the disease. We have performed a screening of a chemical library of small molecules and identified compounds that increase the clearance of C99. We now seek to establish a novel screening strategy and further develop hit compounds for the treatment of Alzheimer's disease.

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

Alzheimer's disease is a huge health problem that imposes a severe social and economic burden; in the absence of an effective disease-modifying treatment, it is projected to become a dominant source of health care expenditures over the next several decades. Unfortunately, existing treatments are palliative, providing only temporary symptomatic benefit. Through a number of Cure Alzheimer's Fund and National Institutes of Health awards, we have discovered and developed a series of highly potent compounds known as gamma-secretase modulators (GSMs). These compounds have been shown to inhibit the formation of

amyloid beta-42, the primary component of the amyloid plaques thought to play a major role in the initiation and progression of the disease. Despite the therapeutic promise of this series of GSMs, such as BPN-15606 and UCSD/MGH-776890, little is known about how these compounds work. The research described in this interim report, combined with studies planned for year 2, provides critical insight into the complex mechanisms of how this enzyme produces amyloid beta-42 and how GSMs are able to attenuate the production of this neurotoxic species.

The Effect of Chronic Gamma-Secretase Modulation on the Prevention of Traumatic Brain Injury-Provoked and Alzheimer's Disease-Relevant Biochemical, Pathological and Behavioral Alterations

STEVEN L. WAGNER, PH.D., University of California, San Diego

BRIAN HEAD, PH.D., University of California, San Diego

The clinical manifestations of traumatic brain injury (TBI) are complex and are associated with sensory, motor, psychiatric and cognitive impairments stemming from a multifaceted series of biochemical, morphological and structural alterations resulting in axonal accumulation and aggregation of a number of proteins and peptides. Among these proteins and peptides are amyloid precursor protein, amyloid beta-42, hyperphosphorylated tau and neurofilament light chain; additional proteins increase in plasma such as S100B (cerebrovascular damage), GFAP (astroglial injury), UCH-L1 (neuronal damage) and NFL. Morphologically, diffuse axonal injury occurs immediately after TBI. Increases in intra-axonal APP, a well-established marker for DAI following TBI, used to identify DAI in forensic medicine. In addition, TBI-induced elevations in amyloid beta peptides, especially amyloid beta-42, chronically has been shown to potentiate amyloid beta deposition in transgenic Alzheimer's disease mouse models. Therefore, interventions targeting mechanisms generating amyloid beta-42 may serve to ameliorate axonal damage as well as amyloidosis elicited by TBI, and reduce the risk of

developing AD or related dementias. Gamma-secretase is one of the two enzymes responsible for amyloid beta-42 production; therefore, compounds that modulate (rather than inhibit) this pivotal enzyme may be able to safely curtail amyloid beta-42. We successfully developed a series of novel GSMs through iterative rounds of medicinal chemistry optimization. UCSD/MGH-776890 and UCSD/MGH-779690 potently (IC₅₀ = 4.1 nM and 5.3 nM, respectively) lower amyloid beta-42 *in vitro* and exhibit excellent drug-like properties (*in vitro* ADMET and *in vivo* pharmacokinetic parameters) in multiple species. Repeat-dose efficacy studies in rodents (5–10 mg/kg/day) dramatically lower amyloid beta-42 levels in brain, cerebrospinal fluid and plasma while displaying no toxicity at a dose of greater than 50 mg/kg/day. Pharmacodynamics studies show that a single oral dose (5–10 mg/kg) suppresses amyloid beta-42 levels in brain and plasma for up to 24 hours. These strong proof-of-concept findings support the further preclinical evaluation of UCSD/MGH-776890 and UCSD/MGH-779690 as potential preventative treatments for TBI-induced chronic neurodegeneration.

Dear Friends,

We are pleased to report that 2019 was the 15th consecutive record year for research dollars distributed and funds raised by Cure Alzheimer's Fund. (See the chart on the next page). Donations for the year totaled \$25.2 million, an increase of 23% from 2018, and those dollars came from more than 20,000 contributions.

