Cure Alzheimer's FUND
2018 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.

Annual Report 2018

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Dear Friends,

Thank you for making 2018 another record year for Cure Alzheimer's Fund (CureAlz). Last year our research output of $19.7 million enabled 74 projects carried out by 85 top Alzheimer's disease researchers in 35 institutions. This represents a 25% increase over research distributions in 2017 and includes support for 34 new investigators, as we continue to expand our Research Leadership Group.

This record research support was made possible by our 14th consecutive year of record fundraising. Nearly 17,000 contributors gave $20.5 million in donations, up 11% from 2017, thereby surpassing $20 million for the first time in our history.

Since our inception, we have funded more than $85 million in Alzheimer's disease research for more than 380 projects around the world. In 2019, we will surpass the milestone of $100 million in funded research. Since 2011, our contributions have grown at an annual compounded rate of 25%, and our distributions to research have grown 38%. This is extraordinary growth for any nonprofit organization! As we get larger, the growth rate inevitably will slow, but nevertheless should continue at a substantial pace based on the ever-increasing recognition within the scientific/funding community of the excellence of our research.

It's All About the Science

Fundraising records are fine, but the funds raised must be productively used to finance the finest science to lead to a cure for Alzheimer's disease, our fundamental objective.

STATE-OF-THE-ART GENOMIC ANALYSES OF ALZHEIMER'S DISEASE HAVE LED TO THE DISCOVERY OF ADDITIONAL GENETIC RISK FACTORS COMPILED IN OUR ALZHEIMER'S GENETIC DATABASE—ONE OF THE MOST COMPREHENSIVE IN THE WORLD.

A very important feature distinguishing our foundation from all other nonprofits in the Alzheimer's research community is our emphasis on understanding the genetics of Alzheimer's disease as a key to finding the causes of the disease and creating medicines to counteract those causes. We already have informed you of our discovery of dozens of new Alzheimer's genes as part of our Alzheimer's Genome Project™.

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

In addition to finding new Alzheimer's genes, we have been carrying out state-of-the-art sequencing of the entire genomes of families with Alzheimer's disease to uncover the genetic variants and mutations that increase risk or protect against the disease. These Alzheimer's-associated genetic variants can affect either the proteins involved in Alzheimer's pathology, or the regulation of the many genes that contribute to risk for the disease. The effects of these genetic variants on either risk or protection for Alzheimer's disease are tested in our Alzheimer's in a Dish system.

ALZHEIMER'S IN A DISH (ADID): EXPANSION AND NEW USES

ADiD is a mini-brain organoid model of Alzheimer's disease that can be studied in a Petri dish. The model system has been used to recapitulate the pathology of Alzheimer's disease and study the effects of Alzheimer's-associated gene mutations on the disease process. The breakthrough tool was announced to widespread acclaim five years ago and now is being used by scientists worldwide to analyze a variety of diseases. In 2018, we funded enhancements to the tool not only to recreate the plaques and tangles, but also neuroinflammation and the role of the blood-brain barrier. The tool is important for a variety of reasons: one actually can see how the pathology of Alzheimer's disease develops; one can test medicines against real human neurons (not just modified mouse neurons); and one can accelerate analysis time. To use a transgenic mouse for analysis takes months to years; ADiD with human neurons allows the analysis to be performed in less than a month—a tremendous speed-up and improvement in analysis capability, and at a fraction of the cost of studies in mice.

"Fundraising records are fine, but the funds raised must be productively used to finance the finest science to lead to a cure for Alzheimer's disease, our fundamental objective."

"...based on direct drug screening in our Alzheimer's in a Dish model and subsequent deep learning algorithms to identify additional drugs, we have identified approximately 75 existing drugs and natural products that may help Alzheimer's patients."

REPURPOSING EXISTING DRUGS FOR APPLICATION WITH ALZHEIMER'S DISEASE

A possible shortcut to finding a cure for AD is to identify, from among the hundreds of currently existing medications (including natural products) that already have been approved for other diseases or ailments, those that have the potential to be converted into important medications for Alzheimer's disease (drug repurposing). To test medications for their potential to be converted into Alzheimer's drugs using Alzheimer's disease mice is expensive and time-consuming. Now, with ADiD, we are performing these analyses 10 times faster and at one-tenth of the cost. We already have analyzed more than 1,200 existing drugs and more than 1,500 other brain-penetrant compounds and natural products. As a result, based on direct drug screening in our Alzheimer's in a Dish model and subsequent deep learning algorithms to identify additional drugs, we have identified approximately 75 existing drugs and natural products that may help Alzheimer's patients. We now are financing the investigation of these drugs in our Alzheimer's in a Dish model, as well as with Alzheimer's mice. Given that many of these drugs already have been shown to be safe in human clinical trials for other disorders, new human trials for use in Alzheimer's disease can be expedited.

VALIDATION AND EXPANSION OF THE ANTIMICROBIAL PROTECTION HYPOTHESIS (APH) OF ALZHEIMER'S DISEASE

Due to a series of groundbreaking studies funded by Cure Alzheimer's Fund, we now know that amyloid is an important part of the innate immune system of the brain. In response to the entry into the brain of pathogens (such as bacteria or yeast), or activation in the brain of viruses, amyloid is quickly created around the microbes to trap them in amyloid plaques and protect brain cells. If too much amyloid is deposited and not cleared away, it can cause tangles to form in brain nerve cells, leading to their death.

The antimicrobial protection hypothesis further was validated by a Cure Alzheimer's Fund-supported study published in the prestigious journal *Neuron*, showing a key role for herpes viruses in driving amyloid deposition in the brain. Therefore, people with chronic recurring herpes infections may experience a buildup over time of amyloid plaques, tangles and brain inflammation. Our funded research has demonstrated that additional pathogens may have a similar impact. A logical extension of these findings is that one avenue to protecting against Alzheimer's disease may involve the use of antiviral or other antimicrobial drugs.

The conclusion that can be derived from the APH is that amyloid, as a part of the brain's immune system intended to protect the brain, is highly beneficial, but too much of it is bad for the brain. So we must be careful not to develop a drug for AD that totally eliminates amyloid. We have been supporting the development of a

drug called a "gamma secretase modulator" (GSM), which modulates the quantity of amyloid in the brain to keep it at acceptable levels. We hope to have the drug in human clinical trials in 2019.

NEW INSIGHTS INTO THE ENTRY AND EXIT SYSTEMS OF THE BRAIN

Four years ago, researchers at the University of Virginia made an incredible discovery: a lymphatic system serving the brain. This was an amazing discovery because the medical community, in more than a century of examining every part of the human anatomy, had never identified it. Prior to the discovery, it was thought the brain was devoid of lymphatic phenomena; that it only was protected by the innate immune system (amyloid) but not by the adaptive immune system (antibodies), nor was it capable of performing other lymphatic functions. But even more encouraging—it now is understood that the brain lymphatic system clears neurological detritus and, importantly, amyloid. So science has discovered a new vehicle for amyloid clearance. We have an active program exploring this possibility being managed by Dr. Jonathan Kipnis, who made the original discovery.

At the same time, Dr. Berislav Zlokovic, one of the world's experts on the blood-brain barrier, has found an important gene that clears amyloid from the brain, and he is working hard with our funding to optimize that possibility. And just recently, Dr. Kipnis discovered an entirely new set of pathways into the brain, in the skull—tiny passageways through the meninges that perform functions we do not yet fully understand. We now are considering creating a small consortium to better understand the fluid system of the brain and how it relates to Alzheimer's disease.

OTHER MAJOR INITIATIVES

All of our 74 research projects funded in 2018 are described in this annual report, but a few additional projects deserve special mention—those involving the following:

- APOE, the major gene correlated with Alzheimer's disease
- Neuroinflammation, the third stage of Alzheimer's pathology
- Women and Alzheimer's, and the causes of increased susceptibility of women to the disease

And, we are pleased to announce that human trials with Amylyx Pharmaceuticals are in process. Amylyx is a startup company with a combination drug product called AMX0035 aimed at curbing the detrimental effects of neuroinflammation on the brain. This drug shows promise in treating Alzheimer's disease in patients who are in the early to middle stages of the disease. We were the first organization to provide technological support and seed financing of the technology on which the product is based. The two trials are being funded by our organization as well as the Alzheimer's Association and the Alzheimer's Drug Discovery Foundation.

Conceptual and Financial Leverage and Leadership

One of our core strategies has been to use our research accomplishments and funding abilities to help—and join with others—to carry out and fund the most promising areas of AD-related science. We have become a true thought leader in the Alzheimer's field.

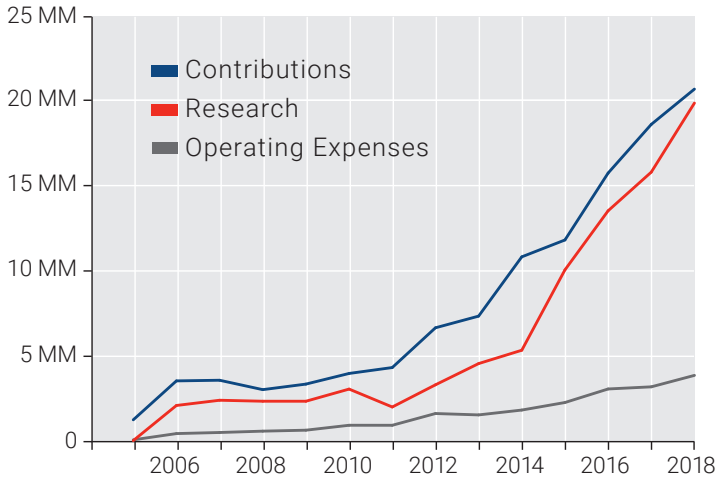
EDUCATING THE SCIENTIFIC COMMUNITY THROUGH OUTSTANDING PEER-REVIEWED PAPERS

Our hope in providing support to researchers with cutting-edge ideas is that their theories can be proven or de-risked, thereby enabling the researchers to become eligible for follow-on grants from the National Institutes of Health (NIH). An important step in this process is the publishing of a paper in significant, peer-reviewed scientific journals that detail original theories and the resulting findings. Since inception, the work we have funded has resulted in the publication of 447 papers, with many in the highest-impact scientific journals, e.g., *Nature*, *Science* and *Cell*. 2018 was the most productive year using this metric, with 87 papers published. Even more impressive, other scientists outside of Cure Alzheimer's Fund have cited our scientists' papers more than 21,000 times, demonstrating the extensive contributions being made by our researchers to the entire field's understanding of Alzheimer's disease.

CONCEPTUAL AND FINANCIAL LEVERAGE

As a thought leader, we welcome the opportunity to leverage our funding by joining with others to fund projects we are undertaking or have undertaken. An example of this is the gamma secretase modulator project, which we funded from the outset, but which subsequently was taken on by NIH with its prestigious "blueprint grant" of millions of dollars. Another example: In 2018, we introduced Open Philanthropy, a nonprofit interested in initiating Alzheimer's research, to our Research Leadership Group. This resulted in Open Philanthropy's granting $10.5 million over three years to five members of our Research Leadership Group organized within a mini-consortium to study the microbiome and its role in Alzheimer's disease. We hope this will be the first of many similar associations.

Growth: Inception Through 2018



Cure Alzheimer's Fund's historical growth rate. 2018 was the 14th consecutive record year for research dollars distributed and funds raised.

PUBLIC AWARENESS AND EDUCATION

(One of the 10 Best U.S. Medical Research Charities)

One of the ways the public becomes aware of our work

is through charitable rating organizations. In 2018, we were gratified to be recognized by several outside organizations for our work:

- CureAlz was selected by Charity Navigator as one of the *10 Best Medical Research Charities in the Country.*
- We were honored to be selected by Forbes as one of the *12 Best Charities to be Considered for Holiday Giving.*
- Finally, the Better Business Journal selected us for its *Best Charity List* through Give.org.

In addition, our public service announcement created *pro bono* by BBDO for distribution on social media received several awards, and the short film, "Daughter and Mother," was featured in 1,200 movie theaters across the country.

As we enter 2019, we are more committed than ever to support breakthrough research to find a cure for the disease. Alzheimer's disease is truly the 21st century's health crisis:

- There are 50 million people worldwide who have been diagnosed with the disease, and 6 million live in the United States.
- As the population ages, these numbers will grow. If no effective therapies are found, 15 million Americans will suffer from Alzheimer's by 2050.
- Two-thirds of patients and caregivers are women.
- 16 million caregivers provide more than 18 billion hours of annual unpaid caregiving, with a collective value of nearly $235 million.
- And, 1 of every 5 Medicare dollars is spent on caregiving for someone with the disease, at an estimated cost in 2019 to the U.S. government of $290 billion.

Despite these challenging facts, we can't help but feel the progress and momentum, all made possible by your continued generous support. We are deeply grateful for each and every donor. We also thank our expanding group of wonderful world-class researchers, and our growing dedicated, professional staff.

The Alzheimer's health care crisis, as well as personal stories of Alzheimer's patients and their families, reminds us of the importance of our mission. Through venture philanthropy, Cure Alzheimer's Fund will continue to support breakthrough research with the highest probability of slowing, preventing or reversing this disease. We are making significant progress toward a set of effective therapies.

Together, we will succeed.

With Many Thanks,

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 & Aging Unit, Massachusetts General Hospital

KARSTEN MORAN/The New York Times/Redux

The World Has Lost an Extraordinary Researcher, and Cure Alzheimer's Fund Has Lost a Treasured Friend

Paul Greengard, Nobel Laureate, Transformed Our Understanding of How Brain Cells Communicate

On April 13, 2019, Nobel Laureate Paul Greengard, Ph.D., passed away at age 93.

Dr. Greengard was a pioneer in understanding how brain cells communicate and his work was rewarded with the Nobel Prize for Physiology or Medicine. He was a true collaborator within the science community and provided guidance to researchers at all career levels. In 1983, he joined The Rockefeller University, where he established the Laboratory of Molecular and Cellular Neuroscience. Toward the end of his life, his research turned to understanding the cell signaling defects in specific disorders, including Alzheimer's disease, Parkinson's disease, schizophrenia and depression.

Cure Alzheimer's Fund was privileged to begin working with Dr. Greengard in 2006 and he became an important member of our Scientific Advisory Board and Research Leadership Group. So many of the researchers we fund looked to Dr. Greengard for his expertise, but also for his willingness to be a mentor, as he truly was committed to the success of others. In all, Cure Alzheimer's Fund provided grants for 13 projects in his lab. Our work with his lab will continue.

"Paul was clearly one of the greatest neuroscientists that ever lived; he was a true giant among all scientists," said Dr. Rudy Tanzi, Chair of the Cure Alzheimer's Fund Research Leadership Group. "His legacy of brilliance, originality and unwavering curiosity about the brain, together with his incomparable degree of kindness, generosity and respect for everyone he knew, will be fondly remembered for a long time. While we have lost one of the greatest scientists who ever lived, there is no doubt that his lifelong body of work will inspire innumerable new discoveries for many decades to come."

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 plaques 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.

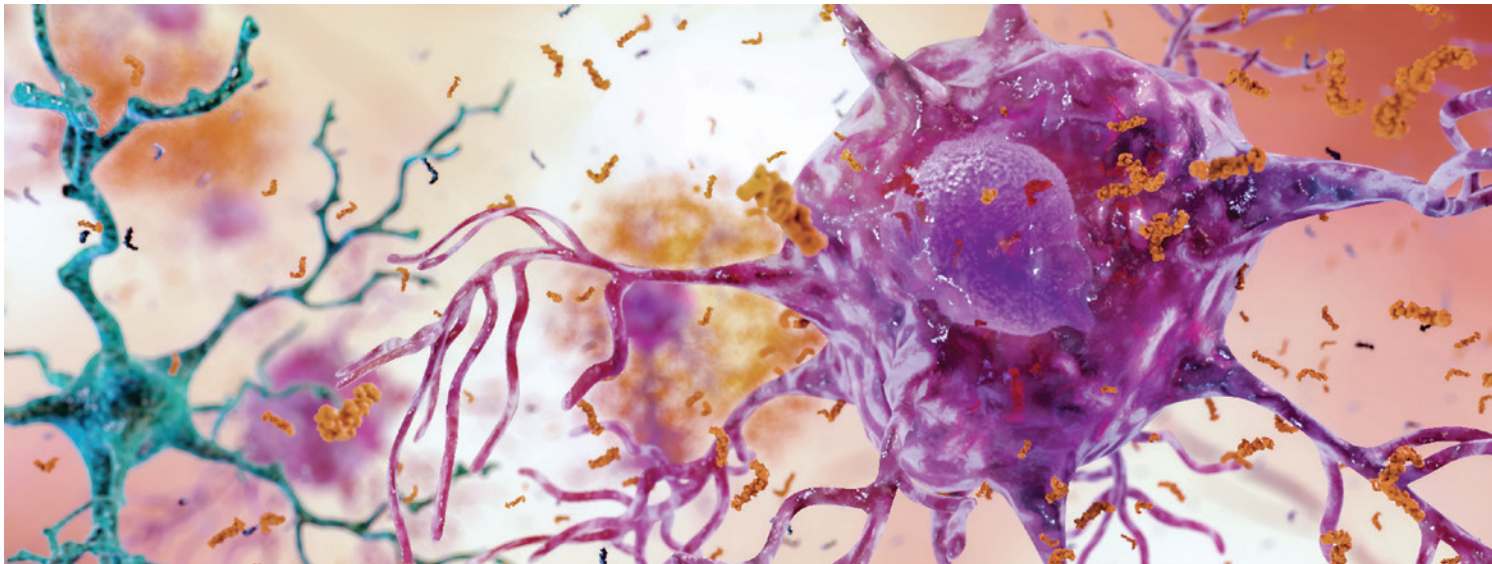
Chronic Inflammation

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.com*



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. In 2018 we modified our structure and now have two scientific entities acting on behalf of Cure Alzheimer's Fund.

