



2020 ANNUAL REPORT

OUR MISSION

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

Annual Report 2020

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Dear Friends,

2020 was a truly remarkable year:

- Despite the COVID-19 pandemic, we were fully functional with all of our wonderful staff working from their homes. We were able to pay and retain all of our employees, thanks to the generosity of our directors.
 - And, amazingly, we were able to increase our fundraising by 2%, in this very tough year, to \$25.9 million provided by 21,000 donors.
 - The above enabled us to fund 59 research grants totaling \$16.5 million. We have, since inception, financed 525 grants, representing \$125 million in cumulative funding through March 2021.
 - We have one therapy well on its way through clinical trials, and another expected to enter clinical trials in late 2021 or 2022.
-

Our Scientists

Approximately 175 scientists affiliated with 75 institutions around the world are working on our projects. They are profiled in the pages that follow. Many labs faced funding challenges during COVID-19, and our consistent support was very beneficial for ensuring that vital staff could be retained and scientific progress was preserved. So, despite the pandemic, their contributions to science were significant. Funding by us resulted in 133 publications of their work in the major journals of science. Keep reading for details on the important work of each of them.

Some Research Themes

The selection of research projects is done as a consequence of careful research strategy meetings, in which our core scientists review current research findings and brainstorm new ideas, always focused on our goal of finding a cure as soon as possible. Those discussions result in major themes, which guide our selection of research. Some of those major themes, and related projects, are described below.



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

CONTINUING TO UNRAVEL INTERACTIONS OF AMYLOID AND TAU IN AD PATHOLOGY

How amyloid and tau interact is a basic conundrum of research on Alzheimer's disease (AD). Drs. Rudy Tanzi and Brad Hyman of Massachusetts General Hospital have shown in their research—as a result of a long-term study of AD patients—that the rate of decline of individual patients, as measured by cognitive tests and other indicators, correlates closely with the rate of negative change of biological factors (particularly tau tangle spreading) as measured on an ongoing basis and as revealed in subsequent autopsies. This finding will provide benchmark information for treatment options for individuals based partly on their rate of cognitive decline.

UNDERSTANDING THE ROLE OF THE BLOOD-BRAIN BARRIER IN ALZHEIMER'S DISEASE PATHOLOGY

Research led by Berislav Zlokovic, M.D., Ph.D., of the Keck School of Medicine at USC shows that the breakdown of the blood-brain barrier (BBB) occurs during normal aging, starting in the hippocampus. In AD, by the time mild cognitive impairment has developed from the presence of amyloid beta and tau pathology, the BBB also has lost significant integrity. Zlokovic found a link between BBB breakdown and the strongest genetic risk factor for AD, the APOE4 gene variant. The results appeared in the journal *Nature*.

The findings suggest that people carrying at least one copy of APOE4 may have earlier and more significant damage to the BBB than noncarriers, even if they do not have any cognitive decline. The level of certain biomarkers of BBB breakdown in APOE4 carriers predicted future cognitive decline before being observed clinically. The research also

showed that an inflammatory pathway promotes the breakdown of the BBB; blocking inflammation may reduce this breakdown, demonstrating the therapeutic potential of alleviating neuroinflammation and BBB breakdown in AD.

FINDING NEW SEX-SPECIFIC RISK FACTORS FOR ALZHEIMER'S DISEASE

Women are twice as likely to develop AD than men, and evidence indicates that sex-specific risk factors may drive this difference, in addition to women's longer average lifespan.

Lisa Mosconi, Ph.D., of Weill Cornell Medical College, used brain imaging to look for risk factors other than genetics associated with brain changes related to AD. Images were used to evaluate changes with levels of amyloid beta and decreased glucose

metabolism, as well as the volume of gray and white matter in the brain. The study's findings suggest that among a wide range of risk factors for AD, including depression, smoking and AD family history, menopause status was second to female sex as most strongly associated with the examined brain changes. Other strong associations were hormone therapy, thyroid disease and hysterectomy status. The study concludes that if hormonal risk factors were to be targeted for therapy, a window of opportunity for prevention for women would be in early mid-life. The results appeared in the journal *Neurology*.

In another study led by Drs. Rudy Tanzi and Dmitry Prokopenko as part of the CureAlz Alzheimer's Genome Project™, whole human genome sequences of more than 5,000 Alzheimer's patients and family members were scanned to reveal four novel sex-specific AD genes that confer opposite AD risk impact in men versus women. Variations in three of these genes increased AD risk in men but seemed to be protective in women. However, the strongest

association with AD risk was the so-called ZBTB7C gene, variants of which conferred high risk in women but protection in men. The protein made by the ZBTB7C gene has been shown to play a role in maintaining blood-brain barrier function, potentially linking increased female risk of AD to the integrity of the blood-brain barrier and state of the brain's vasculature. The results of the study were published in the journal *Nature Scientific Reports*.

"Women are twice as likely to develop AD than men, and evidence indicates that sex-specific risk factors may drive this difference, in addition to women's longer average lifespan."

FIGHTING INFLAMMATION, A MAJOR CAUSE OF AD: TARGETING CD33 AND TREM2 FOR NEW THERAPIES

Since our founding, Cure Alzheimer's Fund has supported studies into the genetics of AD to discover new targets for AD therapy. The fastest-growing number of new AD genes are associated with innate immunity, and the first in this group was CD33, which was identified in our Alzheimer's Genome Project in 2008. This was followed by TREM2. Both CD33 and TREM2 regulate the brain's resident immune cells, microglia, determining whether they will clean up debris such as amyloid or promote neuroinflammation and kill nerve cells. In 2020, we saw the publication of two CureAlz-funded studies testing novel therapeutic approaches that affect microglia by targeting CD33 or TREM2:

- **CD33 plays a signaling role:** its activation in microglia diminishes the cells' clearing of amyloid beta and makes microglia more likely to induce neuroinflammation. Researchers Ana Griciuc, Ph.D., Rudy Tanzi, Ph.D., and Casey Maguire, Ph.D., all of Massachusetts General Hospital, showed that gene therapy against CD33 successfully turned down the gene's expression in a mouse model of AD, leading microglia to clear more amyloid beta and cause less neuroinflammation. The results of the study appeared in the journal *Human Molecular Genetics*.
- **TREM2 also plays a signaling role in microglia.** In contrast to CD33, activation of TREM2 increases amyloid beta uptake by microglia, and the effect is therefore neuroprotective. CureAlz Research Leadership Group member Marco Colonna, M.D., of Washington University School of Medicine in St. Louis, suggested that an antibody designed to increase TREM2 activation can reduce amyloid beta pathology in an AD mouse model. Furthermore, Dr. Colonna also demonstrated that this antibody's variant was safe and effectively engaged its TREM2 target in a first-in-humans Phase 1 clinical trial. The results of this study appeared in the *Journal of Experimental Medicine*.

FINDING A NEW BLOOD TEST TO DIAGNOSE ALZHEIMER'S DISEASE, NOW AVAILABLE

In what may be the most important development in the diagnosis of Alzheimer's disease in many years, Drs. Randall Bateman and David Holtzman of Washington University School of Medicine in St. Louis developed the first blood test to aid physicians in assessing patients for Alzheimer's disease. Under the name PrecivityAD™, the blood test, along with the APOE genotype, predicts with high accuracy whether there are amyloid plaques in the brain in patients 60 years of age or older with cognitive impairment. The blood test is already approved for clinical use in the EU and most U.S. states, and will be more accessible and less expensive to administer than other current diagnostic tools, such as brain imaging.

DEVELOPING A MEDICATION TO PREVENT ALZHEIMER'S DISEASE PRIOR TO ONSET OF DEMENTIA: GAMMA SECRETASE MODULATORS (GSMs)

For a number of years, we have referenced and provided funding for research into GSMs developed by Drs. Steve Wagner and Rudy Tanzi. Gamma secretase is a complex of proteins that cuts the amyloid precursor protein (APP) to produce amyloid beta protein, the main component of plaques. The GSMs are small molecules that influence this cutting of APP to favor production of shorter, more benign forms of amyloid beta instead of the longer forms (amyloid beta 42) that are neurotoxic and prone to forming amyloid plaques. In 2021, more than \$7 million in federal funding from the National

Institutes of Health was awarded to this project to carry out the first Phase 1 clinical trial in healthy participants, to test the GSMs for safety. CureAlz has funded studies exploring the potential of this exciting class of drugs for well more than a decade.

"In 2021, more than \$7 million in federal funding from the National Institutes of Health was awarded to this project... CureAlz has funded studies exploring the potential of this exciting class of drugs for well more than a decade."

CARRYING OUT AN AMYLYX PHASE 2 TRIAL FOR THE TREATMENT OF AD

For the first time in our history, Cure Alzheimer's Fund helped finance a Phase 2 Alzheimer's disease clinical trial (called PEGASUS by Amylyx) for an investigational therapy for late mild cognitive impairment and early dementia due to Alzheimer's disease. AMX0035, a combination therapy of two active compounds—sodium phenylbutyrate (PB) and taurursodiol (TURSO)—provides neuroprotection against cellular events linked to neuronal cell death, including accumulation of toxic misfolded proteins in the endoplasmic reticulum and cellular stress in the mitochondria. AMX0035 was first developed by Justin Klee, Josh Cohen and Dr. Rudy Tanzi, beginning in 2007, with seed funding

from Cure Alzheimer's Fund. AMX0035 recently was successful in a clinical trial of patients with amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease). The company has said it will seek marketing approval this year for ALS in the EU and Canada, and start the phase 3 trial to prepare for application to the FDA.