Research spending for 2019 totaled \$19.9 million, an increase of 1% from 2018, funding 72 projects.

We continue to keep our overhead costs low. Since inception through the end of 2019, our Board of Directors has contributed \$42.7 million to support operating expenses totaling \$26.6 million. While keeping pressure on costs, we also allow—and our Board encourages—appropriate investment for growth to fuel our ability to raise more money for research. Our fiscal responsibility combined with our commitment to transparency once again has earned Cure Alzheimer's Fund the honorable distinction of a 4-star rating by Charity Navigator for the ninth consecutive time, the highest rating the charity watchdog offers.

Since our inception in 2004 and through the end of 2019, Cure Alzheimer's Fund has distributed more than \$106 million to 160 researchers around the world. Although the disease still is with us, great progress has been achieved in understanding Alzheimer's. Researchers tell us they are more enthusiastic and optimistic about finding the pathways to effective therapies than they ever have been.

Our belief in the value of innovative, breakthrough research to unravel the complexities of Alzheimer's pathology has yielded significant contributions described elsewhere in this report. The continued generosity of

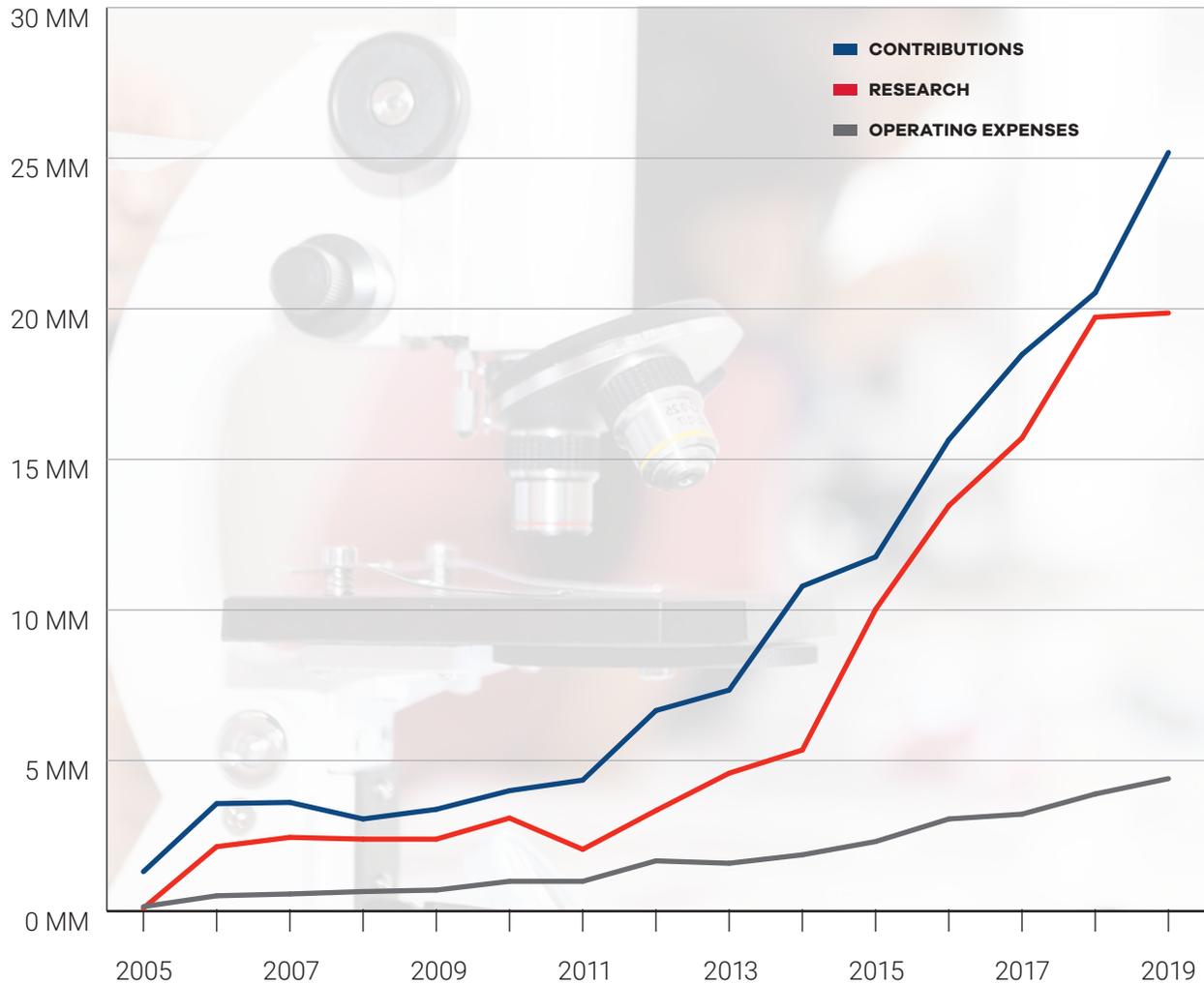


our Board and thousands of donors, the commitment and professionalism of the staff, and the extraordinary dedication of the hundreds of researchers focused on ending this disease give us all solid reasons for hope.

We are deeply grateful to all who have made this progress possible and are committed to build on that progress to stop, slow or even reverse Alzheimer's disease.

Sincerely,
Tim Armour
President and CEO

Growth: Inception Through 2019



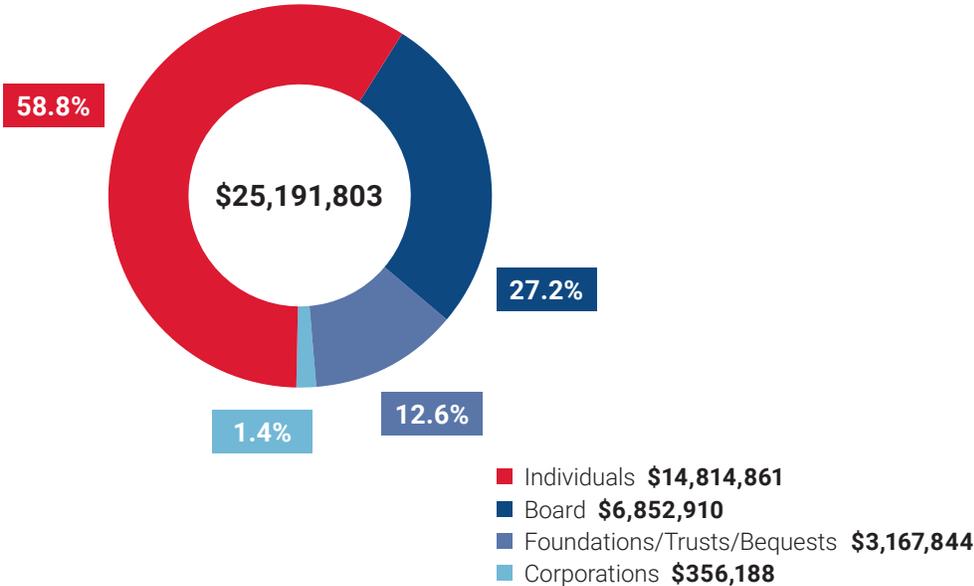
A Record of Extraordinary Growth:

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

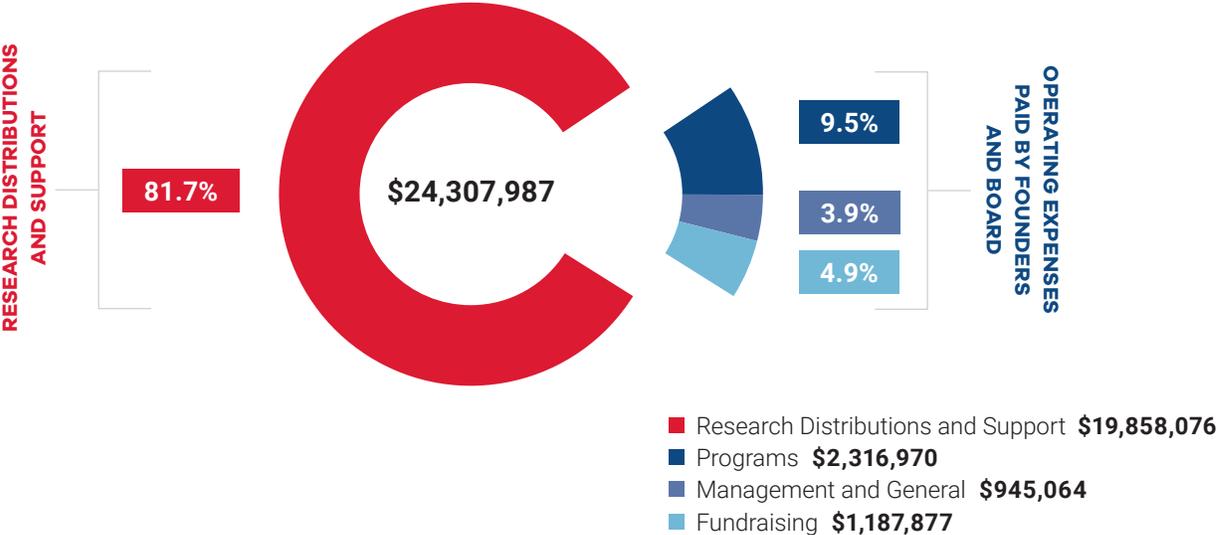
2019 Fundraising

In 2019, Cure Alzheimer’s Fund received 20,426 gifts—from individuals, the Board, corporations and foundations—totaling \$25,191,803. Cumulative contributions from inception given by our Founders and Board total \$42,734,198. Cumulative operating expenses from inception paid by the Founders and Board total \$26,632,967.

SOURCE OF FUNDS



USE OF FUNDS



Cure Alzheimer’s Fund has no endowment—our objective is to move money from donors to research as quickly as possible. Source of Funds source: Internal records. Use of Funds source: Audited financial statements, Dec. 31, 2019.

2019 Financials (Year ended Dec. 31, 2019)

Statement of Financial Position

| | |
|---|---------------------|
| Assets | |
| Current Assets: | |
| Cash and cash equivalents | \$4,797,158 |
| Contributions receivable | 219,130 |
| Pledges receivable, current portion | 2,805,010 |
| Investments | 2,255,465 |
| Prepaid expenses and other current assets | 65,952 |
| Total current assets | <u>10,142,715</u> |
| Pledges receivable, less current portion, net | 3,285,560 |
| Equipment, net | 26,595 |
| Total Assets | <u>\$13,454,870</u> |
| Liabilities and Net Assets | |
| Current Liabilities: | |
| Accounts payable | \$143,095 |
| Accrued expenses | 409,173 |
| Total current liabilities | <u>552,268</u> |
| Net Assets: | |
| Without donor restrictions | 6,344,297 |
| With donor restrictions | 6,558,305 |
| Total net assets | <u>12,902,602</u> |
| Total Liabilities and Net Assets | <u>\$13,454,870</u> |

Statement of Activities

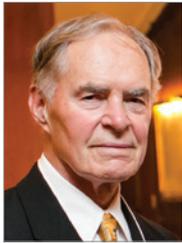
| | |
|------------------------------------|---------------------|
| Revenue and Support: | |
| Contributions | \$30,497,342 |
| Investment income | 24,010 |
| Total revenue and support | <u>30,521,352</u> |
| Expenses: | |
| Program expenses: | |
| Research distributions and support | 19,858,076 |
| Other program expenses | 2,316,970 |
| Total program expenses | <u>22,175,046</u> |
| Management and general | 945,064 |
| Fundraising | 1,187,877 |
| Total expenses | <u>24,307,987</u> |
| Change in net assets | 6,213,365 |
| Net Assets, beginning of year | <u>6,689,237</u> |
| Net Assets, end of year | <u>\$12,902,602</u> |

Source: Audited financial statements

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/about-us/our-people/.