First, our Research Leadership Group includes 31 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 2018, as well as the members of our Research Leadership Group and Research Strategy Council.

SRDJAN D. ANTIC, M.D.

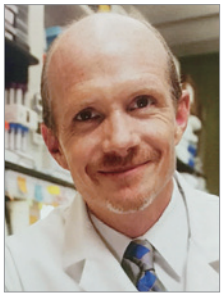
University of Connecticut Health

Associate Professor of Neuroscience

DARREN J. BAKER, M.S., PH.D.

Mayo Clinic Rochester

Assistant Professor of Biochemistry and Molecular Biology



RANDALL J. BATEMAN, M.D.

Washington University School of Medicine

Charles F. and Joanne Knight Distinguished Professor of Neurology

LARS BERTRAM, M.D.

University of Lübeck

Platform Head, Lübeck Interdisciplinary Platform for Genome Analytics (LIGA)

GEORGE S. BLOOM, PH.D.

University of Virginia Medical Center

Professor of Biology

GUOJUN BU, PH.D.

Mayo Clinic Jacksonville

Professor of Neuroscience and Associate Director, Center for Regenerative Medicine

Research Leadership Group

OLEG BUTOVSKY, PH.D.

Brigham and Women's Hospital

Assistant Professor of Neurology, Harvard Medical School

LUCÍA CHÁVEZ-GUTIÉRREZ, PH.D.

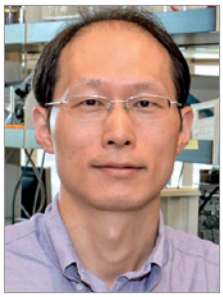
VIB-KU Leuven Center for Brain & Disease Research (Belgium)

Group leader, VIB-KU Center for Brain and Disease Research; Assistant Professor at the University of Leuven

MENG CHEN, PH.D.

Massachusetts General Hospital

Research Fellow, Genetics and Aging Research Unit



HANSANG CHO, PH.D.

University of North Carolina at Charlotte

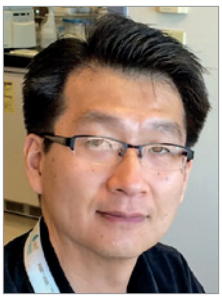
Assistant Professor of Mechanical Engineering and Engineering Science

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

Stony Brook University
School of Medicine

Chair, Department of Neurology;
Co-Director of Neurosciences Institute

Research Strategy Council



SE HOON CHOI, PH.D.

Massachusetts General Hospital

Assistant Professor of Neurology,
Harvard Medical School

WON-SUK CHUNG, PH.D.

KAIST Korea Advanced Institute of
Science and Technology

Assistant Professor, Department of Biological Sciences

MARCO COLONNA, M.D.

Washington University
School of Medicine

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

Research Leadership Group

RICHARD DANEMAN, PH.D.

University of California, San Diego

Assistant Professor, Departments of
Pharmacology and Neuroscience

SANDEEP ROBERT DATTA, M.D., PH.D.

Harvard Medical School

Associate Professor of Neurobiology

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

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

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

Research Leadership Group

MARC DIAMOND, M.D.

University of Texas Southwestern
Medical Center

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

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

Yale School of Medicine

Waldemar Von Zedtwitz Professor of
Comparative Medicine and Immunobiology

MURALI DORAISWAMY, M.B.B.S.

Duke University

Professor of Psychiatry and Behavioral Sciences; Director, Neurocognitive Disorders Program; Professor in Medicine

Research Leadership Group

KAREN DUFF, PH.D.

Columbia University

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

Research Leadership Group

JOSEPH R. ECKER, PH.D.

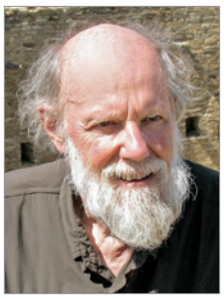
The Salk Institute for Biological Studies

Professor, Plant Molecular and Cellular Biology Laboratory; Director, Genomic Analysis Laboratory; Howard Hughes Medical Institute Investigator; Council Chair in Genetics

GIUSEPPE FARACO, M.D., PH.D.

Weill Cornell Medical College

Assistant Professor of Research in Neuroscience, Brain and Mind Research Institute



CALEB FINCH, PH.D.

University of Southern California

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

Research Leadership Group

MARC FLAJOLET, PH.D.

The Rockefeller University

Research Associate Professor

PASCAL GAGNEUX, PH.D.

University of California, San Diego

Professor of Pathology and Anthropology

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

Mount Sinai School of Medicine

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

Research Leadership Group

BRUNO GIORDANI, PH.D.

University of Michigan

Professor, Neuropsychology; Associate Director, Michigan Alzheimer's Disease Center

CHARLES GLABE, PH.D.

University of California, Irvine

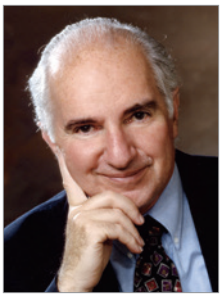
Professor, Molecular Biology and Biochemistry

Research Leadership Group

CHRISTOPHER K. GLASS, M.D., PH.D.

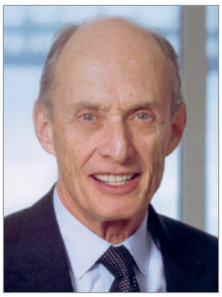
University of California, San Diego

Distinguished Professor of Medicine and Cellular and Molecular Medicine; Ben and Wanda Hildyard Chair in Hereditary Diseases



ALFRED L. GOLDBERG, PH.D.
Harvard Medical School
Professor of Cell Biology

TERESA GOMEZ-ISLA, M.D.
Massachusetts General Hospital
Associate Professor, Neurology, Harvard Medical School; Neurologist



PAUL GREENGARD, PH.D., AND NOBEL LAUREATE
The Rockefeller University
Vincent Astor Professor and Head of the Laboratory of Molecular and Cellular Neuroscience; Nobel Prize in Physiology or Medicine, 2000
Research Leadership Group
(Deceased April 2019)

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

VINCE GROPPI, PH.D.
University of Michigan
Director, Michigan Drug Discovery
Research Strategy Council

JAIME GRUTZENDLER, M.D.
Yale School of Medicine
Dr. Harry M. Zimmerman and Dr. Nicholas and Viola Spinelli Professor of Neurology and Neuroscience; Director, Center for Experimental Neuroimaging

CHRISTIAN HAASS, PH.D.
DZNE Munich
Head of the Laboratory of Neurodegenerative Disease Research; Member of the Center for Integrated Protein Science; Speaker of the German Center for Neurodegenerative Diseases; Speaker of the Collaborative Research Center 596
Research Leadership Group

BENJAMIN HAMPSTEAD, PH.D.
University of Michigan
Associate Professor

BRIAN P. HEAD, PH.D.
University of California, San Diego
Associate Adjunct Professor

WINSTON HIDE, PH.D.
Beth Israel Deaconess Medical Center; Harvard Stem Cell Institute
Associate Professor, Co-Director Noncoding RNA Core, Institute for RNA medicine; Principal Faculty, Harvard Stem Cell Institute

DAVID M. HOLTZMAN, M.D.

Washington University
School of Medicine

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

Research Leadership Group

JACOB M. HOOKER, PH.D.

Massachusetts General Hospital

Associate Professor of Radiology and Associate Neuroscientist, Harvard Medical School; Director of Radiochemistry, Martinos Center for Biomedical Imaging; Phyllis and Jerome Lyle Rappaport Massachusetts General Hospital Research Scholar

RICHARD L. HUGANIR, PH.D.

Johns Hopkins University
School of Medicine

Bloomberg Distinguished Professor of Neuroscience and Psychological and Brain Sciences and Director, Department of Neuroscience

Research Leadership Group

BRADLEY T. HYMAN, M.D., PH.D.

Massachusetts General Hospital

John B. Penney Jr. Professor of Neurology, Harvard Medical School; Director, Alzheimer Disease Research Center and Memory Disorder Unit

CONSTANTINO IADECOLA, M.D.

Weill Cornell Medical College

Anne Parrish Titzell Professor of Neurology; Director and Chair, Feil Family Brain and Mind Research Institute, Professor of Neuroscience, Brain and Mind Research Institute

TSUNEYA IKEZU, M.D., PH.D.

Boston University

Professor of Pharmacology and Experimental Therapeutics and Neurology

NANCY IP, PH.D.

Hong Kong University of Science
and Technology

Vice-President for Research and Graduate Studies; The Morningside Professor of Life Science; Director of the State Key Laboratory of Molecular Neuroscience

Research Leadership Group

RUDOLF JAENISCH, M.D.

Masschusetts Institute of Technology

Professor of Biology; Founding Member, Whitehead Institute; National Medal of Science recipient

ROGER KAMM, PH.D.

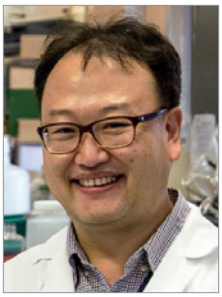
Massachusetts Institute of Technology

Cecil and Ida Green Distinguished Professor of Biological and Mechanical Engineering

MANOLIS KELLIS, PH.D.

Massachusetts Institute of Technology

Head, MIT Computational Biology Group; Principal Investigator, Computer Science and Artificial Intelligence Lab



DOO YEON KIM, PH.D.

Massachusetts General Hospital

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

TAE-WAN KIM, PH.D.

Columbia University

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

JONATHAN KIPNIS, PH.D.

University of Virginia

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

GERALDINE J. KRESS, PH.D.

Washington University

Assistant Professor of Neurology

BRUCE LAMB, PH.D.

Indiana University School of Medicine

Executive Director, Paul and Carole Stark Neurosciences Research Institute

Research Leadership Group

CHRISTOPH LANGE, PH.D.

Harvard School of Public Health

Professor of Biostatistics; Assistant Professor of Medicine at Harvard Medical School

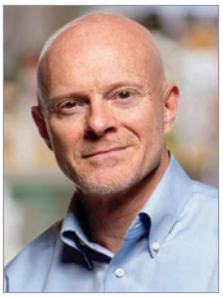
Research Leadership Group

JOHN S. LAZO, PH.D.

University of Virginia Medical Center

Harrison Distinguished Professor, Department of Pharmacology; Associate Director for Basic Science, University of Virginia Cancer Center

Research Leadership Group



GREG LEMKE, PH.D.

The Salk Institute for Biological Studies

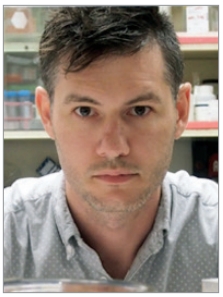
Professor, Molecular Neurobiology Laboratory; Françoise Gilot-Salk Chair

YUEMING LI, PH.D.

Memorial Sloan Kettering Cancer Center

Head, Laboratory of Biochemistry and Molecular Pharmacology

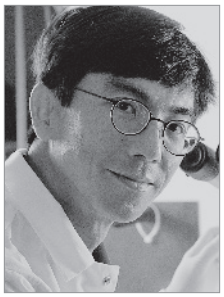
Research Leadership Group



SHANE A. LIDDELOW, PH.D.

New York University Langone Medical Center

Assistant Professor, Department of Neuroscience and Physiology



ENG H. LO, PH.D.

Massachusetts General Hospital

Professor of Neurology and Radiology, Harvard Medical School

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

Stanford University School of Medicine

Pritzker Professor of Psychiatry and Behavioral Sciences; Associate Chair, Department of Psychiatry & Behavioral Sciences; Deputy Director, Wu Tsai Neurosciences Institute

Research Leadership Group

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

University of California, San Diego

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

ECKHARD MANDELKOW, PH.D.

DZNE Bonn

Professor and Group Leader

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

DZNE Bonn

Senior Group Leader

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

University of California, San Diego

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

Research Leadership Group

JOHN MORRIS, M.D.

Washington University School of Medicine

Director of the Charles F. and Joanne Knight Alzheimer's Disease Research Center, Memory and Aging Project; Harvey A. and Dorismae Hacker Friedman Distinguished Professor of Neurology; Professor of Pathology and Immunology

Research Strategy Council, Chair

LISA MOSCONI, PH.D.

Weill Cornell Medical College/ New York-Presbyterian Hospital

Associate Director, Alzheimer's Prevention Clinic; Associate Professor of Neuroscience in Neurology and Radiology; Director, Women's Brain Initiative

KRISTA L. MOULDER, PH.D.

Washington University School of Medicine

Associate Professor of Neurology; Executive Director of the Charles F. and Joanne Knight Alzheimer's Disease Research Center

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Washington University School of Medicine

Assistant Professor of Neurology

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

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

JOSEPH PARK, PH.D.
Massachusetts General Hospital
Instructor in Neurology

STEVEN PAUL, M.D.
Chief Executive Officer and Chairman of the Board for Karuna Pharmaceuticals; Venture Partner at Third Rock Ventures; Former Scientific Director, National Institute of Mental Health
Research Strategy Council

HENRY PAULSON, M.D., PH.D.
University of Michigan
Lucile Groff Professor of Neurology; Director, Alzheimer's and Related Dementias

RONALD C. PETERSEN, M.D., PH.D.
Mayo Clinic
Director, Alzheimer's Disease Research Center and Study of Aging
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ANDREAS R. PFENNING, PH.D.
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KAREN REEVES, M.D.
AZ Therapies
President and Chief Medical Officer
Research Strategy Council

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ELIZABETH R. SHARLOW, PH.D.

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

SUBHASH SINHA, PH.D.

The Rockefeller University

Research Associate Professor

SANGRAM SISODIA, PH.D.

The University of Chicago

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

Research Leadership Group

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National Institute of Aging
Division of Neuroscience

Retired Deputy Director

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BETH STEVENS, PH.D.

Boston Children's Hospital

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

Research Leadership Group

SIDNEY STRICKLAND, PH.D.

The Rockefeller University

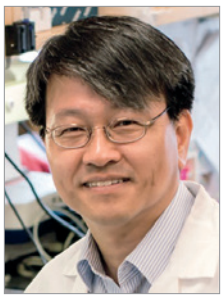
Research Professor; Vice President for Educational Affairs; Dean of Graduate and Postgraduate Studies

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

Stanford University School of Medicine

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

Research Leadership Group



JAEHONG SUH, PH.D.

Massachusetts General Hospital

Assistant Professor of Neurology, Harvard Medical School; Assistant Neuroscientist

FILIP SWIRSKI, PH.D.

Massachusetts General Hospital

Associate Professor

RUDOLPH TANZI, PH.D.

Massachusetts General Hospital

Joseph P. and Rose F. Kennedy Professor of Neurology, Harvard Medical School; Vice Chair of Neurology, Director of the Genetics and Aging Research Unit, Co-Director of the Henry and Allison McCance Center for Brain Health at Massachusetts General Hospital

Research Leadership Group, Chair
Research Strategy Council

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

Tufts University

Associate Professor of Neuroscience

TERRENCE TOWN, PH.D.

University of Southern California

Professor of Physiology and Neuroscience

LI-HUEI TSAI, PH.D.

Massachusetts Institute of Technology

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

Research Leadership Group

AJIT VARKI, M.B.B.S.

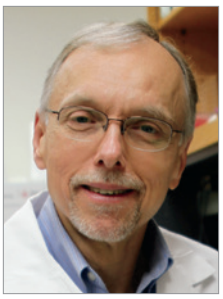
University of California, San Diego

Professor of Medicine and Cellular & Molecular Medicine; Co-Director of CARTA; Co-Director of the Glycobiology Research and Training Center; Adjunct Professor, Salk Institute

NISSI VARKI, M.B.B.S.

University of California, San Diego

Professor of Pathology



ROBERT VASSAR, PH.D.