Despite challenges imposed by COVID-19, AMYLYX announced in November 2020 that the last participant in the ALS trial had received their last treatment, with top-line results targeted for release in the first half of 2021. The trial was designed to assess the safety and tolerability of the therapy and its impact on disease pathology, and participants' cognition and function. We are eager to share its results with you.

Cure Alzheimer's Fund Research Findings Used in COVID Research

Research investments made by Cure Alzheimer's Fund provided dividends in unexpected ways.

- Christoph Lange, Ph.D., of the Harvard T.H. Chan School of Public Health, a world-renowned biostatistician, has been a valued CureAlz scientist for many years. Dr. Lange applied the methodology developed in the CureAlz-funded Alzheimer's Genome Project™ with Dr. Rudy Tanzi to analyze the available genome sequences of the SARS-CoV-2 virus. Dr. Lange showed that his algorithms could predict, a year in advance, the effects of the UK and other variants on COVID infectiousness and severity.
- Vishwa Deep Dixit, D.V.M., Ph.D., of the Yale School of Medicine, investigates age-related inflammation and ways to alleviate certain aspects of this inflammation. In 2020, Dr. Dixit studied how aging impairs the immunometabolic response and compromises defense mechanisms against COVID-19 in the elderly.
- Cheryl Wellington, Ph.D., of the University of British Columbia, uses bioengineered blood vessels to study vascular contributions to AD, including inflammation, and contributed her expertise toward an editorial illustrating the role of the cytokine storm syndrome in the severity of COVID-19.

Leverage and Leadership

OUR RESEARCH FUNDING LEADS TO MORE FUNDING FROM OTHERS

In previous annual reports, we have referenced the financial leverage achieved from the research investments made by Cure Alzheimer's Fund. Upon further study into one specific year—2018—we were able to gauge that the research grants distributed in 2018 already have yielded \$121 million in funding for Alzheimer's disease from the National Institutes of Health. This is a remarkable testimony to the exceptional and diverse areas of study and proof-of-concept science so worthy of our continued investment.

OUR SUBSTANTIAL IMPACT ON THE WHOLE AD SCIENTIFIC COMMUNITY

Through the end of 2020, the 749 papers from studies funded by Cure Alzheimer's Fund have been cited more than 47,000 times. We consider this a significant measure of our breakthrough research and the value of the work of the scientists we fund.

“...we were able to gauge that the research grants distributed in 2018 already have yielded \$121 million in funding for Alzheimer's disease from the National Institutes of Health.”

CURE ALZHEIMER'S FUND'S OUTSTANDING RATINGS BY EXTERNAL ORGANIZATIONS

In recognition of our leadership role, for the 10th consecutive year, Charity Navigator has awarded Cure Alzheimer's Fund a four-star rating, received by only 3% of nonprofit organizations in the United States. We are grateful to again be selected as one of *The 50 Best Charities to Give to Right Now* by Good Housekeeping, and to have achieved Platinum status with charity watchdog GuideStar. These unsolicited endorsements from critical third-party evaluators are reminders that transparency of how we work and how we use your generous donations truly is an essential cornerstone of our operating principles.

"The Board of Directors and Founders continue their commitment—100% of every dollar you donate will go to our research."

Our Gratitude

We owe a debt of gratitude to many people. Our researchers, whose labs were closed or partially open for many months, continued their exceptional work; their momentum and commitment never wavered. The dedicated staff of Cure Alzheimer's Fund, led by Tim Armour, pivoted to working remotely and communicating virtually—with each other and with our supporters. Their efforts provided for another record-breaking year.

Of course, we owe you—our very generous donors—for your continued support. We are honored that you have chosen to provide the financial resources needed to move forward with our vital research. The Board of Directors and Founders continue their commitment—100% of every dollar you donate will go to our research. On behalf of the 50 million people worldwide who have received a diagnosis of Alzheimer's disease, and on behalf of all of our donors, we are committed to winning this battle.

Our Very Best Wishes,

Jeff Morby
Co-Chairman

Henry McCance
Co-Chairman

Rudy Tanzi, Ph.D.
Chairman, Research Leadership Group



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 and disrupt cell function.

Neurofibrillary Tangles

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

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

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

Chronic Inflammation

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

Loss of Neuronal Connections and Cell Death

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

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

The Research

Research Areas of Focus

The Cure Alzheimer's Fund mission—to fund research with the highest probability of preventing, slowing or reversing Alzheimer's disease—involves four phases of research development. In each phase, specific categories of research have been identified for funding and are listed here.

FOUNDATIONAL RESEARCH

The phase of foundational research includes the exploration of basic science and, for Cure Alzheimer's Fund, the distribution of grants to those who are working to understand the facts of the disease. This includes the following subcategories:

- Genetic risk factors
- Biomarkers, diagnostics, and studies of risk and resilience
- Production of new animal and cellular models of Alzheimer's disease
- Epigenetic factors

TRANSLATIONAL RESEARCH

Translational research investigates how the facts of the disease provide opportunities for prevention and intervention. They include studies of:

- Novel Alzheimer's disease genes
- APP and amyloid beta
- Tau
- Apolipoprotein E (APOE)
- Innate immune pathology
- Alternative neurodegenerative pathways



DRUG DISCOVERY AND ENABLING TECHNOLOGIES

In the third phase of the research road map, potential therapeutics and approaches are sought to leverage the identified opportunities for intervention. Efforts include:

- Drug screening
- Drug delivery and design

PRECLINICAL AND CLINICAL DRUG DEVELOPMENT AND TRIALS

In the final stage of the preclinical research continuum, the identified candidate drugs and other therapies are further validated and optimized to maximize their chance of success in human clinical trials. These entail:

- Preclinical drug development
- Clinical trials
- Clinical trial design

Published Papers

In 2020, a record-breaking number of high-impact science papers made possible by support from Cure Alzheimer's Fund were published in the world's leading science journals—a total of 133 in a single year.

Alzheimer's & Dementia

C99 Selectively Accumulates in Vulnerable Neurons in Alzheimer's Disease

Paul Greengard and Victor Bustos

Immunity

Microglia, Lifestyle Stress, and Neurodegeneration

Oleg Butovsky

Nature

Clonally Expanded CD8 T Cells Patrol the Cerebrospinal Fluid in Alzheimer's Disease

Tony Wyss-Coray

The Journal of Clinical Investigation

Type I Interferon Response Drives Neuroinflammation and Synapse Loss in Alzheimer Disease

Virginia Man-Yee Lee and Oleg Butovsky

Molecular Neurodegeneration

VGF-Derived Peptide TLQP-21 Modulates Microglial Function Through C3aR1 Signaling Pathways and Reduces Neuropathology in 5xFAD Mice

Sam Gandy, Michelle E. Ehrlich and Stephen Salton

EBioMedicine

OCIAD1 Contributes to Neurodegeneration in Alzheimer's Disease by Inducing Mitochondria Dysfunction, Neuronal Vulnerability and Synaptic Damages

Weiming Xia and Stephen T.C. Wong

Nature Medicine

Human and Mouse Single-Nucleus Transcriptomics Reveal TREM2-Dependent and TREM2-Independent Cellular Responses in Alzheimer's Disease

David M. Holtzman, Jason Ulrich and Marco Colonna

The Journal of Immunology

Brain Parenchymal and Extraparenchymal Macrophages in Development, Homeostasis, and Disease

Marco Colonna

Nature Neuroscience

Lipid-Droplet-Accumulating Microglia Represent a Dysfunctional and Proinflammatory State in the Aging Brain

Tony Wyss-Coray

Journal of Biological Chemistry

A Synthetic Heparinoid Blocks Tau Aggregate Cell Uptake and Amplification

Marc Diamond

Human Molecular Genetics

Negative Evidence for a Role of APOE ε4 Variant in Alzheimer's Disease

Rudolph Tanzi and Sangram S. Sisodia

Brain Research

ApoE Mimetic Improves Pathology and Memory in a Model of Alzheimer's Disease

Daniel Laskowitz

Acta Neuropathologica Communications

Tau-Tubulin Kinase 1 and Amyloid-β Peptide Induce Phosphorylation of Collapse Response Mediator Protein-2 and Enhance Neurite Degeneration in Alzheimer Disease Mouse Models

Tsuneya Ikezu

Methods

Assessment of Separation Methods for Extracellular Vesicles from Human and Mouse Brain Tissues and Human Cerebrospinal Fluids

Weiming Xia and Tsuneya Ikezu

Neurobiology of Aging

A Three-Dimensional Dementia Model Reveals Spontaneous Cell Cycle Re-Entry and a Senescence-Associated Secretory Phenotype

George S. Bloom, John S. Lazo and Elizabeth R. Sharlow

Journal of Alzheimer's Disease

The GSM BPN-15606 as a Potential Candidate for Preventative Therapy in Alzheimer's Disease

Rudolph Tanzi and Steven L. Wagner

Cell

Posttranslational Modifications Mediate the Structural Diversity of Tauopathy Strains