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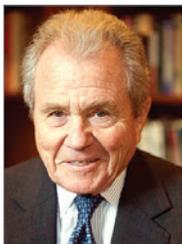
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Our Heroes



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 **2019 heroes, and share a few of their stories on the following pages.**



- A Token Of
- AbbVie Inc.
- Abby Rives
- Adam Eltarhoni
- Addison Mcintyre
- Alan Arnette
- Alan Zhang
- Alexa’s Half Marathon Run
to Cure Alzheimer’s
- Alexander (Alex) Schmidt and
Augustus Snyder
- Axels for Alzheimer’s
- Bellevue High School
- Beth Erickson and Emily Fitzgerald
- Birthday Bash Apocalypse
- Carriage House at Lee’s Farm, A
Northbridge Senior Living Community
- Casey Guinn
- Catherine LaCasce
- Claire Caliento
- Crimson Star Emporium
- Dave and Rita Whetton
- David Blakelock
- David K. Johnson Foundation
- Debbi Geller
- Elijah Henson
- Ellen and Patrick Pinschmidt
- Essex Paddle Tennis Club
- Gabrielle Stern
- Hollie Wheeler and Howie Lowden
- In memory of John M. Ferrero Jr.
- International Brotherhood of
Magicians Ring 122
- Jason Kollat
- JD Core Training
- Jeff Martin
- Jen Noonan
- Jenny Chen
- Jeremy Katz
- Joe Wallace
- Jog Your Memory
- Jordan Skelton
- Julie’s Pedal 2 Prevent Alzheimer’s
- Katie Wilson
- Kurt Thuenemann
- Lake Wales Charter School Students
- Lezlee Sabo
- Maggie McLening
- Maria Luca
- Michael Makar
- Mike Erickson, A Run in the Woods
Morels & Memories—Mushroom Hunt &
Alzheimer’s Fundraiser
- Nanci (Anders) Schiman
- Nancy Greene
- Nikki Torchon
- Noah Luskus
- Pamela Panahon
- Pasquale Camerlengo/Ice Fantasy
- Paul Coté
- Paul Sappie
- Publish for Charity
- International Association of Fire Fighters
(IAFF) Local 792
- Running 4 Answers
- Sailaja Rangunathan
- Shelly Mellott
- SingStrong A cappella Festival
- Skylar Reed
- Stefan Schnabl
- Stonebridge at Burlington, A Northbridge
Senior Living Community
- The American Red Cross Club
at College of Staten Island
- Thomas Kwan
- Travis Landing Chili Cook-Off
- Xinyu (Simon) Wu

Cure & Coté

“Pretty brutal” is how artist Paul Coté describes the effects of Alzheimer’s disease on his family. His dad and three of his aunts had or are still living with Alzheimer’s. “It’s a family wipeout,” he said. Paul has become an advocate for scientific research by using his art to raise awareness and funds and, in March, he conducted a live painting performance. During this event he created 10 original canvases for auction, with all proceeds benefiting Cure Alzheimer’s Fund. More than \$10,000 was raised. Cure & Coté was generously co-hosted by Boston-based creative agencies Allen & Gerritsen and Proper Villains.



Cure and CycleBar

Considered the largest indoor cycling franchise in the world, CycleBar® commemorated Alzheimer’s Awareness Month in November by partnering with Cure Alzheimer’s Fund. Donna Sharp Suro, owner of CycleBar Greengate in Richmond, Virginia, and daughter of CureAlz board member Sherry Sharp, suggested that CycleBar rally its franchise owners nationwide to conduct a charity ride to benefit CureAlz. The CureAlz and CycleBar marketing teams joined forces to make Donna’s vision a reality. Studios coast to coast held more than 50 events, which raised more than \$12,000 for research funding.