Northwestern University

Scientific Director of Behavioral Neurology in the Department of Neurology; Davee Professor of Alzheimer Research; Professor of Neurology and Cell and Molecular Biology

Research Leadership Group

STEVEN L. WAGNER, PH.D.

University of California, San Diego

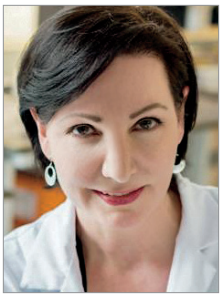
Professor in Residence, Neurosciences

Research Leadership Group

WILMA WASCO, PH.D.

Massachusetts General Hospital

Associate Professor of Neurology, Harvard Medical School; Associate Geneticist



CHERYL WELLINGTON, PH.D.

University of British Columbia

Professor, Department of Pathology and Laboratory Medicine

STEPHEN T. WONG, PH.D.

Houston Methodist Research Institute

John S. Dunn, Sr. Distinguished Endowed Chair in Biomedical Engineering; Associate Director of Translational Research, Chief of Medical Physics and Chief Research Information Officer

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CHRISTIANE WRANN, D.V.M., PH.D.

Massachusetts General Hospital

Assistant Biologist; Assistant Professor in Medicine, Harvard Medical School

TONY WYSS-CORAY, PH.D.

Stanford University

D.H. Chen Endowed Professor, Professor of Neurology & Neurological Sciences

WEIMING XIA, PH.D.

Boston University School of Medicine

Professor, Pharmacology & Experimental Therapeutics

HUAXI XU, PH.D.

Sanford Burnham Prebys Medical Discovery Institute

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

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Professor and Chair, Department of Neuroscience

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Washington University School of Medicine

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ZHEN ZHAO, PH.D.

University of Southern California

Assistant Professor of Physiology and Neuroscience, Zilkha Neurogenetic Institute

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

University of Southern California

Chair and Professor of Physiology and Neuroscience; Mary Hayley and Selim Zilkha Chair in Alzheimer's Disease Research; Director, Zilkha Neurogenetic Institute

Research Leadership Group

2018 Funded Research

Cure Alzheimer's Fund spent **$19.7 million to support 74 research projects** across our focus areas, an all-time high record. Visit **CureAlz.org/the-research** to read about all of our current research projects.

Project/Researcher	Distribution Amount
Functional Genomics	
Whole Genome Characterization of DNA Methylation Changes in the Aged and Alzheimer's Disease Human Brain Rudolf Jaenisch, M.D., Masschusetts Institute of Technology, and Joseph R. Ecker, Ph.D., The Salk Institute for Biological Studies	**$287,500**
Functional Analysis of Alzheimer's Disease Risk Genes Using Human-Induced Pluripotent Stem Cells Li-Huei Tsai, Ph.D., and Manolis Kellis, Ph.D., Massachusetts Institute of Technology	**$460,000**
Epigenetic Determinants of Human Cognitive Aging Lars Bertram, M.D., University of Lübeck	**$199,600**
Utilizing Functional Maps to Prioritize Therapeutic Targets in Alzheimer's Disease Winston Hide, Ph.D., Beth Israel Deaconess Medical Center; Harvard Stem Cell Institute	**$209,725**
iPS Cells and the Human Brain Bradley T. Hyman, M.D., Ph.D., Massachusetts General Hospital	**$148,732**
Interpreting Alzheimer's Disease-Associated Genetic Variation at Enhancer Regions Andreas R. Pfenning, Ph.D., Carnegie Mellon University	**$198,021**
Genes to Therapies™/Stem Cell Drug Screening: Translational studies investigating established and newly confirmed AD genes	
The Role of PICALM Mutations in Alzheimer's Disease Berislav V. Zlokovic, M.D., Ph.D., and Zhen Zhao, Ph.D., University of Southern California	**$345,000**
APOE Proteoforms in the Human Central Nervous System and Validation of Translational APOE Pharmacodynamic Markers Randall J. Bateman, M.D., Washington University School of Medicine	**$250,000**
Effects of Peripheral APOE on Central Nervous System Functions and Alzheimer's Disease Pathogenesis Guojun Bu, Ph.D., Mayo Clinic Jacksonville	**$250,000**
The Role of APOE in Microglia Regulation in Neurodegeneration Oleg Butovsky, Ph.D., Brigham and Women's Hospital	**$250,000**
Impact of APOE and Sex on Vulnerable Neuron-Specific Functional Networks Paul Greengard, Ph.D., The Rockefeller University	**$250,000**
Understanding the Effect of APOE on Tau-Mediated Neurodegeneration David M. Holtzman, M.D., Washington University School of Medicine	**$300,000**
Alzheimer's Disease-Associated Mutations in Protein Kinase C Alexandra C. Newton, Ph.D., University of California, San Diego	**$287,500**
Behavorial Phenotyping and Evaulation of Sleep-EEG in Transgenic Mice PsychoGenics	**$85,500**
Role of Ataxin-1 in Regulating BACE1 Activity Jaehong Suh, Ph.D., Massachusetts General Hospital	**$287,500**
G2T Research Models and Materials Taconic Biosciences	**$2,455,711**
Functional Characterization of GGA3 Mutations Associated with Alzheimer's Disease Giuseppina Tesco, M.D., Ph.D., Tufts University	**$150,000**
Genes to Therapies™ (G2T) Centralized Research Core Wilma Wasco, Ph.D., Massachusetts General Hospital	**$193,890**
Using Human Bioengineered Cerebral Vessels to Explore How Native APOE Affects Cerebrovascular Properties Relevant to Alzheimer's Disease Cheryl Wellington, Ph.D., University of British Columbia	**$251,378**
PICALM Gene Therapy and Drug Screening for Amyloid Beta Clearance Berislav V. Zlokovic, M.D., Ph.D. , University of Southern California	**$300,000**

Project/Researcher	Distribution Amount
Genetics	
Analytical and Statistical Tools for Sequence Analysis for Alzheimer's Disease Christoph Lange, Ph.D., Harvard School of Public Health	**$250,000**
The Impact of Alzheimer's Disease-Associated Genetic Variants in 3-D Human Mixed Neural-Glial Models of Alzheimer's Disease Joseph Park, Ph.D., Massachusetts General Hospital	**$172,500**
Alzheimer's Genome Project™ Rudolph Tanzi, Ph.D., Massachusetts General Hospital	**$1,725,000**
Identification: Early detection via biomarkers, imaging, etc.	
Neurobiological Basis of Cognitive Impairment in African Americans: Deep Phenotyping of Older African Americans at Risk of Dementia Henry Paulson, M.D., Ph.D., Bruno Giordani, Ph.D., and Benjamin Hampstead, Ph.D., University of Michigan	**$241,738**
Imaging Microglial Homeostasis and Disruption: P2RY12 Radiotracer Development Jacob M. Hooker, Ph.D., and Michael S. Placzek, Ph.D., Massachusetts General Hospital	**$172,500**
Alzheimer's Disease Pharmacomics in 3-D Weiming Xia, Ph.D., Boston University School of Medicine	**$172,500**
Immune System Structures and Processes: Role of inflammation and other responses in AD	
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**
The Role of the Contact System in Alzheimer's Disease Sidney Strickland, Ph.D., and Erin H. Norris, Ph.D., The Rockefeller University	**$150,000**
Study of Reactive Astrocytes-Derived Oxidative Stress and Microglial Neurodegenerative Inflammation in Alzheimer's Disease Hansang Cho, Ph.D., University of North Carolina at Charlotte	**$200,000**
Synapse Pruning by Astrocytes: A Potential New Target for Treating Alzheimer's Disease Won-Suk Chung, Ph.D., KAIST Korea Advanced Institute of Science and Technology	**$150,000**
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**
Interpretation of Noncoding Risk Alleles for Alzheimer's Disease Christopher K. Glass, M.D., Ph.D., University of California, San Diego	**$250,000**
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**
Inhibiting CD33 Function and Modulating Microglial Activation State for Alzheimer's Disease Therapy Ana Griciuc, Ph.D., Massachusetts General Hospital	**$172,500**
The Neuroprotective Glial Barrier: A Multicellular Reaction with Therapeutic Potential in Alzheimer's Disease Jaime Grutzendler, M.D., Yale School of Medicine	**$172,500**
Neuroimmune Molecular Imaging: Redefining the Landscape of Opportunities in Alzheimer's Disease Jacob M. Hooker, Ph.D., Massachusetts General Hospital	**$100,000**
Microglial TAM Receptors as Modulators of Alzheimer's Pathology Greg Lemke, Ph.D., The Salk Institute for Biological Studies	**$150,000**
Neurotoxic Reactive Astrocytes in Alzheimer's Disease Shane A. Liddelow, Ph.D., New York University Langone Medical Center	**$250,000**
Temporal Analysis of Infection in Alzheimer's Disease Models Judith Steen, Ph.D., Boston Children's Hospital	**$149,999**
Microglial Heterogeneity and Transcriptional State Changes in Alzheimer's Disease Beth Stevens, Ph.D., Boston Children's Hospital	**$299,924**
Interleukin-3 in Alzheimer's Disease Filip Swirski, Ph.D., Massachusetts General Hospital	**$171,932**
Targeting Beneficial Innate Immunity in Alzheimer's by Interleukin-1 Receptor-Associated Kinase M Deletion Terrence Town, Ph.D., University of Southern California	**$172,500**
Rejuvenation of Microglia in Brain Aging and Neurodegeneration Tony Wyss-Coray, Ph.D., Stanford University	**$172,500**

Project/Researcher	Distribution Amount
Other: Novel approaches, targets or therapies aligned with the Cure Alzheimer's Fund mission	
Effects of Cerebrovascular Insufficiency and Exercise on the Alzheimer's Brain Eng H. Lo, Ph.D., Massachusetts General Hospital	**$170,907**
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	**$170,861**
Scientific Directions for the Exploration of Racial Disparities in Alzheimer's Disease Krista L. Moulder, Ph.D., Washington University School of Medicine	**$79,594**
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	**$172,500**
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	**$172,500**
Dietary Salt, Tau Phosphorylation and Cognitive Impairment Giuseppe Faraco, M.D., Ph.D., and Constantino Iadecola, M.D., Weill Cornell Medical College	**$172,500**
Pathological Pathways and Systems	
Cell Cycle Re-Entry in 3-D Human Neuron Cultures George S. Bloom, Ph.D., John S. Lazo, Ph.D., and Elizabeth R. Sharlow, Ph.D., University of Virginia Medical Center	**$230,000**
Amyloid Beta-Mediated Inhibition of Gamma-Secretase Activity Induces Alzheimer's Disease-Relevant Cellular Phenotypes William C. Mobley, M.D., Ph.D., University of California, San Diego, and Lucía Chávez-Gutiérrez, Ph.D., VIB-KU Leuven Center for Brain & Disease Research	**$236,067**
The Role of Neurexins in Alzheimer's Disease Rudolph Tanzi, Ph.D., and Meng Chen, Ph.D., Massachusetts General Hospital	**$172,500**
Identifying Blood-Brain Barrier Enhancers and Role of Neutrophils in a 3-D BBB Vascularized Model of Alzheimer's Disease Se Hoon Choi, Ph.D., Massachusetts General Hospital, and Roger Kamm, Ph.D., Massachusetts Institute of Technology	**$268,750**
Reversal of Tau Pathology by an Adenosine A1 Receptor Antagonist Eva-Maria Mandelkow, M.D., Ph.D., and Eckhard Mandelkow, Ph.D., DZNE Bonn	**$287,500**
Senescent Cells and Alzheimer's Disease Darren J. Baker, Ph.D., Mayo Clinic Rochester	**$172,500**
Identifying the Blood-Brain Barrier Changes During Alzheimer's Disease Richard Daneman, Ph.D., University of California, San Diego	**$172,500**
Genetic Targets to Block Tau Propagation: Test Knockdown of Heparan Sulfate Proteoglycan Genes *In Vivo* Marc Diamond, M.D., University of Texas Southwestern Medical Center	**$172,500**
Understanding Human Brain Resilience to Alzheimer's Pathology Teresa Gomez-Isla, M.D., Massachusetts General Hospital	**$300,000**
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	**$172,500**
Meningeal Lymphatic Function and Antibody Therapy in Alzheimer's Disease Jonathan Kipnis, Ph.D., University of Virginia	**$230,000**
Central Clock Influence on Alzheimer's Disease Pathogenesis Geraldine J. Kress, Ph.D., Washington University	**$172,500**
The Circadian Clock Modulates Neurodegeneration in Alzheimer's Disease Via REV-ERBα Erik S. Musiek, M.D., Ph.D., Washington University	**$172,137**
The Role of Impaired Synaptic Vesicle Machinery Proteostasis in Alzheimer's Disease Pathogenesis Jeffrey Savas, Ph.D., Northwestern University	**$172,500**

Project/Researcher	Distribution Amount
Therapeutic Strategies and Drug Discovery	
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 P. Head, Ph.D., University of California, San Diego	**$230,000**
The Development of DNA-Encoded Libraries to Discover Therapeutically Valuable Low Molecular Weight Compounds for Alzheimer's Disease Marc Flajolet, Ph.D., and Subhash Sinha, Ph.D., The Rockefeller University	**$172,500**
Neuroprotective Effects of the Exercise Hormone Irisin in Alzheimer's Disease Se Hoon Choi, Ph.D., and Christiane Wrann, D.V.M., Ph.D., Massachusetts General Hospital	**$345,000**
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 APP Beta-CTF in Cells Paul Greengard, Ph.D., The Rockefeller University	**$517,500**
Novel Chemical Modulators for BACE1-Mediated Cleavage of Amyloid Beta Precursor Protein Tae-Wan Kim, Ph.D., Columbia University	**$150,000**
High-Throughput Drug Screening for Alzheimer's Disease Using 3-D Human Neural Culture Systems Doo Yeon Kim, Ph.D. , Massachusetts General Hospital	**$345,000**
Pharmacologically Protecting and Rescuing Synapses from Beta Amyloid by Raising Synaptic PSD-95 Roberto Malinow, M.D., Ph.D., University of California, San Diego	**$143,750**
Uncovering the Molecular Mechanism of Selected Drug Candidates Derived from Systematic Alzheimer's Drug Repositioning Stephen T. Wong, Ph.D., Houston Methodist Research Institute	**$287,500**

Functional Genomics

Whole Genome Characterization of DNA Methylation Changes in the Aged and Alzheimer's Disease Human Brain

RUDOLF JAENISCH, M.D., Massachusetts Institute of Technology
JOSEPH R. ECKER, PH.D., The Salk Institute for Biological Studies

Alzheimer's disease is the most common age-related neurodegenerative disorder. Changes to the patterns of DNA methylation in the brain have been observed in both normal aging and Alzheimer's disease. Epigenetics refers to the study of heritable changes that do not involve alterations in the DNA sequence. One example is methylation—the process by which methyl groups are added to a DNA molecule. Methylation can change the activity of a segment of DNA without changing the sequence. DNA methylation is an epigenetic mark with the capacity to alter the expression of genes to enhance stability.

An open question in the field is to understand the importance of these changes to DNA methylation. Using human neurons from post-mortem tissue acquired in the context of normal aging and Alzheimer's disease, this work has started to characterize the changes in genome-wide DNA methylation patterns that occur. This research has initiated the development of *in vitro*—outside a living organism—models of Alzheimer's disease using induced stem cells. Induced stem cells refer to stem cells derived from other cell types by deliberate reprogramming. These experiments are a critical first step in understanding the potential epigenetic mechanisms of Alzheimer's disease.

Functional Analysis of Alzheimer's Disease Risk Genes Using Human-Induced Pluripotent Stem Cells

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

Our incomplete understanding of the genetic pathways underlying the development of late-onset Alzheimer's disease has hampered efforts to treat and cure the disease. Incidences of late-onset Alzheimer's disease account for the majority of individuals with Alzheimer's. To address this critical shortcoming, we developed a discovery platform that takes advantage of recent advances in induced pluripotent stem cells (iPSCs), genomics, epigenetics and the technologies of genome editing to identify genes and gene-controlling elements driving the development of disease. We have made important technical advances that allow us to identify from different regions of the Alzheimer's brains the epigenetic landscapes unique to each of the major cell types implicated in the disease. We also have generated several iPSC lines that can be induced to become a specific type of brain cell, and in which a particular gene or its controlling element involved in Alzheimer's can be turned on or off with high chemical precision. We are leveraging these powerful tools to

our discovery platform to identify the critical genetic players and pathways driving Alzheimer's disease. A better understanding of the genetic dysregulation behind the disease should lead to new and effective therapeutic strategies for the treatment and cure of Alzheimer's disease.