Leonard Petrucelli and Anthony Fitzpatrick

Current Opinion in Biomedical Engineering

Microphysiological Models of Neurological Disorders for Drug Development

Roger Kamm

Nature Communications

Sex and APOE ϵ 4 Genotype Modify the Alzheimer's Disease Serum Metabolome

P. Murali Doraiswamy

Proceedings of the National Academy of Sciences of the United States of America

Proteins Containing Ubiquitin-Like (Ubl) Domains Not Only Bind to 26S Proteasomes but Also Induce Their Activation

Alfred Goldberg

The Journal of Prevention of Alzheimer's Disease

Rationale for Early Diagnosis of Mild Cognitive Impairment (MCI) Supported by Emerging Digital Technologies

P. Murali Doraiswamy

Scientific Reports

APOE4 is Associated with Differential Regional Vulnerability to Bioenergetic Deficits in Aged APOE Mice

Karen Duff and Tal Nuriel

Cell Reports

Neuronal BIN1 Regulates Presynaptic Neurotransmitter Release and Memory Consolidation

Gopal Thinakaran

Journal of Experimental Medicine

A Critical Role for Plasminogen in Inflammation

Sidney Strickland

Basic & Clinical Pharmacology & Toxicology

Implicating Endothelial Cell Senescence to Dysfunction in the Ageing and Diseased Brain

Darren J. Baker

Neurobiology of Disease

Increased Plasma Bradykinin Level is Associated With Cognitive Impairment in Alzheimer's Patients

Sidney Strickland and Erin Norris

Genetic Epidemiology

The Effects of Misspecification of the Mediator and Outcome in Mediation Analysis

Christoph Lange

Nature Communications

Amyloid- β 42/40 Ratio Drives Tau Pathology in 3D Human Neural Cell Culture Models of Alzheimer's Disease

Weiming Xia, Steven L. Wagner, Se Hoon Choi, Rudolph Tanzi and Doo Yeon Kim

Scientific Reports

Identification of Novel Alzheimer's Disease Loci Using Sex-Specific Family-Based Association Analysis of Whole-Genome Sequence Data

Winston Hide, Lars Bertram, Christoph Lange and Rudolph Tanzi

Molecular Neurodegeneration

Cerebrovascular Amyloid Angiopathy in Bioengineered Vessels is Reduced by High-Density Lipoprotein Particles Enriched in Apolipoprotein E

Cheryl Wellington

Science Translational Medicine

An Ocular Glymphatic Clearance System Removes β -Amyloid from the Rodent Eye

Ali Ertürk and Maiken Nedergaard

Alzheimer's Research & Therapy

Beneficial Association of Angiotensin-Converting Enzyme Inhibitors and Statins on the Occurrence of Possible Alzheimer's Disease After Traumatic Brain Injury

Benjamin Wolozin, Lee Goldstein and Weiming Xia

Seminars in Cell & Developmental Biology

γ -Secretase Inhibitors and Modulators: Mechanistic Insights into the Function and Regulation of γ -Secretase

Yueming Li

Journal of Neuropathology & Experimental Neurology

The Alzheimer Disease-Causing Presenilin-1 L435F Mutation Causes Increased Production of Soluble A β 43 Species in Patient-Derived iPSC-Neurons, Closely Mimicking Matched Patient Brain Tissue

Bradley Hyman

The Journal of Prevention of Alzheimer's Disease

Early Detection of Mild Cognitive Impairment (MCI) in an At-Home Setting

P. Murali Doraiswamy

Cells

Insights from in Vivo Studies of Cellular Senescence

Darren J. Baker

Annals of Biomedical Engineering

Generating Cell Type-Specific Protein Signatures from Non-symptomatic and Diseased Tissues

Shane A. Liddelow

Alzheimer's & Dementia

Proteomic and Biological Profiling of Extracellular Vesicles from Alzheimer's Disease Human Brain Tissues

Weiming Xia and Tsuneya Ikezu

The FASEB Journal

Amplified Protein Kinase C Signaling in Alzheimer's Disease

Alexandra Newton

Nature

APOE4 Leads to Blood-Brain Barrier Dysfunction Predicting Cognitive Decline

Berislav V. Zlokovic

Frontiers in Aging Neuroscience

Channelrhodopsin Excitation Contracts Brain Pericytes and Reduces Blood Flow in the Aging Mouse Brain in Vivo

Zhen Zhao and Berislav V. Zlokovic

The Journal of Nuclear Medicine

Asymmetry of Fibrillar Plaque Burden in Amyloid Mouse Models

Christian Haass

Scientific Reports

Synergistic Depletion of Gut Microbial Consortia, But Not Individual Antibiotics, Reduces Amyloidosis in APPPS1-21 Alzheimer's Transgenic Mice

Sangram S. Sisodia

Acta Neuropathologica Communications

Loss of Homeostatic Microglial Phenotype in CSF1R-Related Leukoencephalopathy

Oleg Butovsky

Langmuir

γ -Secretase Partitioning into Lipid Bilayers Remodels Membrane Microdomains After Direct Insertion

Steven L. Wagner and Yueming Li

Annals of the New York Academy of Sciences

Alternatives to Amyloid for Alzheimer's Disease Therapies—A Symposium Report

David M. Holtzman, Bradley Hyman, Marco Colonna, Manolis Kellis, Cheryl Wellington, Sangram S. Sisodia and Rudolph Tanzi

Neuron

CD49f is a Novel Marker of Functional and Reactive Human iPSC-Derived Astrocytes

Shane A. Liddelow

Plos One

Female Vulnerability to the Effects of Smoking on Health Outcomes in Older People

Caleb Finch

Nature Medicine

Reconstruction of the Human Blood-Brain Barrier in Vitro Reveals a Pathogenic Mechanism of APOE4 in Pericytes

Manolis Kellis and Li-Huei Tsai

Proceedings of the National Academy of Sciences of the United States of America

cGMP via PKG Activates 26S Proteasomes and Enhances Degradation of Proteins, Including Ones That Cause Neurodegenerative Diseases

Alfred Goldberg

Proceedings of the National Academy of Sciences of the United States of America

Cerebral Amyloid Angiopathy-Linked β -Amyloid Mutations Promote Cerebral Fibrin Deposits Via Increased Binding Affinity for Fibrinogen

Erin Norris and Sidney Strickland

Frontiers in Aging Neuroscience

APOE Alleles and Diet in Brain Aging and Alzheimer's Disease

Caleb Finch

Alzheimer's & Dementia

Further Understanding the Connection Between Alzheimer's Disease and Down Syndrome

William C. Mobley

Proceedings of the National Academy of Sciences of the United States of America

DNA-Based Fluorescent Probes of NOS2 Activity in Live Brains

Sangram S. Sisodia

Nature Medicine

Tau Molecular Diversity Contributes to Clinical Heterogeneity in Alzheimer's Disease

Rudolph Tanzi and Bradley Hyman

Cell Reports

Neurotoxic Reactive Astrocytes Drive Neuronal Death After Retinal Injury

Shane A. Liddelow

eLife

Mouse Brain Transcriptome Responses to Inhaled Nanoparticulate Matter Differed by Sex and APOE in Nrf2-Nfkb Interactions

Terrence Town and Caleb Finch

Journal of Experimental Medicine

Anti-human TREM2 Induces Microglia Proliferation and Reduces Pathology in an Alzheimer's Disease Model

Marco Colonna

Neurology

Sex-driven Modifiers of Alzheimer Risk: A Multimodality Brain Imaging Study

Lisa Mosconi

European Journal of Neuroscience

Functional Analysis of CX3CR1 in Human Induced Pluripotent Stem (iPS) Cell-Derived Microglia-Like Cells

Rudolf Jaenisch

Scientific Reports

Hybrid PET/MRI Enables High-Spatial Resolution, Quantitative Imaging of Amyloid Plaques in an Alzheimer's Disease Mouse Model

Yueming Li

Science Advances

Astrocytes and Microglia Play Orchestrated Roles and Respect Phagocytic Territories During Neuronal Corpse Removal in Vivo

Jaime Grutzendler

Neuron

Selective Neuronal Vulnerability in Alzheimer's Disease: A Network-Based Analysis

Jean-Pierre Roussarie and Paul Greengard

Communications Biology

Non-Invasive Red-Light Optogenetic Control of Drosophila Cardiac Function

Rudolph Tanzi

The Journal of Neuroscience

Soluble SORLA Enhances Neurite Outgrowth and Regeneration Through Activation of the EGF Receptor/ERK Signaling Axis

William C. Mobley, Huaxi Xu and Timothy Huang

bioRxiv

Unsupervised Cluster Analysis of SARS-CoV-2 Genomes Reflects Its Geographic Progression and Identifies Distinct Genetic Subgroups of SARS-CoV-2 Virus

Christoph Lange

bioRxiv

Unsupervised Cluster Analysis of SARS-CoV-2 Genomes Indicates That Recent (June 2020) Cases in Beijing are from a Genetic Subgroup That Consists of Mostly European and South(east) Asian Samples, of Which the Latter are the Most Recent

Christoph Lange

Journal of Alzheimer's Disease

Proteomic Profiling of Plasma and Brain Tissue from Alzheimer's Disease Patients Reveals Candidate Network of Plasma Biomarkers