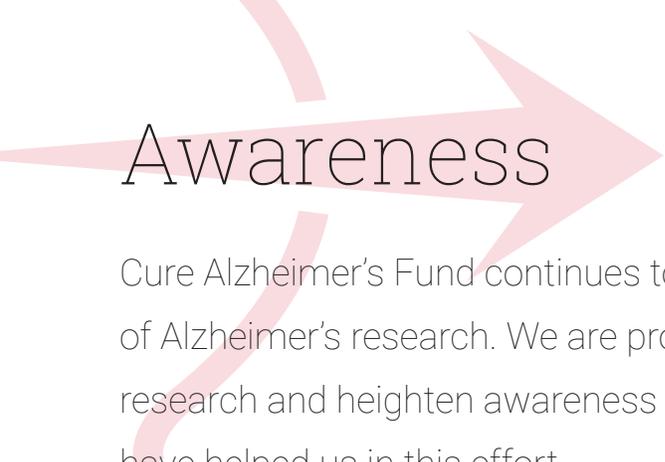
Lake Wales Charter Schools

The students from Lake Wales Charter Schools in Lakes Wales, Florida, wanted to find a special way to thank Henry McCance for his support of their schools. They decided to raise money for Cure Alzheimer's Fund, and created a campaign called "Making Memories Matter for McCance." Their goal was \$10,000 in 10 days. Their creative fundraising efforts involved the district's six schools. By the time the campaign closed, the students had raised \$15,000 for Cure Alzheimer's Fund.



Badgunpla Model-Building Marathon

Alzheimer's has been a part of Jason Kollat's life for as long as he can remember. His grandparents passed away from the effects of the disease and his aunt now has Alzheimer's disease. Under the moniker of Badgunpla, Jason decided to employ his hobby of assembling Gunpla anime models to live stream a 24-hour video model-building marathon on Twitch, with all donations to benefit Cure Alzheimer's Fund. His goal was \$500. Much to his surprise—and ours—Jason's followers donated nearly \$10,000.



Awareness

Cure Alzheimer's Fund continues to shine a national spotlight on the importance of Alzheimer's research. We are proud of the contributions we've made to advance research and heighten awareness of this disease, and are grateful to those who have helped us in this effort.

Cure Alzheimer's Fund Night at Fenway Park

For the second year, the World Champion Boston Red Sox spotlighted the work of Cure Alzheimer's Fund, orienting all pregame activities on June 25 around our organization. On the field and on the air, the Red Sox honored our researchers and Board members for their dedication to ending Alzheimer's disease. Dr. David Holtzman of Washington University in St. Louis—cousin of Ken Holtzman, the three-time World Series pitcher for the Oakland Athletics—threw out the ceremonial first pitch. The national anthem was performed by a cappella ensemble In Choro Novo, of which CureAlz President and CEO Tim Armour is a member. Cure Alzheimer's Fund's public service announcement, "The Face of Alzheimer's," was featured throughout the game on the stadium's big screen. We are deeply grateful to the Red Sox for their generosity in providing this exceptional opportunity to educate fans across Red Sox Nation about Alzheimer's disease and our mission.

Female Fan Nation

Founded by sports industry veteran Laurie Miller Voke, Female Fan Nation is the first national organization dedicated to uniting women who are passionate about sports in a common community. The social platform fosters and promotes the fan experience in all sports through chapters in 14 major cities from Boston to San Francisco. Because Alzheimer's disease disproportionately impacts women—some two-thirds of people with Alzheimer's are women, as are two-thirds of their caretakers—Voke recognized an opportunity to educate her community through a partnership between Female Fan Nation and Cure Alzheimer's Fund. For the month of December, Female Fan Nation dedicated its website homepage to Cure Alzheimer's Fund. "Daughter & Mother," the award-winning short film that illustrates the impact of Alzheimer's disease on women, was featured, along with links to donate.