Epigenetic Determinants of Human Cognitive Aging

LARS BERTRAM, M.D., University of Lübeck

Much like many other human traits, cognitive decline and the development of Alzheimer's disease are determined by the concerted action of genetic, epigenetic and nongenetic factors. Epigenetics refers to changes that occur by modification of gene expression rather than alteration of the genetic code itself. It is becoming increasingly evident that variations in the DNA sequence itself do not fully explain the phenotypic picture of Alzheimer's disease. Over the last decade, genetics research in Alzheimer's has progressed at an unprecedented pace owing to the application of genotyping technology in the context of genome-wide association studies (GWAS). This project seeks to perform one of the largest epigenome-wide association studies to date on Alzheimer's disease relevant neuropsychiatric phenotypes. The study will use a well-characterized cohort of healthy at-risk individuals from Germany. The study will elucidate novel molecular mechanisms underlying cognitive decline and the onset of dementia.

Utilizing Functional Maps to Prioritize Therapeutic Targets in Alzheimer's Disease

WINSTON HIDE, PH.D., Beth Israel Deaconess Medical Center; Harvard Stem Cell Institute

Discovery of the causes of and treatment for Alzheimer's disease is confounded by the complexity of the disease, the interplay between environment and genetic basis of the disease, and the disparate approaches taken by groups to look at specific aspects of the disease. Progress has been slow and there is an urgent need to deliver treatments that are effective and have few side effects. Current studies seek specific genes as treatment targets. Usually there is a strong bias by a single group as to which genes and processes are thought responsible for the disease. Failure rates are high.

This consortium generates many different types of high-dimensional genomics data and integrates them in an unbiased manner to systematically and objectively deliver the key processes and genes that appear to be responsible for the onset and progression of the disease. Using an existing industry-sponsored model pioneered at the Sheffield Centre for Genome Translation, this proposal coordinates the data being generated by the consortium and uses it to rank the derived genes and pathways by their likely impact on the disease. In turn, ranked pathways then are matched for their suitability for targeting by existing drugs. The resulting drug/pathway/gene models will provide invaluable reagents for industry and academia to assess in terms of their direct clinical outcomes on Alzheimer's treatment and progression.

iPS Cells and the Human Brain

BRADLEY T. HYMAN, M.D., PH.D., Massachusetts General Hospital

Recent studies demonstrate that skin cells can be converted into induced pluripotent stem cells (iPSC). These iPSC are derived from skin or blood cells that have been reprogrammed back into an embryonic-like state that enables the development of an unlimited source of any type of human cell needed for therapeutic purposes. Skin cells and iPSC both can be grown in the laboratory and converted into brain cells like neurons and microglia. This project will generate skin cells that can be converted into iPS cells or neurons and microglia in order to determine the extent to which the cells generated in the laboratory resemble the actual brain cells they are intended to model.

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

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

Treating Alzheimer's disease is one of the greatest challenges we face in the coming years; it has the potential to have an enormous impact on human health. Despite its importance, there still are no highly effective treatments for Alzheimer's disease, due in large part to a limited understanding of the underlying disease mechanisms. Our laboratory, as a member of CIRCUITS (Consortium to Infer Regulatory Circuits and to Uncover Innovative Therapeutic Strategies), aims to make progress toward a cure using genomic approaches.

Starting from recent insights into the genetic basis of Alzheimer's disease, we will use a combination of machine learning and experimental techniques to work systematically 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 AD genes

The Role of PICALM Mutations in Alzheimer's Disease

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

Alzheimer's disease, the most common form of dementia in the elderly, is now the most expensive disease in the United States. With the breakthrough of human genetics and high-throughput sequencing, new genetic risk factors for AD have been identified. PICALM, the gene that encodes phosphatidylinositol-binding clathrin assembly protein, plays a key role in mediating clearance of amyloid beta at the blood-brain barrier, as well as in mitigating amyloid beta toxicity in neurons, providing molecular and cellular bases to investigate the amyloid beta-dependent and independent functions of novel PICALM mutations.

The Phase III study of the Alzheimer's Genome Project™, led by Dr. Rudy Tanzi, has carried out whole genome sequencing of 1,510 subjects from 437 AD families and identified 14 novel rare variants and mutations within the PICALM gene. However, the biological functions of these rare variants/mutations and their cell type-specific contributions to AD are yet to be examined. These new AD-associated PICALM variants/mutations represent:

- Missense mutations that altered the protein sequence of PICALM;
- Splicing variants that are located within the splicing sites of PICALM's exons; and
- Mutations that occur within the intronic regions.

We hypothesized that these rare variants/mutations may represent loss-of-function or gain-of-function mutations that affect amyloid beta metabolism and toxicity in different brain cell types, and proposed to prioritize our investigation by first introducing them into induced pluripotent stem cells (iPSCs) with CRISPR-mediated genomic editing. We then would determine the functional impact of these novel PICALM variants/mutations using iPSC-derived brain vascular cells, such as endothelial cells and pericytes, neurons and microglia.

In addition, based on our preliminary findings that the PICALM-H465R mutation potentially offers neuronal protection against amyloid beta toxicity, we also propose to study new transgenic mouse model with knock-in of human PICALM-H465R mutation to determine the potential protective effect of PICALM-H465R mutation on AD-like pathogenesis in *Picalm* $^{465R/R}$;5xFAD mice.

APOE Proteoforms in the Human Central Nervous System and Validation of Translational APOE Pharmacodynamic Markers

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

Apolipoprotein E (APOE) has been recognized as a major genetic risk factor for Alzheimer's disease. However, the mechanisms that link the pathogenic nature of APOE to AD still are not understood fully. The overall goal is to

characterize the forms of APOE that exist in the human central nervous system and to correlate findings to AD pathology. Understanding the different proteoforms that exist in brain, cerebrospinal fluid and blood in normal physiology and in the presence of amyloidosis will help us understand the complexities of the APOE and amyloid beta interaction and potentially help identify and specifically test an APOE-centric therapeutic target for AD.

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

GUOJUN BU, PH.D., Mayo Clinic Jacksonville

Alzheimer's disease as the leading cause of dementia has become a growing epidemic in our aging society. A gene called apolipoprotein E, abbreviated as APOE, is the strongest genetic risk factor for AD. The goal of the APOE consortium is to collectively address how APOE4 protein drives up the risk and how we can target this protein for the development of new therapy. Interestingly, APOE protein is present not just in the brain but also at a high concentration in the blood produced primarily by the liver to transport cholesterol and other lipids among different organs.

In addition to AD, individuals carrying the APOE4 gene also are at a greater risk of developing hypercholesterolemia and atherosclerosis compared with those carrying the APOE3 gene. Despite critical knowledge gained in the past two decades in understanding how brain APOE4 regulates AD-related pathologies, we know very little about how peripheral APOE circulating in the blood impacts brain functions and AD-related pathways. Toward this goal, we have recently developed a new set of animal models that allow for expression of APOE only in the liver but not in the brain, thus allowing studies on how liver APOE populated in the blood affects brain functions and AD pathologies.

Our results showed that blood APOE4 impaired brain functions by injuring blood vessels and by driving up harmful inflammation. In addition, we found that blood APOE4 increased the amount of a toxic molecule in the brain called amyloid beta, which is the major component of amyloid plaques thought to be the central driver of the disease process. In collaboration with other consortium projects using complementary approaches, we expect to determine the vascular effects on disease development and identify novel APOE-related genes and pathways. Our studies will help understand how blood APOE affects brain functions and AD-related pathways, and how we can develop new AD therapy targeting APOE in the blood.

The Role of APOE in Microglia Regulation in Neurodegeneration

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

Microglia, the primary immune cells and the sensor of the brain's health, play a pivotal role in the maintenance of brain homeostasis, but lose their functions during the course of aging and neurodegenerative diseases. There is a gap in our knowledge about how microglial function is maintained in healthy brain and is prone to dysregulation in Alzheimer's disease. There is also a lack of understanding how a prominent genetic risk factor, apolipoprotein E (APOE), is involved in microglia regulation and function. Human APOE has three common alleles, and the e4 allele is the major genetic risk factor for sporadic late-onset AD, with women being more affected than men.

How the different APOE alleles affect microglia functions in AD has not been investigated. This application will investigate the role of human APOE alleles in microglia as potential therapeutic targets of AD. We specifically will delete human APOE alleles in microglia in mouse models of neurodegeneration. In

addition, we will analyze the effect of APOE alleles on peripheral monocytes. We already found that in mice APOE is important in regulating peripheral monocytes. This regulation is clearly different between males and females, which is why it will be important to study gender differences in our investigation.

Impact of APOE and Sex on Vulnerable Neuron-Specific Functional Networks

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

Apolipoprotein E (APOE), the most important genetic predisposition factor for Alzheimer's disease, seems to have direct effects on the formation of amyloid plaques but also many other plaque-independent effects on different types of brain cells, including on neurons. The precise mechanisms of these effects are not known. We have developed tools—a set of genetically engineered mice (so-called bacTRAP mice)—to make the full inventory of all proteins present in any specific type of neuron, in particular in neurons that display differential vulnerability to neurodegeneration.

In this proposal we set out to understand the effects of different alleles of APOE—the risk allele APOE4 as well as the protective allele APOE2—on the most vulnerable neurons of the brain, entorhinal cortex layer II (ECII) and hippocampal CA1 neurons. For that purpose, we first need to breed Cure Alzheimer's humanized APOE mice with our genetically engineered bacTRAP mice for two generations. We obtained the first generation already, and are now setting up the second generation in that breeding scheme.

We will use these crossed mice to comprehensively profile ECII and CA1 neurons in the presence of the different human alleles of APOE, and in both female and male mice, since we have evidence that ECII neurons could display different profiles in males and females, because they are equipped with sensors for estrogen. More specifically, we will investigate if the human risk allele of APOE is putting ECII neurons in an increased vulnerability state compared with the neutral or the protective alleles of APOE.

Understanding the Effect of APOE on Tau-Mediated Neurodegeneration

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

APOE is the strongest genetic risk factor for Alzheimer disease. APOE4 increases risk and APOE2 decreases risk. The Holtzman lab recently found that, in addition to the effect of APOE on amyloid beta, APOE exacerbates tau pathology and tau-mediated brain damage.

The goal of the current grant is to determine whether decreasing the level of APOE in the adult brain using different methods will lessen the brain damage that is caused by the buildup of the tau protein. The mice required to attain the goal have been produced over the first year of the grant. During the second year, we will be able to answer the question whether decreasing APOE levels in the adult brain is an effective way to attenuate brain injury to the buildup of the tau protein.

Alzheimer's Disease-Associated Mutations in Protein Kinase C

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

The research supported by Cure Alzheimer's Fund has shown that a key protein that is 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 Rudolph Tanzi, Ph.D., revealed 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.

Behavioral Phenotyping and Evaluation of Sleep-EEG in Transgenic Mice

PSYCHOGENICS

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

Role of Ataxin-1 in Regulating BACE1 Activity

JAEHONG SUH, PH.D., Massachusetts General Hospital

DNA mutations that increase the length of a certain part of Ataxin-1 gene (ATXN1) is known to cause spinocerebellar ataxia type 1 (SCA1), a neurodegenerative disease that primarily impairs coordinated movement and deteriorates cognitive function in patients. In a recent genetic study of Alzheimer's families, our research group found ATXN1 also is associated with Alzheimer's disease. In this project, utilizing mouse models, we found Ataxin-1 plays a key role in regulating BACE1 expression in the brain. BACE1 is an enzyme to cleave the amyloid precursor protein (APP) and initiates the first step to generate amyloid beta, the main culprit of senile plaques in AD brains. We found Ataxin-1 regulates the transcription of BACE1 in AD-vulnerable brain regions, and the lack of Ataxin-1 can increase amyloid beta plaque deposition in the brain. We also discovered the loss of Ataxin-1 can lead to, potentially through BACE1 regulation, severe deficits in newborn neuron generation and neuronal wiring. These two impairments in the brain, as well as the accumulation of amyloid beta, would establish a predisposition to AD.

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.

Functional Characterization of GGA3 Mutations Associated with Alzheimer's Disease

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

Neurons, highly organized brain cells, are characterized by specialized projections called dendrites and axons. The axon is the longest neuronal projection where proteins move like along a highway, in two different directions and at different speeds. Scientists demonstrated that in the brain of subjects affected by Alzheimer's disease, a disorder characterized by memory loss, this coordinate traffic doesn't work properly, so neurons start to be unhealthy and die. Our goal is to try to understand why this traffic no longer is functioning in order to find a way to prevent the neuronal traffic disruption and possibly find a treatment for Alzheimer's disease. The aim of this study is to determine the extent to which mutations in a trafficking molecule called GGA3 may lead to disruption of protein movements in the axon, ultimately causing neuronal death.

Genes to Therapies™ (G2T) Centralized Research Core

WILMA WASCO, PH.D., Massachusetts General Hospital

The Cure Alzheimer's Fund Genes to Therapies™ group 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 at large. Providing these mouse models and other appropriate reagents to investigators not only will remove the time and effort necessary for each investigator to generate his or her own mouse models and reagents, but importantly, it will ensure all investigators are working with animal models that are consistently and reliably generated, documented and maintained.

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

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

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

PICALM Gene Therapy and Drug Screening for Amyloid Beta Clearance

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

PICALM is highly associated with late-onset AD based on genome-wide association studies. PICALM facilitates clathrin-mediated endocytosis and regulates the internalization and intracellular trafficking of cell surface receptors. Its N-terminus contains an epsin NH2-terminal homology domain for phosphatidylinositol-4,5-bisphosphate binding, which allows PICALM to sense membrane curvatures and regulate the size of clathrin-coated vesicles. These functions are central to its role in amyloid beta transvascular clearance across the blood-brain barrier and tau through autophagy. PICALM is highly expressed in brain endothelial cells and neurons.

We showed that diminished PICALM levels at the BBB in mice accelerated amyloid pathology and behavioral deficits, which can be ameliorated by endothelial re-expression of PICALM using an adeno-associated virus (AAV). In neurons, PICALM regulates internalization and intracellular trafficking of both amyloid precursor protein and the APP-cleaving enzyme gamma-secretase, thereby modulating amyloid beta production. Importantly, PICALM directly protects cultured neurons against amyloid beta toxicity. We confirmed these findings *in vivo* in Picalm +/-; APP Swe mice that show impaired amyloid beta transvascular clearance across the BBB, accelerated amyloid beta pathology and behavioral deficits compared with their littermate controls expressing normal levels of PICALM in brain endothelium and neurons.

Since PICALM protects against development of amyloid beta pathology and cognitive impairment in mice, we hypothesized that gene therapy and/or an FDA-approved drug hit that enhances PICALM expression will increase amyloid beta clearance across the BBB, reduce amyloid beta neurotoxicity and improve cognitive functions in Alzheimer's disease mouse model. In studies previously supported by Cure Alzheimer's Fund, we have validated that AAV-PHP.B-mediated global gene delivery to the brain is superior compared with AAV2-BR1 viral vectors-mediated endothelial gene delivery. We also have performed high-throughput screening that led to 17 hits from an FDA-approved drug library that are capable of upregulating PICALM expression *in vitro*. We confirmed four hits from secondary screening in endothelial cells and further selected one final candidate (T-65) for *in vivo* efficacy testing in PICALM +/-;5xFAD mice. Our *in vivo* data preliminarily demonstrated that administration of T-65 ameliorated amyloid beta pathology and improved cognitive functions in PICALM +/-;5xFAD mice, suggesting that T-65 is a potential drug for AD. Therefore, we propose to continue examining the potential of using AAV-PHP.B-PICALM as a gene therapy for AD, and to fully validate the efficacy of T-65 in a mouse model of AD, under the following two specific aims:

AIM 1: To determine whether gene therapy with AAV-PHP.B-PICALM in PICALM +/-; 5xFAD mice will increase PICALM expression, reduce amyloid beta pathology and improve cognitive functions.

Hypothesis: AAV-PHP.B-PICALM systemic administration will increase PICALM levels in both brain endothelium and neurons, which will enhance amyloid beta transvascular clearance across the BBB and alleviate direct amyloid beta toxic effects on neurons, therefore reducing AD-like pathologies including amyloid burden and neuronal loss, as well as improving hippocampal-dependent learning and memory in PICALM +/-;5xFAD mice model, when compared with AAV-PHP.B-GFP treated mice.

AIM 2: To determine whether an FDA-approved drug T-65 can upregulate PICALM expression *in vivo*, increase amyloid beta clearance, reduce amyloid beta pathology and improve behavioral deficits in AD mouse models.

Hypothesis: Our top drug hit T-65 (which we show upregulates PICALM expression in the mouse brain endothelium) will enhance amyloid beta transvascular clearance via BBB and improve hippocampal-dependent learning and memory in PICALM +/-;5xFAD transgenic mice, but not in PICALM lox/lox; Cdh5 -Cre; 5xFAD mice (with both alleles of PICALM gene deleted from brain endothelium), when compared with vehicle-treated littermate controls.