Weiming Xia

Investigative Ophthalmology & Visual Science

Association of APOE with Primary Open-Angle Glaucoma Suggests a Protective Effect for APOE ϵ 4

Oleg Butovsky

Brain Pathology

Genomic Mechanisms in Alzheimer's Disease

Lars Bertram and Rudolph Tanzi

The EMBO Journal

Local Externalization of Phosphatidylserine Mediates Developmental Synaptic Pruning by Microglia

Beth Stevens

Spectrochimica Acta Part B: Atomic Spectroscopy

Diagnosis of Alzheimer's Disease Using Laser-Induced Breakdown Spectroscopy and Machine Learning

Weiming Xia

Brain Communications

Single-Subject Grey Matter Network Trajectories over the Disease Course of Autosomal Dominant Alzheimer's Disease

Randall J. Bateman

Molecular Neurodegeneration

FRET-Based Tau Seeding Assay Does Not Represent Prion-Like Templated Assembly of Tau Filaments

Eva-Maria Mandelkow and Eckhard Mandelkow

Cell

Therapeutic TVs for Crossing Barriers in the Brain

Zhen Zhao and Berislav V. Zlokovic

Frontiers in Neuroscience

Thrombin, a Mediator of Coagulation, Inflammation, and Neurotoxicity at the Neurovascular Interface: Implications for Alzheimer's Disease

Paula Grammas

Nature Communications

Knockout of Reactive Astrocyte Activating Factors Slows Disease Progression in an ALS Mouse Model

Shane A. Liddelow and Ben Barres

Journal of Alzheimer's Disease

Upregulation of Alzheimer's Disease Amyloid- β Protein Precursor in Astrocytes Both in Vitro and in Vivo

Se Hoon Choi and Rudolph Tanzi

Nature Communications

Multiscale Causal Networks Identify VGF as a Key Regulator of Alzheimer's Disease

Sam Gandy, Michelle E. Ehrlich and Stephen Salton

Molecular Psychiatry

Presenilin 1 Phosphorylation Regulates Amyloid- β Degradation by Microglia

Victor Bustos and Paul Greengard

eNeuro

In Vitro Testing of Voltage Indicators: Archon1, ArcLightD, ASAP1, ASAP2s, ASAP3b, Bongwoori-Pos6, BeRST1, FlicR1, and Chi-VSFP-Butterfly

Srdjan Antic

Trends in Immunology

Microglia and Astrocytes in Disease: Dynamic Duo or Partners in Crime?

Shane A. Liddelow and Beth Stevens

Human Molecular Genetics

Gene Therapy for Alzheimer's Disease Targeting CD33 Reduces Amyloid Beta Accumulation and Neuroinflammation

Ana Griciuc, Rudolph Tanzi and Casey Maguire

Molecular Neurodegeneration

P2RX7 Inhibitor Suppresses Exosome Secretion and Disease Phenotype in P301S Tau Transgenic Mice

Tsuneya Ikezu

Plos One

Lack of a Site-Specific Phosphorylation of Presenilin 1 Disrupts Microglial Gene Networks and Progenitors During Development

Victor Bustos and Paul Greengard

Alzheimer's & Dementia

Tau and Apolipoprotein E Modulate Cerebrovascular Tight Junction Integrity Independent of Cerebral Amyloid Angiopathy in Alzheimer's Disease

Ronald C. Petersen, Takahisa Kanekiyo and Guojun Bu

Cells

Proteomic Profiling of Extracellular Vesicles Derived from Cerebrospinal Fluid of Alzheimer's Disease Patients: A Pilot Study

Tsuneya Ikezu

RSC Medicinal Chemistry

Recent Developments of Small Molecule γ -Secretase Modulators for Alzheimer's Disease

Yueming Li

Nature

Neurotoxic Microglia Promote TDP-43 Proteinopathy in Progranulin Deficiency

Shane A. Liddelow

Journal of Alzheimer's Disease

Increased Contact System Activation in Mild Cognitive Impairment Patients with Impaired Short-Term Memory

Sidney Strickland and Erin Norris

Bioorganic & Medicinal Chemistry

Design and Synthesis of Novel Methoxypyridine-Derived Gamma-Secretase Modulators

William C. Mobley, Rudolph Tanzi and Steven L. Wagner

Nature

The Innate Immunity Protein IFITM3 Modulates γ -Secretase in Alzheimer's Disease

Robert Vassar, Paul Greengard and Yueming Li

Journal of Biological Chemistry

Gallic Acid is a Dual α/β -Secretase Modulator That Reverses Cognitive Impairment and Remediate Pathology in Alzheimer Mice

Terrence Town

bioRxiv

Ketogenesis Restrains Aging-Induced Exacerbation of COVID in a Mouse Model

Vishwa Deep Dixit

Immunity

Dietary Regulation of Immunity

Vishwa Deep Dixit

Cell and Tissue Research

Local TrkB Signaling: Themes in Development and Neural Plasticity

William C. Mobley

Journal of Experimental Medicine

Multi-Omic Comparison of Alzheimer's Variants in Human ESC-Derived Microglia Reveals Convergence at APOE

Rudolph Tanzi, Timothy Huang and Huaxi Xu

Pediatric Allergy and Immunology

An Interaction of the 17q12-21 Locus with Mold Exposure in Childhood Asthma

Christoph Lange

Cell Stem Cell

Deconstructing Stepwise Fate Conversion of Human Fibroblasts to Neurons by MicroRNAs

Andrew Yoo

Molecular Pharmacology

Structure of the Complex of an Iminopyridinedione Protein Tyrosine Phosphatase 4A3 Phosphatase Inhibitor with Human Serum Albumin

Elizabeth R. Sharlow and John S. Lazo

Neuron

Neuronal Activity Regulates Blood-Brain Barrier Efflux Transport Through Endothelial Circadian Genes

Richard Daneman

Science Translational Medicine

A β -Accelerated Neurodegeneration Caused by Alzheimer's-Associated ACE Variant R1279Q is Rescued by Angiotensin System Inhibition in Mice

Leah Cuddy, Winston Hide, Rudolph Tanzi and Robert Vassar

European Respiratory Journal

Confronting the Controversy: Interleukin-6 and the COVID-19 Cytokine Storm Syndrome

Cheryl Wellington

Nature Neuroscience

Mapping the Epigenomic and Transcriptomic Interplay During Memory Formation and Recall in the Hippocampal Engram Ensemble

Manolis Kellis and Li-Huei Tsai

Alzheimer's & Dementia

Vascular Contributions to Cognitive Impairment and Dementia (VCID): A Report From the 2018 National Heart, Lung, and Blood Institute and National Institute of Neurological Disorders and Stroke Workshop

Berislav V. Zlokovic and Cheryl Wellington

Neuron

Endothelial Tip Cell Finds Its Way with Piezo1

Zhen Zhao and Berislav V. Zlokovic

Blood Advances

The Association of ABO Blood Group With Indices of Disease Severity and Multiorgan Dysfunction in COVID-19

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Fluids and Barriers of the CNS

Identification and in Vivo Characterization of a Brain-Penetrating Nanobody

Bart De Strooper and Maarten Dewilde

eLife

APOE2 is Associated with Longevity Independent of Alzheimer's Disease

Takahisa Kanekiyo, John Fryer and Guojun Bu

Current Protocols in Human Genetics

The AD Knowledge Portal: A Repository for Multi-Omic Data on Alzheimer's Disease and Aging

Guojun Bu

Nature Communications

Gene Expression and Functional Deficits Underlie TREM2-Knockout Microglia Responses in Human Models of Alzheimer's Disease

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Cellular and Molecular Neurobiology

High Glucose and Hypoxia-Mediated Damage to Human Brain Microvessel Endothelial Cells Induces an Altered, Pro-Inflammatory Phenotype in BV-2 Microglia in Vitro

Paula Grammas

Cells

An Overview of Astrocyte Responses in Genetically Induced Alzheimer's Disease Mouse Models

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Molecular Neurodegeneration

APOE2: Protective Mechanism and Therapeutic Implications for Alzheimer's Disease

Guojun Bu

Neuron

Apolipoprotein E: Structural Insights and Links to Alzheimer Disease Pathogenesis

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Science Advances

Dedifferentiation and Neuronal Repression Define Familial Alzheimer's Disease

Steven L. Wagner

Nature Neuroscience

Severe Reactive Astrocytes Precipitate Pathological Hallmarks of Alzheimer's Disease Via H₂O₂-Production

Doo Yeon Kim and Hansang Cho

Science Translational Medicine

Gga3 Deletion and a GGA3 Rare Variant Associated with Late Onset Alzheimer's Disease Trigger BACE1 Accumulation in Axonal Swellings

Rudolph Tanzi and Giuseppina Tesco

Molecular Neurodegeneration

An in Vitro Bioengineered Model of the Human Arterial Neurovascular Unit to Study Neurodegenerative Diseases

Cheryl Wellington

Biochemistry and Biophysics Reports

Short-Term Treatment with Dabigatran Alters Protein Expression Patterns in a Late-Stage Tau-Based Alzheimer's Disease Mouse Model

Paula Grammas

Alzheimer's & Dementia

The APOE Gene Cluster Responds to Air Pollution Factors in Mice with Coordinated Expression of Genes That Differs by Age in Humans