The Face of Alzheimer's

Graphis is the premier international publisher of books on communications design and visual imagery. To be recognized with a Graphis award is considered to be one of the most exceptional honors a creative work can receive. Last year, "The Face of Alzheimer's" campaign, created by agency Proper Villains on behalf of Cure Alzheimer's Fund, was honored with a Gold Award in the category of Public Service. The publication observed that "while Alzheimer's is generally thought of as an 'old persons' disease,' its true impact is actually felt across all age brackets, by people of every race, sex, and gender. The Face of Alzheimer's campaign combines stark, portrait-style cinematography with a quiet score to present powerful statistics that highlight the unexpected impact that Alzheimer's has on people not typically associated with the disease."



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Female fan Nation Unites All Women Who Are Interested In Sports In A Common Community. We make a difference in causes that we care about, which is why we have partnered with the Cure Alzheimer's Fund.

100% of funds go to directly to research.

Alzheimer's disproportionately impacts women.

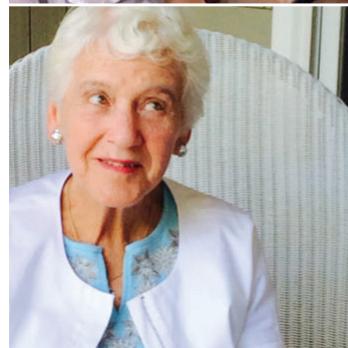
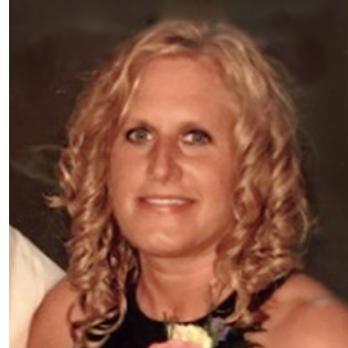
The Cure Alzheimer's Fund supports the brightest scientific minds in the field, the majority women.

[DONATE TO CURE ALZHEIMER'S FUND](#)



THE FACE OF ALZHEIMER'S





In Memory and In Honor

Cure Alzheimer's Fund receives many gifts in memory or in honor 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 memory or in honor 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.

Support Our Research

Cure Alzheimer's Fund has been fortunate to have thousands of donors make contributions in all sizes to support our cause. We are grateful to each and every donor. Here are some of the ways you can give today.

Donor Advised Funds

We are pleased to accept gifts from your Donor Advised Funds (DAF). Donors with funds held by Fidelity Charitable, Schwab Charitable or Great Kansas Community Foundation can use the DAF Direct form to process donations directly on our website. For all other Donor Advised Fund holders, please mail checks to: Cure Alzheimer's Fund, 34 Washington St., Suite 310, Wellesley Hills, MA 02481.

Planned Giving

We offer a number of Planned Giving options, some of which may offer tax incentives. If you choose to make a bequest or planned gift to Cure Alzheimer's Fund, you will become a member of our Legacy Society, joining others who have committed to ending Alzheimer's disease through continued scientific research. All members of the Legacy Society remain anonymous to the public and outside entities.

Qualified Charitable Distribution

If you are 70½ or older and have a traditional IRA, there's a smarter way to give to Cure Alzheimer's Fund. You can make a contribution, also known as a Qualified Charitable Distribution (QCD), from your IRA that is 100% tax free, whether or not you itemize deductions on your tax return.

Monthly Giving

We also offer the option of Monthly Giving, allowing you to select a specific gift amount for automatic, recurring contributions. Monthly Giving is a powerful way to show your support for research to cure Alzheimer's disease.

To explore these and other ways to give, please visit CureAlz.org/giving/ways-to-donate/ or contact Laurel Lyle at LLyle@CureAlz.org, or by calling 781-237-3800.

100% of your donation goes directly to research.

Recognized for Excellence



Cure Alzheimer's Fund has been awarded the highest rating of 4 stars for nine consecutive years.



Cure Alzheimer's Fund has received the designation of Platinum level, the highest recognition offered by GuideStar.



Cure Alzheimer's Fund meets all 20 BBB Standards for Charity Accountability.





 **Cure Alzheimer's FUND**

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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.

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