Genetics

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

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

This project supports the data analysis efforts of the Cure Alzheimer's Fund whole-genome sequencing project in the National Institute of Mental Health family study. It develops the necessary statistical methodology to fully utilize the wealth of genetic information contained in the whole-genome sequencing studies for rare variant analysis. This study develops new methodology that take into consideration the sparseness of the data and does not require asymptotic approximations. This project aims to employ a new algorithm for family-based studies that is computationally efficient and can be applied to whole-genome sequencing scans in family samples with sample sizes of several thousand. The new algorithm enables the exact genetic variance to be computed. This new algorithm, along with the software, has been made publicly available via the FBAT (family-based association test) package.

The Impact of Alzheimer's Disease-Associated Genetic Variants in 3-D Human Mixed Neural-Glial Models of Alzheimer's Disease

JOSEPH PARK, PH.D., Massachusetts General Hospital

A growing number of Alzheimer's disease-associated genes are linked to innate immunity and neuroinflammatory pathways. Microglial gene networks are strongly associated with AD neuropathology. Using whole-genome sequencing and whole-exome sequencing datasets have revealed variants in Alzheimer's disease-associated microglial genes that include CD33, TREM2, PILRA/B, MS4A cluster, ABCA7 and CR1, to name a few. Whole-exome sequencing is a genetic technique for sequencing all of the protein-coding genes in a genome. Using these datasets as well as our novel human neuron-astrocyte-microglia triculture AD model referred to commonly as "Alzheimer's in a Dish," we will validate the effects of microglial AD-risk gene mutations and identify novel mechanisms of the disease related to innate immunity and neuroinflammation.

Alzheimer's Genome Project™

RUDOLPH TANZI, PH.D., Massachusetts General Hospital

As new Alzheimer's disease-associated gene variants are found within the four known AD genes—APP, PSEN1, PSEN2 or APOE—the variants are tested for effects on AD pathology (plaques, tangles and neuroinflammation) in our Alzheimer's in a Dish models. We also use the identified genes in bioinformatic analyses to identify functional pathways involved in AD pathology, and existing drugs and natural products that may slow, stop or reverse the progression of neurodegeneration in AD. This testing also occurs for the 35 confirmed AD genes identified from genome screening, e.g., CD33 and TREM2, or rare AD candidate genes, e.g., ATXN1 and GGA3. We continue to analyze our database of approximately 1.5 petabyte of whole-genome sequence (WGS) and whole-exome (WES) data from our own and other currently available family-based and case-control AD samples with the goal of identifying novel AD genes and AD-associated genomic variants that affect gene function. These include genomic variants in existing and novel AD genes that are either common or rare (<1 percent) in the population. The WGS and WES data are being obtained from multiple datasets. First, we look for association with AD in a "discovery" set, consisting of the National Institute of Mental Health AD family sample and National Institute on Aging AD family sample. We then attempt to validate these findings in a "replication" set, consisting of WGS data from the Alzheimer's Disease National Imaging sample and WES of the Alzheimer's Disease Sequencing Project sample.

Identification

Early detection via biomarkers, imaging, etc.

Neurobiological Basis of Cognitive Impairment in African Americans: Deep Phenotyping of Older African Americans at Risk of Dementia

HENRY PAULSON, M.D., PH.D., University of Michigan
BRUNO GIORDANI, PH.D., University of Michigan
BENJAMIN HAMPSTEAD, PH.D., University of Michigan

The activities of the Michigan Alzheimer's Disease Center seek to explore the neurobiological basis of dementia in African Americans, an understudied population. These research efforts intend to uncover fundamental knowledge about biomarkers of cognitive impairments. The focus of this research will be to determine whether vascular dysfunction and increased amyloid and/or tau deposition have independent or synergistic effects on cognition. The information obtained will be used to design both novel pharmacological and nonpharmacological interventions. This study intends to provide information about targeted enrollment for interventions of this nature.

Imaging Microglial Homeostasis and Disruption: P2RY12 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 P2ry12-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.

Alzheimer's Disease Pharmacomics in 3-D

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

This project is a part of the three-dimensional cell culture consortium (3DDS) supported by Cure Alzheimer's Fund for the purpose of drug screening. The next two years of the project will focus on refining the Alzheimer's in a Dish model while using it to assess the impact of genetic variants in microglial-associated genes. This research will test newly identified molecules, including those from a library of natural compounds, to understand whether they can be optimized to reverse disease progression. Finally, this project will assess the potential of specific inhibitors of microglial activity in ameliorating Alzheimer's disease, with a focus on expanding the Alzheimer's in a Dish model to include more of the cell types and structures implicated in Alzheimer's disease. Of note, materials from both female and male patients with Alzheimer's disease will be used in order to provide a more complete picture of the disease.

Immune System Structures and Processes

Role of inflammation and other responses in AD

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., University of California, San Diego
PASCAL GAGNEUX, PH.D., University of California, San Diego
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Humans are 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 called microglia. Such recognition by a Siglec called "CD33" already is known to regulate immune reactions that are important in late-onset AD risk and progression; 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 forms of Alzheimer's. We propose a detailed structural and functional exploration of the many human variations in CD33, which may reveal other protective forms that may identify novel therapeutic approaches.

The Role of the Contact System in Alzheimer's Disease

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

Impairments with the blood vessels in the brain are common in Alzheimer's disease and are thought to contribute to cognitive decline. This proposal seeks to further understand the blood-based system called the contact system and its role in Alzheimer's disease. The contact system is involved in blood clotting and inflammation, and is activated in patients with Alzheimer's disease. It is thought that the contact system contributes to disease pathology in mouse models of Alzheimer's. A better understanding of the contact system has the potential to improve diagnosis in patients with vascular contributors to dementia. In addition, this proposal seeks to explore the potential of targeting the contact system as a novel treatment strategy.

Study of Reactive Astrocytes-Derived Oxidative Stress and Microglial Neurodegenerative Inflammation in Alzheimer's Disease

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

Over the past couple of decades, we have learned a great deal about the mechanisms of Alzheimer's disease pathogenesis, but many critical questions remain unanswered. As the recent failures of clinical trials in AD have raised questions as to the amyloid hypothesis validity, the "neuroinflammation hypothesis" begins to gain attention to explain AD pathogenesis. More research into the interactions between astrocytes and microglia—key players of the innate immune system—is required. Immune cells are dynamic and complex, giving rise to challenges in characterizing their function. The goal of this project is to determine the significant impact of astrocyte-derived oxidative stress on microglial inflammation and neurodegeneration during progression of Alzheimer's disease. To achieve the goal, we will create a physiologically relevant human Alzheimer's disease brain model by adopting human-induced pluripotent stem cell-derived AD neural progenitor cells. This project subsequently will investigate how oxidative stress is induced by reactive astrocytes in response to AD cues. Finally, this research will determine the involvement of oxidative stress in microglial neurodegeneration. Taken together, the application of technologies and quantitative analysis tools to create 3-D microfluidic cellular platforms of human AD brain models (Alzheimer's in a Dish) will allow us to explore the pathways underlying AD pathology. We expect these experiments to aid in identifying new points for therapeutic intervention in the treatment of the disease.

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

WON-SUK CHUNG, PH.D., KAIST Korea Advanced Institute of Science and Technology

How can we restore impaired brain homeostasis in Alzheimer's disease? Previously, we have found that astrocytes, a star-shaped glial cell of the central nervous system, participates in clearing synaptic and neuronal debris in the brain. Through research funded by Cure Alzheimer's Fund, we uncovered that astrocytes lose their capacity to clear out amyloid beta when they are pre-exposed to amyloid beta oligomers. These data suggest that one of the potential reasons for amyloid beta accumulation in AD is that the initial production of amyloid beta oligomers may change the gene expression patterns of astrocytes. This change in gene expression reduces their ability to uptake amyloid beta. By examining changes in mRNA expression of astrocytes with or without the pre-exposure to amyloid beta, we have found several critical candidate genes, including LDLR, which can be responsible for the reduced uptake by astrocytes. In the next funding period, we are aiming to test the following hypothesis: restoring astrocyte-mediated engulfment in the early AD brain reduces the accumulation of debris as well as amyloid beta burdens. We think our research will provide new therapeutic strategies in treating AD by correcting defective functions of astrocytes.

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 is primarily 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. In order 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.

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 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 studies, 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 AD 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. The proposed studies will use powerful new experimental and computational approaches to directly examine whether DNA sequences associated with risk of AD 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 AD and may lead to identification of new therapeutic targets.

Role of Microglial Matricellular Protein SPARC in Control of Inflammasome Activation

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

The process of aging is the single biggest risk factor for development of Alzheimer's disease. The development of inflammation in a specialized brain cell type called microglia is thought to be responsible for neuronal death and dementia. This proposal will study a novel protein that controls inflammation in microglial cells to develop new approaches to protect against age-related loss of memory and cognition. This research builds on the idea that late-onset chronic diseases such as Alzheimer's disease are the consequence of the prolonged overworking of various tissues with vulnerabilities. Proteins such as SPARC that are highly expressed in microglial activation could be a target for protecting against age-related loss of memory and cognition.

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

ANA GRICIUC, PH.D., Massachusetts General Hospital

High-throughput screens are scientific methods that enable hundreds of thousands of experimental samples to be tested under identical conditions. They are used to identify the targets that modulate a specific biological pathway. Using this technology, medications were identified that increased amyloid beta uptake and maintained an anti-inflammatory state in the brain. One of the regulators of amyloid beta clearance in Alzheimer's disease is a microglial regulator called CD33. The screen identified CD33-specific antibodies that dramatically reduced CD33 levels. 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. Effective anti-inflammatory medications and CD33 inhibitors have the potential to provide a novel therapeutic approach for Alzheimer's disease.

The Neuroprotective Glial Barrier: A Multicellular Reaction with Therapeutic Potential in Alzheimer's Disease

JAIME GRUTZENDLER, M.D., Yale School of Medicine

Our research group has discovered that microglia play a critical role in compressing and insulating amyloid plaques. This process renders the plaques less toxic to adjacent neurons. This proposal seeks to use sophisticated live-imaging and high-resolution microscopy combined with molecular manipulations to investigate how microglia interact with astrocytes during the protective encapsulation of amyloid plaques. The hypothesis for this research is that the coordination between these two glial cells, astrocytes and microglia, is critical for preventing damage to the long, threadlike part of a nerve cell called an axon that propagates an electrical signal to the synapse. The hope is that understanding this interaction will enable a therapeutic intervention to diminish the progression of neural dysfunction in Alzheimer's disease.

Neuroimmune Molecular Imaging: Redefining the Landscape of Opportunities in Alzheimer's Disease

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

Cure Alzheimer's Fund has recognized the importance of studying the relationship between the brain and its immune system in Alzheimer's disease. The immune system is likely the next target of drugs to treat this intractable disease. There are huge gaps that exist in this emerging field, and CureAlz is committed to filling them by linking experts across the field in a consortium that will work together. The goal of this proposal is to begin filling a technology gap. More specifically, this proposal addresses the essential need to be able to see into the AD brain, since we cannot access it through biopsy. The ability to image immune processes that are elucidated and being studied in model systems and in post-mortem brain tissue from consortium members supported by CureAlz is essential. However, the data magnitude is overwhelming and there is no clear, persuasive starting point for the technology development. Rather than make assumptions about what targets in the brain immune system can and should be imaged, we will mine existing public and CureAlz scientist data to prioritize targets for imaging the brain. We will use this process to develop a road map to the technologies of the future for brain immune imaging. Ultimately, these road maps will lead to new radiotracers for brain imaging to translate the basic research knowledge to patient observation, and ultimately care and treatment. This proposal is a critical nine-month primer to the launch of a full-scale imaging agent development project.

Microglial TAM Receptors as Modulators of Alzheimer's Pathology

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

Unrestrained inflammation of the central nervous system precipitates and exacerbates a wide range of debilitating neurodegenerative diseases, including Alzheimer's disease. Our understanding of the mechanisms that regulate neuroinflammation is incomplete. Microglia perform two activities that are crucial to the regulation of neuroinflammation: 1) the inhibition of neurotoxic inflammatory cytokines and chemokines; and 2) the engulfment of dead cells and membranes. Multiple lines of evidence demonstrate that these microglial activities are controlled by signaling through Tyro3, Axl, MERTK (TAM) receptor tyrosine kinases. Receptors for TAM are called Axl and Mer.

In Alzheimer's disease, the expression of these genes in microglia is elevated. This elevation is thought to be in order to restrain the disease. Through experiments supported by Cure Alzheimer's Fund, it was found that a key ligand of TAM associates with plaques. The loss of a TAM receptor, Mer, in the APP/PS1 mouse model of Alzheimer's seriously worsens the disease. Several drugs that inhibit TAM inhibitors are given to patients as a cancer therapy without considering the effect on Alzheimer's disease. This research will address the role of microglial TAM receptors in the engulfment of Alzheimer's-related plaques.

Neurotoxic Reactive Astrocytes in Alzheimer's Disease

SHANE A. LIDDELOW, PH.D., New York University Langone Medical Center

The brain is composed of neurons that transmit signals to enable thought, memory and motion, as well as glial cells, which provide support to neurons and outnumber them at least 2-to-1. Recent genetic association studies have implicated many disease-associated genes in patients with Alzheimer's disease that are almost exclusively associated with glial cells. One type of glial cell, astrocytes, are the most abundant cells in the brain. They deliver nutrients and support to neurons, and provide the environment necessary for neurons to correctly wire together and transmit signals. During diseases like AD, these astrocytes become "reactive," switching from a supportive state to a diseased state, secreting a toxin that can actively kill neurons. We have recently localized this toxin reactive state of astrocytes to regions of dead and dying neurons in both animal models of AD as well as in human patients. These observations suggest that the altered function of "reactive astrocytes" likely plays a causative role in either the initiation or progression of AD.

The proposed studies employ powerful single-cell sequencing technologies to determine how many populations of reactive astrocytes exist in the human brain. In addition, we will investigate the role that neurotoxic reactive astrocytes have in both the initiation and the progression of AD. Results from these studies will give us a better understanding of basic astrocyte biology in the context of AD and will provide new targets for development of therapies.

Temporal Analysis of Infection in Alzheimer's Disease Models

JUDITH STEEN, PH.D., Boston Children's Hospital

Infection as a cause of Alzheimer's disease has been debated for decades; however, the connection between infection and the molecules tau and amyloid beta, which are associated with the hallmarks of the disease, is not clear. Proteins are the machines that largely keep our bodies functioning, and in AD and other neurodegenerative diseases, proteins such as tau and amyloid beta become chemically modified and malfunction. The Steen lab is large-data driven—we collect and mine quantitative protein datasets of approximately 10,000 proteins from human brain tissues and cells using a unique analytical and informatics platform that we developed. Recently, we used this approach to study more than 130 post-mortem patient brain tissue samples with AD, other tauopathies and control tissues. Strikingly, our network analysis of the data showed a strong response for AD patients and identified specific molecules associated with microbial infection. This supports the study from the Moir and Tanzi labs that described a role of amyloid beta peptide as an antimicrobial agent, thereby linking a molecule that is genetically associated with AD as having a role in the response to infection. This and other data in the literature lead us to hypothesize that infection plays a major role in AD. To further investigate this hypothesis, we propose the study of the infection process in both a mouse AD model and a human neuronal cell model to understand the temporal events of infection of neuronal cells at the molecular level. Our proteomics and informatics platform identifies and quantifies a large proteome and currently surpasses any other platform applied to neuronal/brain samples with respect to the depth of the proteome. Thus, the data enables the identification of key molecules responsible for disease. By identifying molecules in the infection process that result in the death of neurons, we can intervene in the progression of disease and cognitive decline.

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 post-mortem 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

Relatively recent research has shown that the immune system is an important component of Alzheimer's disease. Specifically, interspersed throughout the brain among and between the neurons are immune cells called microglia that reside in the brain throughout life and participate in many normal functions, but that also can be critical in AD. Understanding microglia in AD is therefore vital, as it 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. For this application, we have generated preliminary data suggesting that a specific molecule, a growth factor and cytokine called IL-3, is protective in AD. We show that a cluster of immune cells called mast cells inhabiting specific locations on the periphery of the brain produce IL-3, which then activates microglial cells, instructing them to remove harmful amyloid beta plaques, the accumulation of which is thought to lead to the development of the disease. In the absence of IL-3, however, microglia are unable to find amyloid beta plaques, which worsens disease. IL-3, therefore, might be an important therapeutic in AD. This application will elucidate the role of IL-3 in animal models of AD.