Caleb Finch

The Journal of Head Trauma Rehabilitation

Use of Repetitive Transcranial Magnetic Stimulation in the Treatment of Neuropsychiatric and Neurocognitive Symptoms Associated with Concussion in Military Populations

David Brody

Frontiers in Psychiatry

Advancing Computerized Cognitive Training for MCI and Alzheimer's Disease in a Pandemic and Post-pandemic World

P. Murali Doraiswamy

Brain

Alzheimer's Disease Brain-Derived Extracellular Vesicles Spread Tau Pathology in Interneurons

Tsuneya Ikezu

Molecular Neurodegeneration

Astrocyte-Derived Clusterin Suppresses Amyloid Formation in Vivo

Leonard Petrucelli, Guojun Bu and John Fryer

Acta Neuropathologica Communications

Clusterin Ameliorates Tau Pathology in Vivo by Inhibiting Fibril Formation

Leonard Petrucelli and John Fryer

eLife

REV-ERB α Mediates Complement Expression and Diurnal Regulation of Microglial Synaptic Phagocytosis

Erik Musiek

Frontiers in Aging Neuroscience

γ -Secretase Modulatory Proteins: The Guiding Hand Behind the Running Scissors

Yueming Li

Journal of Experimental Medicine

Molecular Imaging of Alzheimer's Disease-Related Gamma-Secretase in Mice and Nonhuman Primates

Se Hoon Choi, Steven L. Wagner and Rudolph Tanzi

Journal of Biological Chemistry

An "Epitomic" Analysis of the Specificity of Conformation-Dependent, Anti-a β Amyloid Monoclonal Antibodies

Charles Glabe

Cell Systems

Pulse-Chase Proteomics of the App Knockin Mouse Models of Alzheimer's Disease Reveals That Synaptic Dysfunction Originates in Presynaptic Terminals

Jeffrey Savas

Nature Reviews Molecular Cell Biology

Cellular Senescence in Ageing: From Mechanisms to Therapeutic Opportunities

Darren J. Baker

Methods in Molecular Biology

3D Self-Organized Human Blood-Brain Barrier in a Microfluidic Chip

Roger Kamm

Cure Alzheimer's Fund Consortia

Cure Alzheimer's Fund (CureAlz) has identified five scientific areas in Alzheimer's disease (AD) research that will benefit from a larger effort. Each empowers leading researchers affiliated with different institutions to collaborate, bringing disparate expertise to bear on a vital and complex AD topic. Each consortium is a multiyear, multiproject effort investigating different aspects of the specific topic. The labs share biological materials, perform experiments and analyses for one another's projects, and the lead investigators from the projects meet regularly to share findings, discuss implications and consider new areas of exploration.

CIRCUITS (Collaboration to Infer Regulatory Circuits and to Uncover Innovative Therapeutic Strategies) Consortium

CIRCUITS investigates the impact of epigenetics in the development of Alzheimer's disease. Epigenetics refers to how gene expression changes in response to an organism's environment and experience; in other words, although a cell's genetics—its DNA—is stable, the way a cell reads and translates DNA into proteins changes via epigenetic regulation. The consortium has its roots in the Alzheimer's Genome Project™ (AGP), which revealed that genetic variants associated with AD risk were found not only in protein-coding genes, but to a greater extent in regulatory DNA regions that turn nearby genes “on” or “off.” Regulatory regions are subject to epigenetic modifications, the patterns of which determine whether and how a gene is expressed. Genetic variants in regulatory regions can affect AD risk by altering the pattern of epigenetic modifications in ways that lead to development or acceleration of AD pathology.

The Maxine and Richard Berg Brain Entry & Exit (BBEE) Consortium

With a founding grant from the Berg family in honor of their parents, Maxine and Richard Berg, the BBEE Consortium investigates the neuroanatomical features that allow molecules to enter and exit the brain and establish healthy fluid dynamics, therefore maintaining brain homeostasis. Among them, for example, are the blood-brain barrier, and the more recently discovered brain glymphatic and lymphatic system. The early dysfunction of the blood-brain barrier has been recognized as a hallmark of AD and, among other issues, the consortium is investigating whether lymphatic dysfunction is similarly disrupted early on. Understanding the mechanisms involved in maintaining homeostasis of the brain—and changes that impact the entry and exit of helpful and harmful molecules—has the potential to uncover novel targets for treatment of AD.

Three-Dimensional Drug Screening (3DDS) Consortium

The goal of the 3DDS Consortium is to screen thousands of approved drugs and natural products, and identify those that reduce AD pathology (amyloid pathology, tau tangles and neuroinflammation) to be repurposed as treatments for the disease. The 3D cell culture model developed by Drs. Doo Yeon Kim and Rudy Tanzi and known as Alzheimer's in a Dish™ (ADiD) replicates key aspects of the neuronal environment: neurons, microglia, astrocytes, the blood-brain barrier and the recruitment of macrophages from the body's periphery. This human-derived model offers vastly more rapid and accurate assessment of whether a compound reduces amyloid, tau and neuroinflammatory pathology than the historical approach of testing one compound at a time in an animal model. The approved drugs and natural products with the highest demonstrated and validated efficacy against AD pathology in the ADiD model then will be assessed by a task force for their pharmacological promise as central nervous system drugs, and prioritized for clinical trials.

Neuroinflammation Consortium

In addition to misfolded amyloid and tau proteins, neuroinflammation plays a key role in the progression of Alzheimer's disease. CureAlz convened the Neuroinflammation Consortium due to emerging genetic studies implicating the brain's resident immune cells, called microglia, in the pathogenesis of sporadic AD. These cells typically clear the brain of debris, including the removal of misfolded amyloid, and perform a variety of other functions responding to changes in the neural environment. In Alzheimer's, microglia become overactivated and shift from their homeostatic role to a chronic neuroinflammatory state that causes neurodegeneration—destroying more neurons than amyloid and tau do in the process. Restoring microglia from overactive neuroinflammatory to homeostatic normal holds great therapeutic potential in preventing or halting neuroinflammation in AD.

Fleming APOE Consortium

The Fleming Foundation has provided a grant, in honor of Richard and Peggy Fleming, for the funding of the Fleming APOE Consortium. This group investigates the various roles of the APOE protein to determine how and why the APOE4 variant is the biggest genetic risk factor for sporadic AD. APOE4 versus an APOE3 or APOE2 genotype worsens a wide variety of physiological measures known to be implicated in AD, from levels of amyloid beta, to blood-brain barrier function, to neuroinflammation, to higher adiposity in the body's periphery. Having a single copy of the APOE4 allele increases risk of Alzheimer's disease; two copies may increase the risk by as much as 12 times. The investigations into how APOE4 contributes to the pathophysiology of the disease have the potential to provide insights for future therapies for AD.

Our Researchers

This gallery features researchers who received funding in 2020, as well as the members of our Research Leadership Group and Research Strategy Council.



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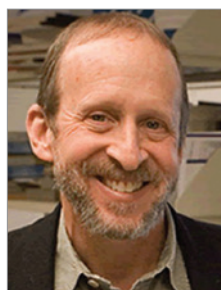
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KU Leuven, Belgium
Group Leader and Assistant Professor



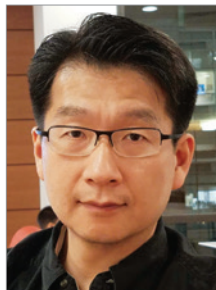
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University of Lübeck
Professor of Genome Analytics and Head, Lübeck Interdisciplinary Platform for Genome Analytics (LIGA)



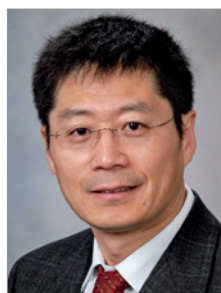
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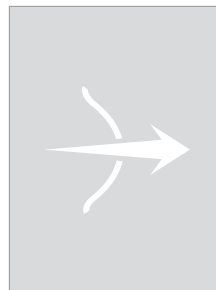
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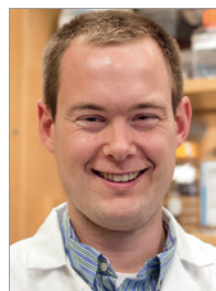
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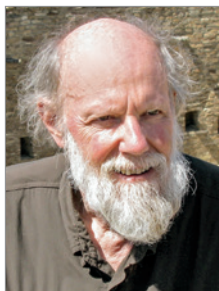
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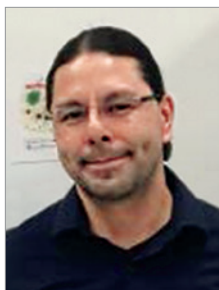
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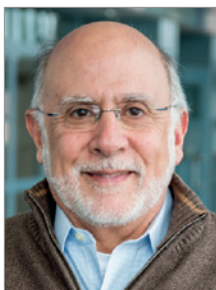
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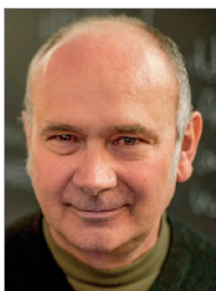
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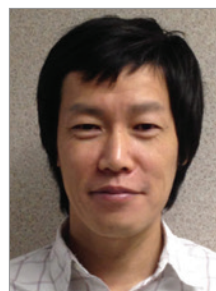
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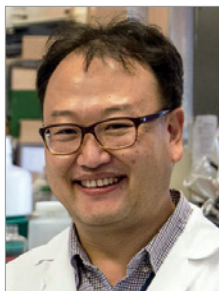


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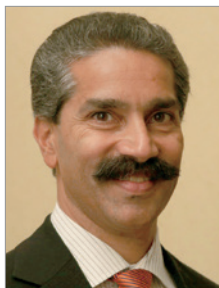


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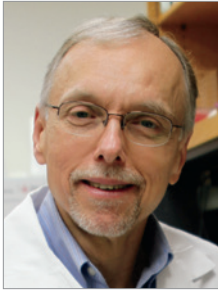


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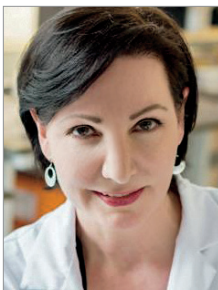
Associate Professor of Neurology, Harvard Medical School; Associate Geneticist



WEIMING XIA, PH.D.