Targeting Beneficial Innate Immunity in Alzheimer's by Interleukin-1 Receptor-Associated Kinase M Deletion

TERRENCE TOWN, PH.D., University of Southern California

A defining feature of Alzheimer's disease is brain accumulation of toxic plaques that induce memory loss. In the healthy brain, innate immune cells are protective; however, in Alzheimer's patients' brains, these cells fail to prevent plaque formation. Innate immune cells express a molecule named Interleukin-1 receptor-associated kinase M (IRAK-M) that ensures immune responses to invading bacteria and viruses are kept under tight control. Yet, this type of immune response is dysfunctional in the Alzheimer's patient brain. Our hypothesis is that rebalancing the brain's immune response by blocking IRAK-M will enable plaque clearance. With Cure Alzheimer's Fund's support throughout 2017, we now report that removal of the anti-inflammatory IRAK-M gene from mice that develop amyloid plaques with age restores deficits in learning and memory. Thus far, this project has provided crucial data on the role of IRAK-M and the innate immune system in Alzheimer's disease, and we seek an additional year of funding to expand on this work to deeply understand the nature of this beneficial brain immune response. This important work represents a major step toward developing a novel immunological therapy for this devastating disorder of the mind.

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.

Other

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

Effects of Cerebrovascular Insufficiency and Exercise on the Alzheimer's Brain

ENG H. LO, PH.D., Massachusetts General Hospital

Vascular comorbidities occur in almost two-thirds of Alzheimer's disease patients. The ways in which cerebrovascular insufficiency interacts with and contributes to Alzheimer's disease remains unknown. Although significant advances have been made in terms of developing Alzheimer's disease transgenic mice to investigate amyloid and tau mechanisms, a rigorous and systematic mapping of vascular profiles in Alzheimer's mouse models is lacking. This project will for the first time provide a map of the *vasculome* in Alzheimer's disease mouse models. In addition, this research will develop and characterize Alzheimer's disease mouse models that include vascular insufficiency. This project will culminate in testing the effects of exercise as an intervention that could potentially rescue the diseased *vasculome* in the Alzheimer's brain.

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

Of every three patients with Alzheimer's disease, two are 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. This project seeks to unravel the biological mechanism that increases AD vulnerability in women by using a novel brain imaging technique that allows quantification of energy production in the brain.

Scientific Directions for the Exploration of Racial Disparities in Alzheimer's Disease

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

Although the U.S. population is increasingly diverse, virtually all research studies into the diagnosis and treatment of Alzheimer's disease and related dementias are conducted with non-Hispanic white volunteers. We will convene expert panels to develop the scientific rationale for the study of possible racial differences in

the risk, expression and causes of Alzheimer's disease, and a road map to do so. To begin, we will explore the differences between non-Hispanic whites and African Americans, the largest under-represented group in AD research in the United States.

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

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 its relation to the increased risk for Alzheimer's disease. We have previously demonstrated the feasibility of generating human neurons by ectopically expressing small RNA molecules, termed microRNAs, in dermal fibroblasts and altering the "fate" of cells directly to neurons. The overall goal of this 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 the 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, including Huntington's disease. Also, this 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.

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

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

Multiple factors will cause or contribute to synaptic dysfunction in Alzheimer's disease. The excessive production or accumulation of amyloid beta peptide has been documented to have deleterious effects on synaptic activity by various mechanisms. Many scaffolding proteins like mGluR proteins, Shank, Homer and postsynaptic density 95 are known to form complexes at synaptic terminals, and amyloid beta accumulation at synaptic terminals leads to disruption of these scaffolding protein interactions. Synaptic changes occur prior to the detection of brain plaques and behavioral changes associated with cognitive deterioration in Alzheimer's disease. Alzheimer's disease is recognized as a disease of synaptic failure. This project proposes the development of an optical imaging method for detection of early changes in synaptic function occurring in animal models of Alzheimer's disease.

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

Alzheimer's disease is the most common cause of dementia in the elderly. It is characterized by the accumulation of amyloid beta in amyloid plaques and hyperphosphorylated tau in neurofibrillary tangles. Vascular factors increasingly are being recognized as an underlying contributor to Alzheimer's disease. Dietary salt has emerged as a risk factor for stroke, white matter disease and cognitive impairment, independent of hypertension. A high-salt diet leads to a reduction in endothelial nitric oxide. Nitric oxide is a key mediator of vascular tone in the brain and is associated with profound cognitive impairment in mice. It is not known how the endothelial dysfunction caused by a high-salt diet affects cognitive function. Research suggests a potential link between a deficit in endothelial nitric oxide and tau phosphorylation. Considering this potential link, it is conceivable that a high-salt diet might promote cognitive impairment through tau phosphorylation. The focus of this research is on investigating the possibility that a high-salt diet-induced endothelial dysfunction induces cognitive impairment by suppressing endothelial nitric oxide production. This suppression likely leads to activation of signaling pathways that increase tau phosphorylation and pathology. Elucidating how endothelial dysfunction induces cognitive impairment may implicate a previously unlinked mechanism of vascular health to tau pathology and cognitive impairment in Alzheimer's disease.

Pathological Pathways and Systems

Cell Cycle Re-Entry in 3-D Human Neuron Cultures

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

Our laboratories have been attempting to unravel the key molecular pathways that convert normal, healthy neurons into dysfunctional neurons. We have made progress toward understanding what may be the most common pathway for neuronal death in Alzheimer's disease: cell cycle re-entry, or CCR. CCR refers to the abnormal reactivation of a process normally reserved for neuronal cell replication. Whereas normal neurons in most of the brain never attempt to divide, up to 5 percent to 10 percent of the neurons in brain regions affected by Alzheimer's disease show signs of CCR over the course of many years. Instead of dividing, these CCR neurons eventually die, and may account for as much as 90 percent of the neuronal loss seen in AD. We have found that CCR is initiated by soluble amyloid beta oligomers, which are the building blocks of the insoluble amyloid plaques that accumulate in AD brain, and that it requires soluble forms of tau, the protein that aggregates inside AD neurons, to form insoluble neurofibrillary tangles. In the next funding period, we will exploit innovative 3-D models to screen "libraries" of small molecules for compounds that can inhibit CCR, and thus have the potential to become drugs that prevent or slow progression of AD.

Amyloid Beta-Mediated Inhibition of Gamma-Secretase Activity Induces Alzheimer's Disease-Relevant Cellular Phenotypes

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LUCÍA CHÁVEZ-GUTIÉRREZ, PH.D., VIB-KU Leuven Center for Brain & Disease Research

Proteolysis refers to the breakdown of proteins into smaller polypeptides or amino acids. Two proteolytic products that are derived from the amyloid precursor protein, C99 and amyloid beta-42, play defining roles in Alzheimer's disease. One angle for preventing Alzheimer's disease clinically is to define how these APP-derived products, especially amyloid beta-42, accumulate in the brain and contribute to disease progression. Our research suggests that an increase in C99 deranges endosome structure and function. Endosomes are membrane-bound structures within a cell that are important for neuronal function and survival. Preliminary data raises the possibility that endosomal dysregulation may occur through an increase in C99 levels that occurs during processing by gamma-secretase. We aim to characterize the cellular consequences of lack of processing of gamma-secretase substrates, including C99. We will employ gamma-secretase modulators, discovered under Cure Alzheimer's Fund and National Institutes of Health funding, to demonstrate the extent to which GSMs mitigate or prevent amyloid beta-mediated inhibition of gamma-secretase activity. Our studies promise unique insights into AD pathogenesis and the therapeutic utility of GSMs.

The Role of Neurexins in Alzheimer's Disease

RUDOLPH TANZI, PH.D., Massachusetts General Hospital
MENG CHEN, PH.D., Massachusetts General Hospital

Alzheimer's disease is the most common form of dementia among the elderly. Current studies strongly support the notion that abnormal processing of amyloid beta and accumulation of amyloid beta peptide are the critical events that are associated to the AD pathogenesis. However, the mechanisms of how amyloid beta accumulates at the synapse and induces synaptic deficits in the AD brain largely are unknown. We recently have identified the presynaptic proteins neurexins as amyloid beta precursor protein (APP)-binding proteins by using an unbiased proteomic screen. Biochemical analysis has been applied to further confirm the interaction between neurexins and APP. Importantly, our preliminary results in cells have shown that modification of neurexin levels alters APP processing and amyloid beta generation. Meanwhile, a family-based genome-wide association testing (GWAS) study has determined that all three NRXN genes (NRXN1, NRXN2 and NRXN3) contain susceptibility loci for late-onset AD. Therefore, the goal of this study is to investigate the role of neurexins in the development of amyloid pathology and amyloid beta-induced synaptic dysfunction in AD.

Identifying Blood-Brain Barrier Enhancers and Role of Neutrophils in a 3-D BBB Vascularized Model of Alzheimer's Disease

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

Neuroinflammation is a pathological hallmark of Alzheimer's disease. In Alzheimer's patients, the number of neutrophils is increased on the walls of the blood vessels. Neutrophils are a type of white blood cell that protect the human body from infections. In an Alzheimer's mouse model, neutrophils are found near amyloid plaques. Our laboratory has taken a crucial next step in the development of a model for Alzheimer's disease that recapitulates the multifaceted pathologies of the disease. We have developed a physiologically relevant 3-D human neural cell culture model of Alzheimer's disease that models the blood-brain barrier. Using this model for the blood-brain barrier, we will explore how neutrophils interact with the BBB and neurons to understand how neutrophils influence the progression of Alzheimer's disease. We also propose to test the drugs identified in our 3-D AD-BBB models in mouse models for Alzheimer's disease.

Reversal of Tau Pathology by an Adenosine A1 Receptor Antagonist

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

The loss of memory at advanced age that is typical of Alzheimer's disease begins silently and progresses steadily over a long period of time. During this time, misfolded protein clumps (amyloid plaques and tau tangles) build up in the brain. The currently available drugs only modestly can slow down failing memory,

but they cannot reverse the process and bring memory back. Most work on animal models of AD confirms this seemingly irreversible progression of the pathology. However, there are exceptions: one is the discovery that certain drugs that bind to a class of adenosine receptors on neurons (AdoRA1) can restore memory in transgenic mice with memory impairments. This project will test a specific blocker of AdoRA1 called rolofylline to see whether it reverses the aggregation of tau and enhances neuronal activity.

Senescent Cells and Alzheimer's Disease

DARREN J. BAKER, PH.D., Mayo Clinic Rochester

Aging is the greatest risk factor for Alzheimer's disease. One potential culprit driving age-associated pathologies are senescent cells (ScCs). Cellular senescence refers to the phenomenon by which normal cells stop dividing. These cells accumulate with advancing age and are found at the locations of dysfunction in age-related diseases.

It is thought that senescent cells are not simply innocent bystanders and may in fact be driving tissue deterioration. One proposed mechanism for the involvement of senescent cells is the acquisition of a senescence-associated secretory phenotype, SASP. This condition refers to a state where senescent cells produce and secrete a variety of growth factors and pro-inflammatory cytokines. Senescent cells have been shown to shorten life and actively drive age-related neurodegeneration in mice; along with neurofibrillary tangles and amyloid beta plaques, Alzheimer's patients have exhibited increased indicators of cellular senescence. Treating mice to prevent senescent cell accumulation decreased tau-dependent degeneration and cognitive decline. With the potential for senescent cell pharmacological modulation on the horizon, it is imperative to determine whether removal of senescent cells in Alzheimer's mouse models has a beneficial impact.

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

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

Alzheimer's disease is the leading cause of dementia. It has been suggested recently that dysfunction of the blood vessels in the brain may be an important component of this disease; however, very little is known about how blood vessels in the brain change during Alzheimer's disease and how this may contribute to the onset and progression of dementia. We aim to determine how the blood vessels in the brain change during Alzheimer's and how these changes affect the brain. Our ultimate goal is to determine whether the blood vessels in the brain may be a potential therapeutic target to treat patients with Alzheimer's disease.

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

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

It is unknown why neurodegenerative diseases such as Alzheimer's disease are progressive. It is clear that neurodegeneration in AD is caused by accumulation of the protein tau in highly ordered assemblies, or aggregates, inside neurons. Our work and that of many labs around the world suggests that progression of AD is due to these aggregates escaping one cell and moving to others, where they are taken up. Once inside the second cell, the aggregate acts like a pathological crystal, or "seed," interacting with normal protein and converting it to an abnormal, aggregated form. This idea can explain why neurodegeneration starts in a defined area of the brain and spreads inexorably through it. In 2013, we originally determined the mechanism by which tau binds the cell surface to enter and corrupt normal protein on the cell interior. This involves tau aggregate binding to specific cell surface "receptor" proteins, which have to go through a defined cellular processing pathway to become functional. Multiple processing enzymes modify the receptors in a stepwise fashion. Once tau aggregates bind these surface receptors, they trigger their own uptake. This process is not well understood, and appears to involve multiple signaling pathways. Each step in this pathway might represent a "pressure point" to stop the progression of AD. This proposal extends our prior work in this regard. Whereas our first study tested 23 genes in a defined pathway important for uptake of tau, we now have individually tested virtually every gene in the human genome. We have identified approximately 900 new candidate genes that must be validated in further tests, but promise to improve our therapeutic options for AD. We also will use mouse models to definitively test the candidate genes that we identified in the prior years.

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 in the elderly. This project will perform detailed quantitative pathologic and biochemical studies in a large series of human postmortem 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 postmortem (N=54), cognitively intact individuals whose postmortem exam demonstrated significant amounts of AD changes ("resilient") (N=59), and typical demented AD patients (N=53). 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 phosphor-tau 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 results 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 think the studies proposed here will 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.

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

Alzheimer's disease is the most prevalent neurodegenerative disorder in the world. It is characterized by the presence of senile plaques and the formation of neurofibrillary tangles. Neurofibrillary tangles are found in neurons and are made of filamentous tau protein, which normally binds to axon molecules, yet is aggregated in damaged neurons in the brain. It has been shown recently that tau aggregation can be transmitted from one neuron to another. It is unknown how the tau protein is transported between neurons and whether this transmission is due to the direct transport of tau protein through synapses or is mediated by other cells, such as glia, in the brain.

We hypothesize that small nanometer-scale vesicles secreted from neuronal cells carry the tau protein and facilitate the spread of tau pathology in the brain. We will utilize genetically engineered mouse models to determine whether the specific molecules play a critical role in the spread of tau pathology in the brain. Our long-term goal is to prevent disease progression by targeting microglia and exosome pathways in order to suppress the progression of pathogenic tau.

Meningeal Lymphatic Function and Antibody Therapy in Alzheimer's Disease

JONATHAN KIPNIS, PH.D., University of Virginia

Until recently, it was believed that the mammalian central nervous system was devoid of lymphatic vessels, despite early works indicating the contrary. Our group recently has described a lymphatic vasculature embedded within the meninges that surround the brain. Meningeal lymphatic vessels perform an important role of draining both molecules and immune cells from the central nervous system to peripheral lymph nodes. We now show that decreased function of these CNS-draining lymphatics is observed in old mice, and that function of meningeal lymphatics affects amyloid pathology in mice models of Alzheimer's disease. In this proposal, we will further address how this important drainage pathway affects currently suggested therapeutic strategies for AD, namely immunotherapy against amyloid beta peptides. Furthermore, we will develop new approaches to improve the function of meningeal lymphatics in aged AD mice, and test how it impacts the efficacy of immunotherapy and, ultimately, disease progression and symptomatology.

Central Clock Influence on Alzheimer's Disease Pathogenesis

GERALDINE J. KRESS, PH.D., Washington University

This project will evaluate the association between circadian rhythms and cognitive function during Alzheimer's progression. Cognitive decline is the defining feature of Alzheimer's disease. Circadian rhythms are 24-hour oscillations in behavior and biological processes. Circadian systems are severely blunted with progression of Alzheimer's disease. Recent studies suggest that disruptions to the circadian system occur prior to the clinical onset of memory deficits in Alzheimer's disease.

The mechanism explaining how the circadian system impacts cognitive processes during Alzheimer's disease progression is relatively unknown. The goal of this project is to test the hypothesis that poor circadian rhythms mediated by a dysfunctional central clock directly influences the progression of Alzheimer's disease. The concepts and methods put forward in this project are innovative and have the potential to substantially impact the understanding for the role of circadian function in Alzheimer's disease. The long-term goal of this research is to identify possible therapeutic strategies to ameliorate cognitive impairments and the progression of Alzheimer's disease.

The Circadian Clock Modulates Neurodegeneration in Alzheimer's Disease Via REV-ERBα

ERIK S. MUSIEK, M.D., PH.D., Washington University

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 Alzheimer's disease often exhibit symptoms of circadian dysfunction, such as disrupted sleep at night and excessive daytime napping. Subtle circadian changes can be detected in people with Alzheimer's-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 clock genes can cause inflammation or damage in the brain of mice. A specific clock gene, REV-ERBα, appears to regulate brain inflammation. This research intends to investigate the functions of REV-ERBα in the brain and determine molecular mechanisms by which it may influence neurodegeneration. Novel drugs that activate REV-ERBα will be used to determine whether this might have a protective effect in a mouse model of Alzheimer's disease. The goal of this research is to understand exactly how circadian dysfunction promotes Alzheimer's disease, 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 machinery. Synaptic vesicles found inside the membrane of a cell release neurotransmitters to facilitate communication between neurons. Lack of properly functioning synaptic vesicle machinery over months and years is expected to drive a rundown of neurotransmitter release, eventually halting synaptic communication and contributing to progressive cognitive decline.

Therapeutic Strategies and Drug Discovery

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

The clinical manifestations of traumatic brain injury include impairments in sensory, motor, psychiatric and cognitive function. At the molecular level, traumatic brain injury gives rise to accumulation of a number of proteins in the axons of neurons. Axons are the long projections of neurons that conduct electrical impulses known as action potentials. Several of the proteins that compose these aggregates in the axon include those that play a role in Alzheimer's disease: amyloid precursor protein, amyloid beta-42, hyperphosphorylated tau and neurofilament light chain. Axonal injury is thought to occur immediately after traumatic brain injury. Interventions targeting mechanisms that generate amyloid beta-42 may ameliorate the axonal damage and spread of amyloid elicited by traumatic brain injury.

The implications for this intervention would be the reduction of the risk of developing Alzheimer's disease or related dementias. Gamma-secretase is one of the two enzymes responsible for amyloid beta-42 production. Compounds that modulate this enzyme may be able to curtail the production of toxic amyloid beta-42. Using medicinal chemistry, this research will optimize a series of novel gamma-secretase modulators with the hope of developing a preventive treatment for traumatic brain injury-induced neurodegeneration.

The Development of DNA-Encoded Libraries to Discover Therapeutically Valuable Low Molecular Weight Compounds for Alzheimer's Disease

MARC FLAJOLET, PH.D., The Rockefeller University
SUBHASH SINHA, PH.D., The Rockefeller University

Traditionally, the search for a drug requires a large quantity of starting material, heavy screening costs, and a complex and costly infrastructure that allows for several hundred thousand compounds to be screened. This research proposal intends to use a revolutionary approach to generate 24 million drug-like compounds that have the potential to be relevant for Alzheimer's disease. This new approach, called DNA-encoded library, or DEL, allows for screening of hundreds of millions of compounds and even billions of compounds in some cases. This technique requires a much smaller amount of starting material (on the order of millions of times less than the classical approach) and almost no special infrastructure. The

three libraries of compounds we will build have at least 8 million compounds each. The compounds will be screened based on their size and structure to be useful in the context of Alzheimer's disease.

Neuroprotective Effects of the Exercise Hormone Irisin in Alzheimer's Disease

SE HOON CHOI, PH.D., Massachusetts General Hospital
CHRISTIANE WRANN, D.V.M., PH.D., Massachusetts General Hospital

Exercise, especially endurance exercise, is known to have beneficial effects on brain health and cognition. This improvement in cognitive function largely affects learning and memory. Exercise has been shown in both animal models and clinical studies to be neuroprotective in Alzheimer's disease.

The mechanisms by which exercise protects the brain are diverse and complex. Exercise increases a hormone called fibronectin-domain III containing 5 (FNDC5) that is cleaved and released as "irisin" into circulation. Irisin reduces amyloid beta pathology and cell loss in a cell culture model. Cell culture is the process by which cells from tissue of interest are grown under controlled conditions. This research will test the hypothesis that the novel exercise hormone irisin is neuroprotective in Alzheimer's disease.

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

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

Alzheimer's disease (AD) and several other neurodegenerative diseases often are caused by the accumulation in neurons of misfolded aggregation-prone proteins, including tau and amyloid beta. Presently, no treatment is available to slow the steady accumulation of such toxic proteins. Normally, misfolded proteins in cells are selectively destroyed by the proteasome—the primary site of protein breakdown in our cells. There is growing evidence that proteasome function becomes defective during neurodegeneration in large part due to protein aggregates that disrupt function. This research seeks to understand the biochemical adaptations by which neurons can compensate for impairments in proteasome function and slow disease progression. The primary goal will be to identify novel pharmacological agents that activate the 26S proteasome and stimulate the degradations of such misfolded, potentially toxic proteins. In research from our lab, we demonstrate that drugs that stimulate proteasome activity decreased the levels of the disease-causing mutant proteins, and reduced neuronal death and the associated pathology. This evidence indicates that proteasome activation is a potential approach for the treatment of Alzheimer's disease. In future research, we hope to clarify the mechanisms of actions for these drugs and test whether other agents can clear the pathogenic protein.

Discovery of Chemical Compounds That Induce Degradation of APP Beta-CTF in Cells

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

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. The amyloid plaque is composed of amyloid beta peptide, which originates from an amyloid precursor protein. Multiple lines of evidence suggest that a defective clearance mechanism is involved in the progression of Alzheimer's disease. Our laboratory has discovered a novel molecular pathway regulating protein clearance, which represents an attractive therapeutic target for developing drugs for Alzheimer's disease. We seek to build on our screen of a chemical library of small molecules that identified compounds that increase the clearance of the amyloid beta peptide.

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

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

The beta-site amyloid precursor protein (APP)-cleaving enzyme 1 (BACE1) is an enzyme that mediates the generation of amyloid beta peptide, a core component of amyloid plaque in Alzheimer's disease. The current research is intended to understand how BACE1 is regulated in neurons in order to gain insights as to how to therapeutically control BACE1 activity. This regulation has implications for regulating amyloid beta generation in a safer and more effective manner. We discovered several compounds that contain a characteristic drug-like chemical core known as 8-hydroxyquinoline (8HQ). These compounds play a role in regulating the function of BACE1 in processing APP. Based on this observation, the current proposal will investigate the mechanism underlying the BACE1-regulating action of 8HQ, with the ultimate goal of evaluating this compound for its therapeutic potential as an AD drug candidate.

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

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

Alzheimer's disease has become a major public health problem, but there is no cure for the disease. Previously, we developed a novel three-dimensional human neural cell culture model of AD (Alzheimer's in a Dish), which recapitulates the key pathological events in AD in a human brain-like environment. In this ongoing project, we have been using our 3-D AD cellular model as a platform to screen novel AD drug candidates and to identify druggable cellular pathways that can reduce AD pathogenesis. In this year, we will continue our efforts to validate and test the efficacy of lead AD drug candidates in more physiologically relevant 3-D cellular models, including 3-D cell models from female and male patient-derived AD neurons. This year, we also will start a pilot

drug library screening project from a natural compound library. The overarching goals of our study are to provide novel mechanistic insights on how to block the pathological cascade of AD in human neural cells and to find novel AD drug candidates that can be applicable directly in human clinical trials.

Pharmacologically Protecting and Rescuing Synapses from Beta Amyloid by Raising Synaptic PSD-95

ROBERTO MALINOW, M.D., PH.D., University of California, San Diego

While the underlying cause of Alzheimer's disease is unknown, evidence from human genetics and transgenic mouse studies implicate amyloid beta. This protein greatly impacts synapses—gaps between two neurons that serve as the sites of transmission of electrical or chemical information—leading to their inability to function normally. The Malinow laboratory seeks to leverage recent findings indicating that synapses can be protected from amyloid beta by increasing the amount of an important synaptic protein, PSD-95. This increase in PSD-95 at synapses can be achieved pharmacologically using drugs that are being developed for human use. These studies provide important pre-clinical data.

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

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

This project seeks to advance drug discovery for Alzheimer's disease through the 3-Dimensional Drug Screening consortium. Via collaboration with the Tanzi and Kim labs at Massachusetts General Hospital, this research intends to combine bioinformatics-based screening and modeling methods with the 3-D human neural cell culture system of Alzheimer's in a Dish to test the drug candidate, Ebselen. Using the SMART framework (SysteMatic Alzheimer's disease drug ReposiTioning), 2,640 carefully selected compounds were physically screened, 30 compounds were found to inhibit phosphorylated tau in 3-D culture, and Ebselen was found ready for animal studies to test long-term toxicity and efficacy. Ebselen is a drug molecule with anti-oxidant and anti-inflammatory activity.

Dear Friends,

We are pleased to report that 2018 was the 14th consecutive record year for research dollars distributed and funds raised by Cure Alzheimer's Fund. (See the chart on page 63). Donations for the year totaled $20.5 million, an increase of 11% from 2017, and those dollars came from 17,000 contributions.

Research spending for 2018 totaled $19.7 million, an increase of 25% from 2017, funding 74 projects.

We continue to operate lean, keeping our overhead costs low. Since inception through the end of 2018, our Board of Directors has contributed $35.9 million to support operating expenses totaling $22.2 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 eighth consecutive time, the highest rating the charity watchdog offers.

Since our inception in 2004, Cure Alzheimer's Fund has distributed nearly $85 million to more than 150 researchers around the world. Although the disease still is with us, progress toward its demise has accelerated. Researchers tell us they are more enthusiastic and hopeful about finding the pathways to effective therapies than they ever have been.

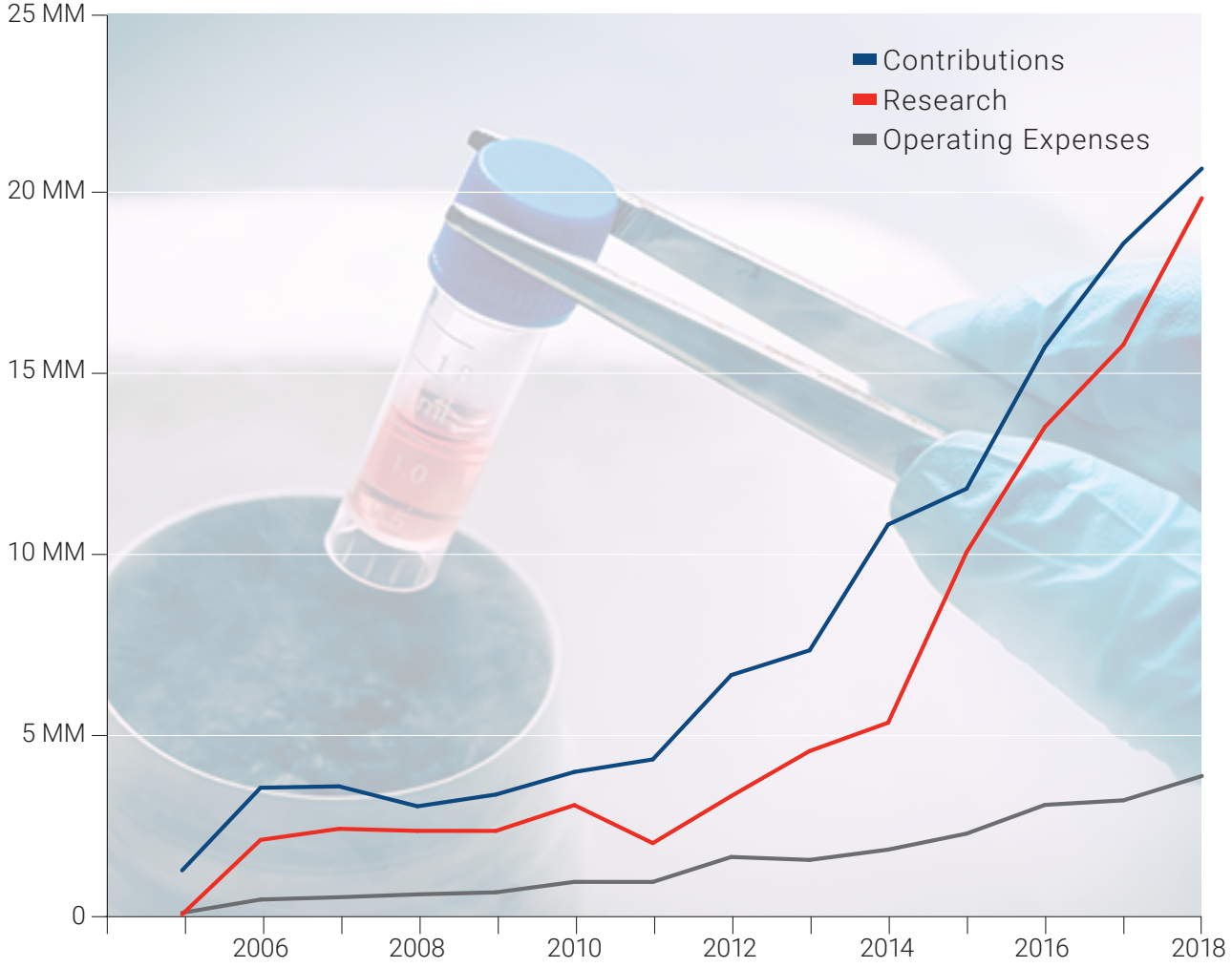
Our belief in the value of innovative, breakthrough research to unravel the complexities of Alzheimer's pathology has yielded significant contributions described elsewhere in this report. The continued generosity of

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 those 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 2018

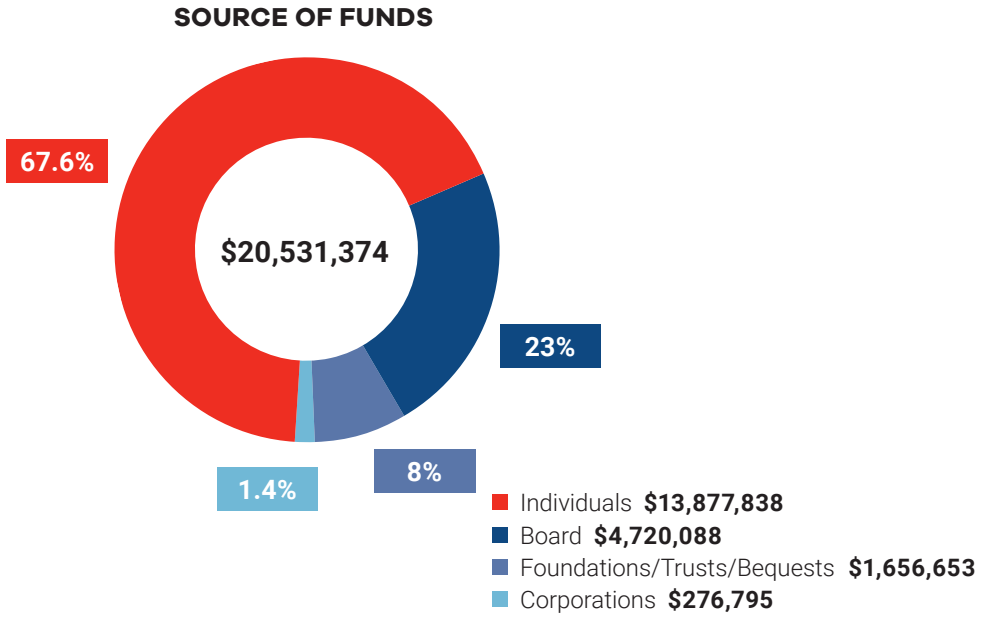


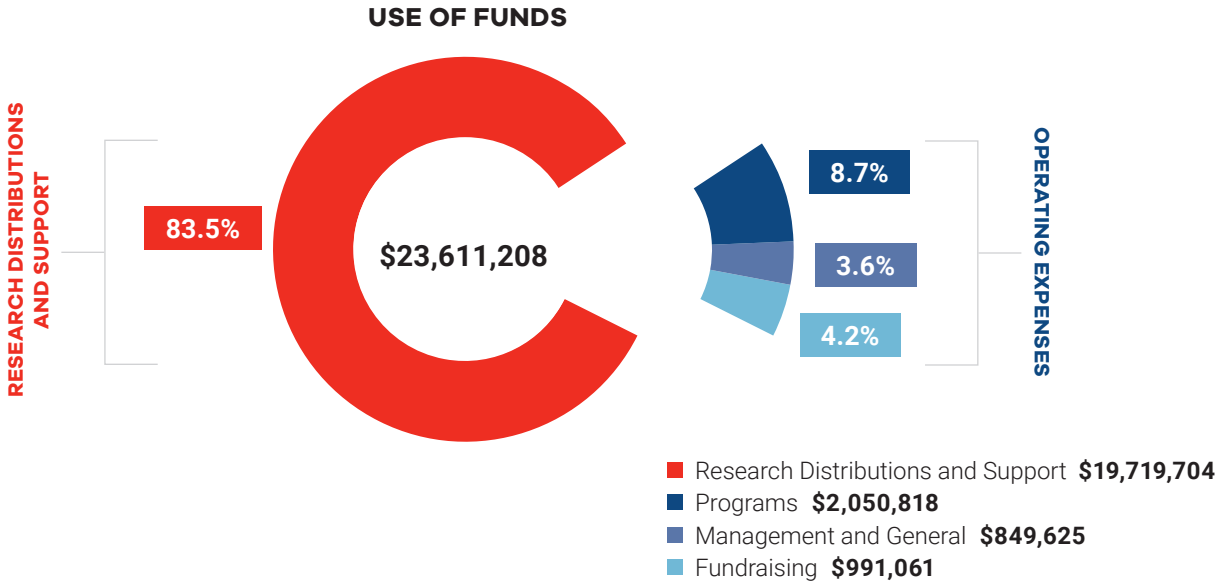
A Record of Extraordinary Growth:

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

2018 Fundraising

In 2018, Cure Alzheimer's Fund received 16,196 gifts—from individuals, corporations and foundations—totaling $20,531,374 in cash and in-kind revenues. Cumulative contributions from inception given by the Founders and Board total $35,881,288.Cumulative expenses from inception paid by the Founders and Board total $22,183,056.