Boston University School of Medicine

Professor, Pharmacology and Experimental Therapeutics



CHERYL WELLINGTON, PH.D.

University of British Columbia

Professor, Department of Pathology and Laboratory Medicine

Research Leadership Group



RIQIANG YAN, PH.D.

University of Connecticut Health Center

Professor and Chair, Department of Neuroscience

Research Leadership Group



STEPHEN T.C. WONG, PH.D.

Houston Methodist Research Institute

John S. Dunn, Sr., Presidential Distinguished Chair in Biomedical Engineering and Professor of Computer Science and Bioengineering in Oncology, Houston Methodist Academic Institute; Associate Director, Shares Resources, Houston Methodist Cancer Center; Director, T. T & W. F. Center for BRAIN, Houston Methodist; Professor of Radiology, Neurosciences, Pathology and Laboratory Medicine, Weill Cornell Medicine

Research Leadership Group



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

University of Southern California

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

Research Leadership Group

New Researchers

This gallery features researchers who received funding from Cure Alzheimer's Fund for the first time in 2020.



MATHEW BLURTON-JONES, PH.D.

University of California, Irvine

Associate Professor, Department of Neurobiology and Behavior; Director, UCI ADRC iPS cell core and UCI Stem Cell CRISPR core

Research Leadership Group



LIISA GALEA, PH.D.

University of British Columbia

Professor and Lead, Women's Health Research Cluster; Scientific Advisor, Women's Health Research Institute; Director, Graduate Program in Neuroscience; Distinguished University Scholar, Psychology; Associate, Psychiatry, Djavad Mowafaghian Center for Brain Health



PAOLA BOVOLENTA, PH.D.

CSIC-UAM, Spain

Research Professor and Chair of the Program "Homeostasis of Tissue and Organs," Center for Molecular Biology Severo Ochoa



CHRISTINA M. LILL, M.D., M.SC.

University of Lübeck

Head, Translational Epidemiology Group, Lübeck Interdisciplinary Platform for Genome Analytics; Lecturer, Ageing Epidemiology Unit, School of Public Health, Imperial College London, UK



LEAH CUDDY, PH.D.

Northwestern University

Research Assistant Professor of Neurology



RICHARD B. LIPTON, M.D.

Albert Einstein College of Medicine

Professor, Departments of Neurology, Psychiatry and Behavioral Sciences, and Epidemiology & Population Health (Epidemiology); Edwin S. Lowe Chair in Neurology; Vice Chair, The Saul R. Korey Department of Neurology; Director, Montefiore Headache Center



PILAR ESTEVE, PH.D.

CSIC-UAM, Spain

Assistant Professor, Center for Molecular Biology Severo Ochoa



MIRANDA E. ORR, PH.D.

Wake Forest School of Medicine

Assistant Professor, Gerontology and Geriatric Medicine; Research Health Scientist



ALI EZZATI, M.D.

Albert Einstein College of Medicine

Assistant Professor of Neurology



GENTRY PATRICK, PH.D.

University of California, San Diego

Professor, Neurobiology Section of the Division of Biological Sciences



KENNETH PEARCE JR., PH.D.

University of North Carolina

Professor, Center for Integrative Chemical Biology and Drug Discovery, UNC Eshelman School of Pharmacy; Director, Lead Discovery and Characterization



NANDA KUMAR NAVALPUR SHANMUGAM, PH.D.

Massachusetts General Hospital

Research Associate; Instructor, Harvard Medical School



LUISA QUINTI, PH.D.

Massachusetts General Hospital

Instructor in Neurology



JOHN SONDEK, PH.D.

University of North Carolina

Professor of Pharmacology and Biochemistry & Biophysics; Member, Lineberger Comprehensive Cancer Center; Director, UNC Center for Structural Biology



JEAN-PIERRE ROUSSARIE, PH.D.

The Rockefeller University

Senior Research Associate



RIK VAN DER KANT, PH.D.

Amsterdam University Medical Center

Assistant Professor, Functional Genomics and Neurodegeneration, VU University Amsterdam and the Alzheimer Center



PHILIP SCHELTENS, M.D., PH.D.

Amsterdam University Medical Center

Professor of Cognitive Neurology; Director of the Alzheimer Center



QISHENG ZHANG, PH.D.

University of North Carolina

Associate Professor, Department of Pharmacology and Division of Chemical Biology and Medicinal Chemistry



ANJA SCHNEIDER, M.D.

DZNE, Germany

Professor and Director, Clinic for Neurodegenerative Diseases and Gerontopsychiatry, Bonn University Hospital; Senior Group Leader

2020 Funded Research

Cure Alzheimer's Fund spent **\$16.5 million to support 59 research projects** across our focus areas. Visit CureAlz.org/the-research to read about all of our current research projects.

Project/Researcher	Distribution Amount
FOUNDATIONAL RESEARCH	
GENETIC RISK FACTORS	
Analytical and Statistical Tools for Sequence Analysis for Alzheimer's Disease Christoph Lange, Ph.D., Harvard T.H. Chan School of Public Health	\$172,500
The Alzheimer's Genome Project™ Rudolph Tanzi, Ph.D., Massachusetts General Hospital	\$1,725,000
BIOMARKERS, DIAGNOSTICS, AND STUDIES OF RISK AND RESILIENCE	
Sex Differences in Alzheimer's Disease Progression: Framingham Heart Study P. Murali Doraiswamy, MBBS, Duke University	\$203,281
Understanding Molecular Biomarker Changes in Alzheimer's Disease Using Genetically Defined Mouse Models Mathias Jucker, Ph.D., and Stephan Kaeser, Ph.D., University of Tübingen, Germany	\$172,500
Characterization of Alzheimer's Disease Molecular Biomarker Profiles Throughout the Pathobiological Continuum Krista L. Moulder, Ph.D., Washington University School of Medicine in St. Louis	\$21,984
Personalized Disease Prediction for Alzheimer's Disease Using Proteome Profiling: The EPIC4AD Study Christina M. Lill, M.D., M.Sc., and Lars Bertram, M.D., University of Lübeck	\$459,977
A Transcriptional Rejuvenation Signature for Alzheimer's Disease Tony Wyss-Coray, Ph.D., Stanford University School of Medicine	\$172,500
PRODUCTION OF NEW ANIMAL AND CELLULAR MODELS OF ALZHEIMER'S DISEASE	
Creation of a Fibroblast/iPS Cell Bank to Facilitate Peripheral/Brain Comparisons, and Allow Molecular Investigations into Molecular Mechanisms Underlying Differences in Disease Aggressiveness Bradley Hyman, M.D., Ph.D., Massachusetts General Hospital	\$250,000
Genes to Therapies™ (G2T) Research Models and Materials Taconic Biosciences	\$1,969,647
Genes to Therapies™ (G2T) Centralized Research Core Wilma Wasco, Ph.D., Massachusetts General Hospital	\$172,500
EPIGENETIC FACTORS	
Identifying Novel Epigenetic Biomarkers of Human Cognitive Aging Lars Bertram, M.D., University of Lübeck	\$177,375
Using Epigenetics to Characterize the Regulation of Cellular States in Microglia That Contribute to Alzheimer's Disease Pathology Christopher K. Glass, M.D., Ph.D., University of California, San Diego	\$250,000
Integrating Functional Maps to Discover MicroRNAs in Alzheimer's Disease Winston Hide, Ph.D., Beth Israel Deaconess Medical Center	\$172,500
Impact of Genetic, Epigenetic and Cellular Variants on Alzheimer's Disease Pathology Rudolf Jaenisch, M.D., Massachusetts Institute of Technology, and Joseph R. Ecker, Ph.D., The Salk Institute	\$287,500
CIRCUITS (Collaboration to Infer Regulatory Circuits and to Uncover Innovative Therapeutic Strategies) Consortium Production Group Manolis Kellis, Ph.D., and Li-Huei Tsai, Ph.D., Massachusetts Institute of Technology	\$550,000

TRANSLATIONAL RESEARCH	
NOVEL ALZHEIMER'S DISEASE GENES	
Single Nucleus RNA Sequencing Analysis of ACE1 R1284Q Knockin Mice GENEWIZ, Robert Vassar, Ph.D., and Leah Cuddy, Ph.D., Northwestern University	\$234,796
ABCA7 Loss of Function in Aging and Alzheimer's Disease Takahisa Kanekiyo, M.D., Ph.D., and Guojun Bu, Ph.D., Mayo Clinic	\$172,500
The NEDD4-1 and PKCa Connection in Alzheimer's Disease Gentry Patrick, Ph.D., University of California, San Diego	\$172,500
Understanding and Mimicking the Biological Effects of the Phospholipase C-gamma-2 P522R Variant That Protects Against Alzheimer's Disease Rik van der Kant, Ph.D., and Philip Scheltens, M.D., Ph.D., Amsterdam University Medical Center	\$172,485
APP AND AMYLOID BETA	
SFRP1 as a Therapeutic Target and Diagnostic/Prognostic Factor in Alzheimer's Disease Paola Bovolenta, Ph.D., and Pilar Esteve, Ph.D., CSIC-UAM, Spain	\$172,500
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., KU Leuven, Belgium	\$220,408
In Vivo Characterization of a Loss-of-Function GGA3 Rare Variant Associated with Alzheimer's Disease Giuseppina Tesco, M.D., Ph.D., Tufts University School of Medicine	\$172,500
TAU	
Mechanisms of Tau Propagation Across the Plasma Membrane Marc Diamond, M.D., University of Texas Southwestern Medical Center	\$250,000
Reversal of Tau Pathology by an Adenosine A1 Receptor Antagonist Eva-Maria Mandelkow, M.D., Ph.D., Eckhard Mandelkow, Ph.D., and Anja Schneider, M.D., DZNE, Germany	\$287,500
Investigating the Role of Tau Protein in Neuronal Senescence Induction and Maintenance Miranda E. Orr, Ph.D., Wake Forest School of Medicine	\$172,500
APOLIPOPROTEIN E (APOE)	
Assessing the Added Diagnostic Value of Peripheral Apolipoprotein E Protein Levels in Current Blood-Based Biomarker Assays for Central Nervous System Amyloidosis Randall J. Bateman, M.D., Washington University School of Medicine in St. Louis	\$247,922
Counteracting Pathogenic Events in Alzheimer's Disease with Peripheral or Central Apolipoprotein E Guojun Bu, Ph.D., Mayo Clinic	\$250,000
The Role of Apolipoprotein E in Microglia Regulation in Neurodegeneration Oleg Butovsky, Ph.D., Brigham and Women's Hospital	\$250,000
Sex Matters: Understanding the Influence of Sex and Apolipoprotein E (APOE) Genotype on Hippocampal Plasticity and Cognition Liisa Galea, Ph.D., University of British Columbia	\$172,500
Understanding the Effect of Apolipoprotein E on Tau-Mediated Neurodegeneration David M. Holtzman, M.D., Washington University School of Medicine in St. Louis	\$300,000
Toward Developing High-Density Lipoprotein Enriched in Apolipoprotein E as a Potential Biomarker and Therapeutic Targeting Vascular Contributions to Alzheimer's Disease Cheryl Wellington, Ph.D., University of British Columbia	\$249,999
Regulation by Apolipoprotein E of Selective Neuronal Vulnerability to Alzheimer's Disease Jean-Pierre Roussarie, Ph.D., The Rockefeller University	\$250,000

FUNDED RESEARCH (CONTINUED)

Project/Researcher	Distribution Amount
TRANSLATIONAL RESEARCH <small>(CONTINUED)</small>	
INNATE IMMUNE PATHOLOGY	
Examining the Role of Human Microglia in the Transition Between Parenchymal and Vascular Amyloid Beta Pathology Mathew Blurton-Jones, Ph.D., University of California, Irvine	\$250,000
Assessing the Links Between the MS4A Risk Genes, Microglia and Alzheimer's Disease Sandeep Robert Datta, M.D., Ph.D., Harvard Medical School	\$250,000
Role of Secreted Protein Acidic and Rich in Cysteine (SPARC) in Immunometabolic Control of Age-Related Inflammation Vishwa Deep Dixit, D.V.M., Ph.D., Yale School of Medicine	\$172,500
VGF-Derived Peptide Therapy for Alzheimer's Disease: Studies of Mouse and Human TLQP-21 and its Receptor, C3aR1 Michelle E. Ehrlich, M.D., and Stephen R. Salton, M.D., Ph.D., Icahn School of Medicine at Mount Sinai	\$172,500
Investigating the Contribution of Astrocytic-Dependent Inflammation on Amyloid-Induced Tau Pathology Gilbert Gallardo, Ph.D., Washington University School of Medicine in St. Louis	\$172,500
Discovery and Development of Chemical Probes to Elucidate MS4A Protein Function Jacob M. Hooker, Ph.D., Massachusetts General Hospital	\$200,000
Investigation of Alzheimer's Disease Risk Alleles in Astrocytes—Focus on Cholesterol Transport and Microglia Interactions Shane A. Liddelow, Ph.D., Neuroscience Institute at NYU Langone Health	\$250,000
Understanding the Consequences of Noncoding Alzheimer's Disease Risk Alleles on Microglia Function Beth Stevens, Ph.D., Boston Children's Hospital	\$300,000
ALTERNATIVE NEURODEGENERATIVE PATHWAYS	
Senescent Cells and Alzheimer's Disease Darren J. Baker, Ph.D., M.S., Mayo Clinic	\$172,500
Gut Microbiota, Endothelial Dysfunction and Tau-Mediated Cognitive Impairment Giuseppe Faraco, M.D., Ph.D., and Costantino Iadecola, M.D., Weill Cornell Medicine	\$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
Characterizing Gut Microbiome Synergy With Emphasis on Mycobiome and Its Impact on Alzheimer's Disease (AD) Pathology in AD Mouse Models Deepak Kumar Vijaya Kumar, Ph.D., Nanda Kumar Navalpur Shanmugam, Ph.D., William Eimer, Ph.D., and Rudolph Tanzi, Ph.D., Massachusetts General Hospital	\$250,000
Microbes and Alzheimer's Disease: Metagenomics on Saliva, Cerebrospinal Fluid, Blood and Brain Nanda Kumar Navalpur Shanmugam, Ph.D., William Eimer, Ph.D., Deepak Kumar Vijaya Kumar, Ph.D., and Rudolph Tanzi, Ph.D., Massachusetts General Hospital	\$350,000
Effect of Gut Microbiome Dysbiosis on Neuroinflammation and Amyloid Beta Deposition: A Longitudinal Micro-PET Study in Alzheimer's Transgenic Mice Sangram S. Sisodia, Ph.D., University of Chicago	\$168,434
Molecular Signatures of APOE-Mediated Blood-Brain Barrier Dysfunction Causing Neuronal and Synaptic Dysfunction Berislav V. Zlokovic, M.D., Ph.D., University of Southern California	\$250,000

DRUG DISCOVERY AND ENABLING TECHNOLOGIES**DRUG SCREENING**

Adult Human iNeurons: A Next-Generation Drug Screening Platform for Alzheimer's Disease George S. Bloom, Ph.D., John S. Lazo, Ph.D., and Elizabeth R. Sharlow, Ph.D., University of Virginia	\$229,249
Modulating CD33 Function and Neuroinflammation as a Therapeutic Approach for Alzheimer's Disease Ana Griciuc, Ph.D., Massachusetts General Hospital	\$172,500
Pharmacologically Protecting and Rescuing Synapses from Amyloid Beta by Raising Synaptic PSD-95 Roberto Malinow, M.D., Ph.D., University of California, San Diego	\$143,750
Virtual High-Throughput Screening for CD33 Inhibitors Subhash Sinha, Ph.D., Weill Cornell Medicine	\$172,500
Small Molecule Activators of Phospholipase C-gamma-2 as Novel Therapeutics for Alzheimer's Disease Qisheng Zhang, Ph.D., John Sondek, Ph.D., and Kenneth Pearce Jr., Ph.D., University of North Carolina	\$172,500
Uncovering the Molecular Mechanisms of Selected Drug Candidates Derived from Systematic Alzheimer's Drug Repositioning Stephen T.C. Wong, Ph.D., Houston Methodist Research Institute	\$200,000
High-Throughput Drug Screening for Alzheimer's Disease Using Three-Dimensional Human Neural Culture Systems Doo Yeon Kim, Ph.D., and Luisa Quinti, Ph.D., Massachusetts General Hospital	\$230,000
Proteomics of Alzheimer's Disease Three-Dimensional Cultures Weiming Xia, Ph.D., Boston University School of Medicine	\$172,500
DRUG DELIVERY AND DESIGN	
Novel Entry Routes for Therapeutic Biologicals to the Brain Maarten Dewilde, Ph.D., KU Leuven, Belgium, and Bart De Strooper, M.D., Ph.D., VIB-KU Leuven, Belgium	\$172,500

PRECLINICAL AND CLINICAL DRUG DEVELOPMENT AND TRIALS**PRECLINICAL DRUG DEVELOPMENT**

Comprehensive Analyses of Chronic Efficacy Studies with GSM 776890 for Submission of the Pre-IND Brochure to the FDA Prior to Pre-IND Meeting and IND Filing for the SAD/MAD Phase I Safety/Toxicity and Ultimately for Phase II and Phase III Efficacy Clinical Trials to Support the NDA Steven L. Wagner, Ph.D., University of California, San Diego	\$259,366
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CLINICAL TRIALS

PEGASUS Clinical Study of AMX0035 in Alzheimer's Disease AMYLYX	\$100,000
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CLINICAL TRIAL DESIGN

Improving Alzheimer's Disease Clinical Trials' Design by Machine Learning Models Ali Ezzati, M.D., and Richard B. Lipton, M.D., Albert Einstein College of Medicine	\$100,000
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FOUNDATIONAL RESEARCH

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

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

We will develop statistical methodology for rare variant analysis in whole genome sequencing (WGS) studies that takes the sparseness of the data into account and does not require any asymptotic approximations. We

will reanalyze the Cure Alzheimer's Fund WGS family study with the new methodology and distribute software implementation of the approaches via our Family-Based Association Test (FBAT) package.