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

2018 Financials (Year ended Dec. 31, 2018)

Statement of Financial Position

Assets	
Current Assets:	
Cash and cash equivalents	$2,051,994
Pledges receivable, current portion	275,000
Investments	4,445,787
Prepaid expenses and other current assets	259,681
Total current assets	7,032,462
Pledges receivable, less current portion, net	510,013
Equipment and leasehold improvements, net	38,351
Total Assets	$7,580,826
Liabilities and Net Assets	
Current Liabilities:	
Accounts payable	$392,536
Accrued expenses	499,053
Total current liabilities	891,589
Net Assets:	
Without donor restrictions	5,466,208
With donor restrictions	1,223,029
Total net assets	6,689,237
Total Liabilities and Net Assets	$7,580,826

Statement of Activities

Revenue and Support:	
Contributions	$19,798,072
Investment income	108,435
Loss on disposal of equipment and leasehold improvements	(14,448)
Total revenue and support	19,892,059
Expenses:	
Program:	
Research distributions and support	19,719,704
Documentary project	25,164
Other program expenses	2,025,654
Total program expenses	21,770,522
Management and general	849,625
Fundraising	991,061
Total expenses	23,611,208
Change in net assets	(3,719,149)
Net Assets, beginning of year	10,408,386
Net Assets, end of year	$6,689,237

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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Chairman of the Morby Family Charitable Foundation

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President and Chief Executive Officer

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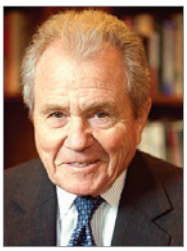

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Plexus Capital

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Christian Writer

President and Director of The Rick Sharp Alzheimer's Foundation

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DOROTHY VACARO
Gift Processing Associate

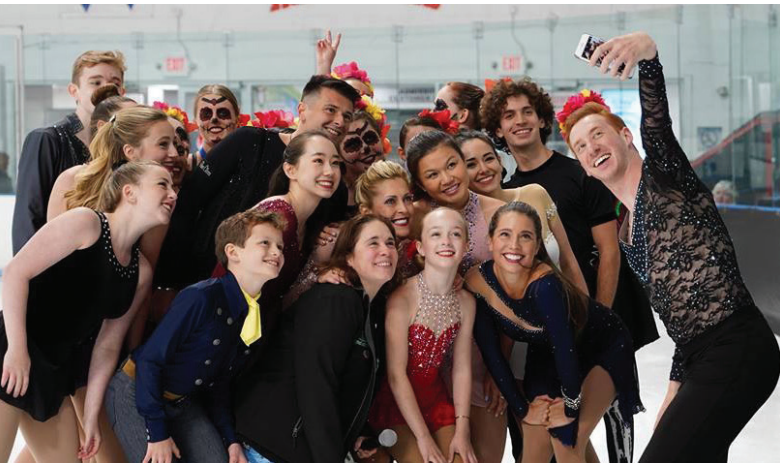
Our Heroes

So many have been affected by Alzheimer's disease and every year we learn of those individuals who selflessly reach out to their friends and families to organize events that provide contributions to our fund. We are amazed—and humbled—by all of our donors and by these heroes. We thank all of our 2018 heroes, and share a few of their stories on the following pages.

Administration Department,
Wilcox State Prison,
Georgia Department of Corrections
Alan Arnette
Alexa Burton
Andy Lee
Audra Foshage
Audra Tong
Bart Karnowski
Celina Vo
Cure Alzheimer's Mid-Atlantic
Dan Hulkower and Miriam Fisher
David K. Johnson Foundation
DoubleDown Interactive
Elizabeth Mellerup
FamilyResponseKits.com
Gabrielle de Weck
Gilbert Stubbs
Hailey Richman
Harry and Cesca Williams
Integra Partners
Janine Janaki
Jason Ades
Jeff Madden
Jennifer McNair
Jenny Chen
Jon-Don
Kerry Franklin
Kim Chan
Kimberly R. Bischoff
Kurt Thuenemann
Laura Fitzgerald
Lauren and Jay Burke
Lezlee Sabo
Lili and Tanya Cantu
Lisa Husted
Mahkana
Maithili Hulkarni
Make Alzheimer's a Memory
Manny Reiser
Maria Luca
Max Wallack
Nate and Jarrett Nagengast
National Grid Ventures (NGV)
New England Parking Council
Northbridge
Oliver Vingut
One Hope Wine
Pitching in for Charity
Quincy Fire Fighters Local 792
Ralph "Ed" Willet
Randa Mahmud Ulankiewicz
Ridgway A&G Skydive for Alzheimer's
Robert Bryson
Robert Kiss
Rose M. Grant
Roxana Cabral
Running 4 Answers
SingStrong A cappella Festival
Stephanie Garvey
Susan Callies
Terence Lee
The John M. Ferrero Jr. Family
The Lisa Malin Team
Tracy Holland and Mambo Room
Valerie Greene
Villages at Historic Silvercrest 2018
White Elephant Gifts
Youssef Ben-Youssef

Morels and Memories—Mushroom Hunt and Alzheimer's Fundraiser

In Lake Swede, Minnesota, the annual hunt for the elusive Morel mushroom has become a lot more fun and purposeful, thanks to Courtney Vanderlinde. Since 2016, Courtney has hosted Morels and Memories, a day of foraging, cooking demonstrations and live music, with all proceeds benefiting Alzheimer's research. Courtney started the fundraiser in honor of her mother, Heidi, who was diagnosed with early-onset Alzheimer's disease in 2011 at the age of 49. The event gets bigger and better every year. In just three years, Courtney and her fellow fungi aficionados have raised almost $10,000.



Axels for Alzheimer's

This year, Leah Spencer wanted to use her lifelong passion for ice skating to make a difference. One of Leah's grandmothers has Alzheimer's and the other succumbed to the effects of dementia. It was in their honor that the 24-year-old created the Axels for Alzheimer's figure skating benefit. Leah performed and directed an impressive ensemble of national and regional guest stars that dazzled the audience with their on-ice skills and 32 axel jumps. For every axel landed, sponsors donated to Cure Alzheimer's Fund.

Michael Paley and Rachel Cantor

When it came to gifts for their 2018 nuptials, Michael and Rachel wanted something important and meaningful. It was just a few years before the wedding that Michael's father began to show signs of dementia. Even though he continues to be physically healthy, Alzheimer's disease has taken his ability to communicate and recognize his wife and children. Witnessing firsthand what the disease does to those with Alzheimer's and their families, Michael and Rachel invited their guests to join them in supporting our work. And they did. We are grateful to receive gifts in their honor so that future generations have the possibility of prevention or even a cure.

Jog Your Memory 5K

2018 was a recording-breaking year for Jog Your Memory. The annual 5K run and 1.5-mile walk founded by Jess and Bob Rice in their Needham, Massachusetts, hometown celebrated its fifth anniversary event with more participants, supporters and donations than ever before. An unprecedented $190,000 was raised for Alzheimer's research and caregiving. Since its inception, Jog Your Memory has awarded $500,000 to our organization and is a true force in the fight against Alzheimer's disease.

Awareness

From our own annual research symposium to the big screen to baseball, 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

On the evening of June 5, 2018, the Boston Red Sox spotlighted Cure Alzheimer's Fund, orienting all pregame activities around our organization. On the field and on the air, the Red Sox taught fans about Alzheimer's disease, introduced them to Cure Alzheimer's Fund researchers and Board members, and showcased the hard work the entire team has put into finding a cure. Cure Alzheimer's Night at Fenway Park brought information about our organization and its mission to an unprecedented number of people. We are closer to a cure today thanks to the generosity of the Boston Red Sox.

The Case for Hope

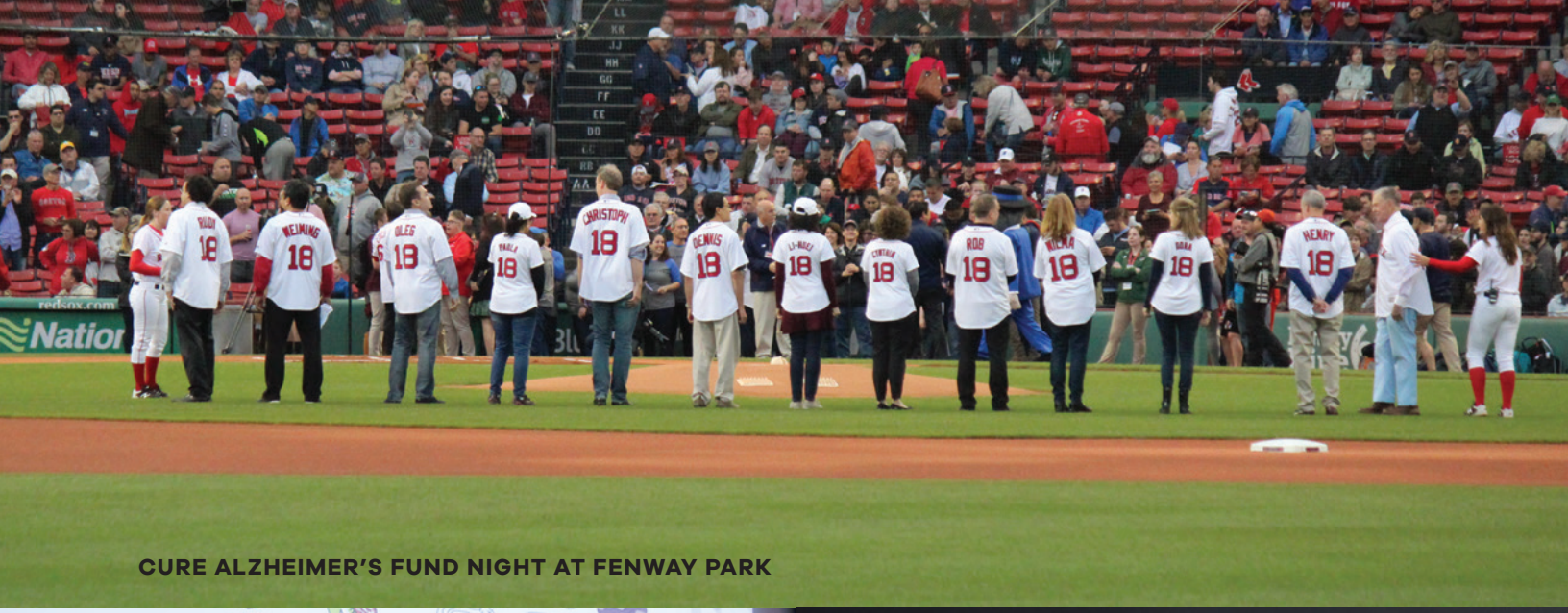
The 8th Annual Cure Alzheimer's Fund Symposium featured award-winning NPR science writer Jon Hamilton moderating a discussion with Ronald Petersen, M.D., Ph.D., Robert Vassar, Ph.D., and Teresa Gomez-Isla, M.D., on the case for hope in Alzheimer's disease research. Dr. Petersen discussed the impact of amyloid and its role as a causative agent of the disease and the impact of tau tangles. Dr. Vassar made the case for antibodies that remove amyloid from the brain, and Dr. Gomez-Isla reviewed the case for disease resilience based on genetic anomalies that may provide insights into Alzheimer's disease. We are grateful for the participation and insights of these three extraordinary scientists, and all of our funded researchers who are dedicated to finding a cure.

The Face of Alzheimer's

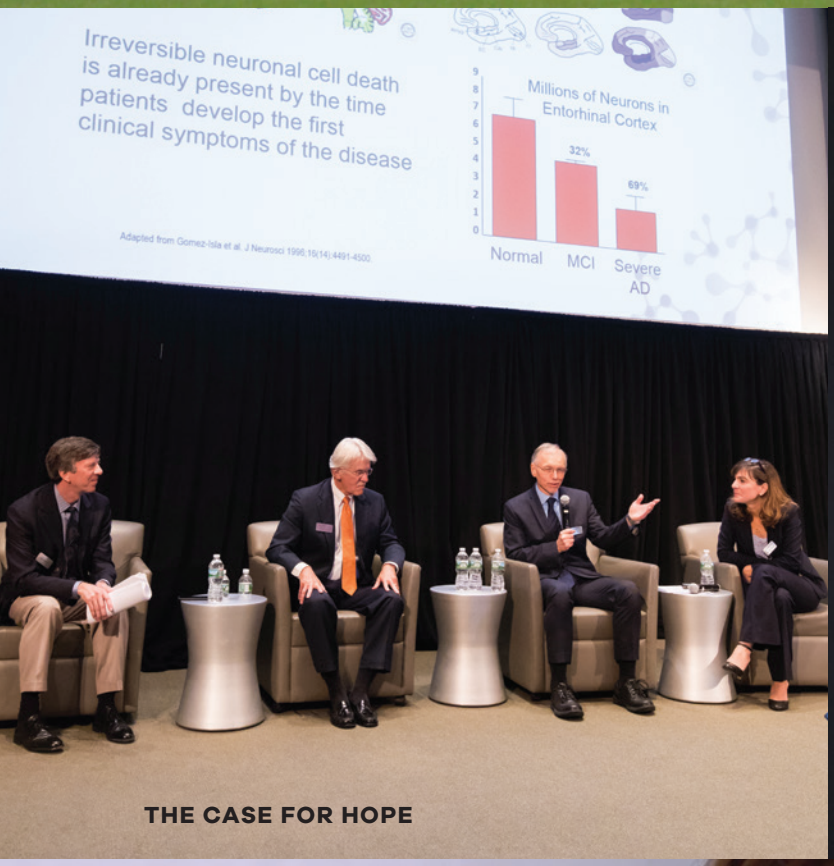
Cure Alzheimer's Fund launched a series of public service announcements designed to educate social media followers about Alzheimer's disease. The Face of Alzheimer's delivers illuminating facts and statistics about those with the disease and the burden it places on their caregivers, set against powerful images of men and women of all ages and races. Simon Malls also generously offered to display The Face of Alzheimer's ads on its interactive motion kiosks, and included videos with touch screens to educate mall shoppers about Alzheimer's disease.

'Daughter and Mother'

Created *pro bono* by BBDO for Cure Alzheimer's Fund, the social media film "DAUGHTER AND MOTHER" tells the heartbreaking story of a young girl tasked with caring for her sick mother, following the pair as they struggle with simple tasks made difficult by the mother's illness. Since its release in 2018, "DAUGHTER AND MOTHER" has received national and international attention, including a Silver Hugo Award and an award from the Association of Independent Commercial Producers, and it has been placed in the permanent archives of the Department of Film of the Museum of Modern Art. As a public service announcement, the film was selected by AMC, Regal and Cinemark to be shown on 16,000 movie screens nationwide and internationally by EuroNews' One Minute of Responsibility, playing throughout Europe and Africa. CureAlz is immensely grateful to BBDO and hopes the short film leads to greater awareness of the devastating consequences of Alzheimer's disease and the urgent need to find a cure.



CURE ALZHEIMER'S FUND NIGHT AT FENWAY PARK



THE CASE FOR HOPE

THE FACE OF ALZHEIMER'S

'DAUGHTER AND MOTHER'

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.

Planned Giving

We offer a number of Planned Giving options, some of which may offer tax incentives. Those choosing to make a bequest or planned gift to our organization 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 this list is not available to outside entities.

Monthly Giving

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

For details on these and other ways to give, please visit our website at **CureAlz.org.**

100% of your donation goes directly to research.

Recognized for Excellence

CHARITY NAVIGATOR ★★★★ Four Star Charity

Cure Alzheimer's Fund has been awarded the highest rating of 4 stars for 8 consecutive years.

GUIDESTAR PLATINUM PARTICIPANT

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

BBB ACCREDITED CHARITY

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

Cure Alzheimer's FUND

Report design: Winking Fish; Copy editor: Colleen O'Neill; Printer: Kirkwood; Paper: Sappi, McCoy Silk Cover and Text

Cure Alzheimer's FUND

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info@curealz.org

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.

Cover Image: Neural network; neurons. 3-D Illustration.