The Alzheimer's Genome Project™

RUDOLPH TANZI, PH.D., Massachusetts General Hospital

The Alzheimer's Genome Project™ (AGP) is aimed at analyzing our large Alzheimer's disease (AD) genetics database consisting of our own, collaborative and all publicly available AD genome-wide association study (GWAS), whole genome sequence (WGS) and whole exome sequence (WES) data. In the AGP, we use these datasets along with a series of unique algorithms to identify genes harboring common and rare genomic variants associated with AD. We currently analyze WGS data from 2,247 subjects from 605 multiplex AD families, and then follow up with replication analyses in WGS from an independent case-control cohort composed of more than 1,650 individuals. To our knowledge, we

are analyzing the largest amount of AD WGS data in the world today. For AD-associated genomic variants predicted to have functional consequences, we will analyze them in our various 3D cell culture models (Alzheimer's in a Dish™). The most promising AD-associated functional variants also are shared with the Cure Alzheimer's Fund Genes to Therapies™ (G2T) Committee, and any resulting mouse models then are made available to all Cure Alzheimer's Fund investigators and the greater AD research community. As in the past, we also will continue to share our genetic data regarding AD-associated functional variants with a growing number of Cure Alzheimer's Fund investigators.

Sex Differences in Alzheimer's Disease Progression: Framingham Heart Study

P. MURALI DORAISWAMY, MBBS, Duke University

The promise of personalized medicine includes understanding sex differences in health and disease. It has been well documented that women have a higher risk of developing Alzheimer's disease compared with men, but this is not simply because women on average live to an older age than men. This proposal

capitalizes on the 70 years of health-related data from the Framingham Heart Study, combining with traditional and machine learning analytic methods, to determine what combination of factors can explain sex differences in Alzheimer's disease risk and progression.

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

MATHIAS JUCKER, PH.D., University of Tübingen, Germany

STEPHAN KAESER, PH.D., University of Tübingen, Germany

Fluid biomarkers have become important for the monitoring of disease progression and treatment response in clinical trials. However, what is largely missing is a mechanistic understanding of what protein changes in cerebrospinal fluid and blood mean, and how they relate to processes in the brain. Our results in the first year of funding suggest that the increases of tau protein in the cerebrospinal fluid of Alzheimer's disease

subjects mainly reflect amyloid beta deposition in the brain and not (as previously thought) neurofibrillary tangle formation in the brain. We also have established that changes of neurofilament light chain protein in the blood are linked to changes in the nervous system. Finally, we have started to identify a set of proteins in cerebrospinal fluid that reflects the different stages of inflammation in the brain of Alzheimer's patients.

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

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

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

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

Personalized Disease Prediction for Alzheimer's Disease Using Proteome Profiling: The EPIC4AD Study

CHRISTINA M. LILL, M.D., M.SC., University of Lübeck

LARS BERTRAM, M.D., University of Lübeck

At the time of a clinical diagnosis of Alzheimer's disease (AD), the underlying disease process already has evolved in the affected individuals for often more than a decade and led to irrecoverable brain damage. Without reliable predisease biomarkers, the development and successful application of effective treatment or preventive strategies thus is severely hampered. However, the identification of predictive biomarkers requires examining large groups of initially healthy individuals and following them over a long time to determine who eventually developed AD and who did not. Such cohort studies are very difficult and laborious to conduct, especially for a late-onset disease such as AD. In this project, EPIC4AD, we will overcome this limitation by utilizing blood samples of participants of one of the largest cohort studies worldwide for systematic biomarker identification, i.e., the EPIC study (European Prospective Investigation into Cancer and Nutrition). For each of the more than 500,000 initially healthy participants, blood samples were collected and stored

at baseline. During the more than 20 years of follow-up, several thousand EPIC participants eventually have been diagnosed with AD. To identify novel predisease biomarkers, we will utilize a recently developed high-throughput technology (SomaScan assay) to determine the concentrations of approximately 5,000 different proteins in blood samples from about 1,000 AD cases and about 5,000 healthy control individuals. The proteomic data will be combined with genetic as well as lifestyle and medical data, along with the measurement of existing established AD biomarkers, to develop disease prediction models using artificial intelligence. Given the enormous size of the EPIC cohort combined with the large number of proteins assayed simultaneously in one experiment, our study is in the unique position to advance the field of AD biomarker research beyond its current state, and will set the stage for finally being able to develop novel early detection/early prevention strategies against this devastating disease.

A Transcriptional Rejuvenation Signature for Alzheimer's Disease

TONY WYSS-CORAY, PH.D., Stanford University School of Medicine

Aging is the leading risk factor for most noncommunicable diseases such as cancer, diabetes and neurodegenerative diseases, including Alzheimer's. Conversely, experimental interventions that can stave off the aging process—or even “reverse” it—protect against age-related maladies. We recently discovered that infusion of young plasma, which rejuvenates old brains, also may protect against Alzheimer's disease. We propose here to identify a gene activity signature of

rejuvenation in Alzheimer's models. We show that such a signature enables the prediction of novel Alzheimer's drugs in humans and propose an experimental pipeline to test candidate compounds in neurons from reprogrammed skin cells of Alzheimer's patients. If successful, our study may provide a foundational pipeline to reverse-engineer the powerful capacities of rejuvenation into actionable targets for novel Alzheimer's therapeutics.

Creation of a Fibroblast/iPS Cell Bank to Facilitate Peripheral/Brain Comparisons, and Allow Molecular Investigations into Molecular Mechanisms Underlying Differences in Disease Aggressiveness

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

An astonishing discovery of how to convert skin cells into other kinds of cells—including brain cells—earned Dr. Shinya Yamanaka the Nobel prize in 2012 and already has opened extraordinary new capabilities in science. Applied to Alzheimer's disease, it has the potential to revolutionize how we do experiments. Right now, we rely on examining brain tissue of patients who have died of the disease to understand the molecular changes that occur, but the promise of Dr. Yamanaka's discovery is that we could use a little piece of skin—from a living patient—instead. The major barrier to doing this is that we do not know whether the "brain" cells that can be made in a few weeks from a piece of skin actually act

like the cells from a brain of a person who has been alive for 70 or 80 years. We propose to create a bank of skin cells taken from the same people who now donate brain tissue at autopsy to directly compare the two, and to make this resource available to the dozens (hundreds) of labs that have developed specialized assays in which comparison of the two different kinds of "brain" cells would be valuable. Our own studies will be directed to understanding whether there are different molecular characteristics in "brain" cells made from the skin of patients whose course of disease was more aggressive—or more benign—to try to develop methods to understand this dichotomy.

Genes to Therapies™ (G2T) Research Models and Materials

TACONIC BIOSCIENCES

Taconic Biosciences GMBH, a global provider of genetically modified mouse models and associated services, is providing customized mouse models (transgenic, conventional/conditional knock out,

conventional/conditional knock in) for each specific gene and type of mutation that will be studied in the Genes to Therapies™ project.

Genes to Therapies™ (G2T) Centralized Research Core

WILMA WASCO, PH.D., Massachusetts General Hospital

The Cure Alzheimer's Fund Genes to Therapies™ (G2T) Centralized Research Core works in concert with the Alzheimer's Genome Project™ (AGP) and in partnership with Taconic Biosciences to create new Alzheimer's disease mouse models. While the models are being validated, they are available to CureAlz grantees; however, all models ultimately will be made available to the scientific community in general. Providing these

mouse models and other appropriate reagents to investigators not only will obviate the time and effort necessary for each investigator to generate their own mouse models and reagents, but importantly, it will ensure that all investigators are working with animal models that are consistently and reliably generated, documented and maintained.

Identifying Novel Epigenetic Biomarkers of Human Cognitive Aging

LARS BERTRAM, M.D., University of Lübeck

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

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

Using Epigenetics to Characterize the Regulation of Cellular States in Microglia That Contribute to Alzheimer's Disease Pathology

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 (AD). 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 extend our previous CureAlz-supported studies suggesting that such "noncoding" changes in DNA affect the amounts of specific proteins that are made within microglia and other cell types in the brain. We will focus specifically on the role of a region of the genome that selectively controls expression of the BIN1 gene in microglia and contains changes in noncoding DNA sequence that are highly associated with risk for AD. As a second

aim, we will define regions in the genome that control microglia functions dependent on proteins that are members of the MS4A gene family. These proteins are encoded by genes that reside in a region of the genome that also contains changes in noncoding DNA sequence that are highly associated with risk of AD. These studies have the objective of determining how MS4A proteins regulate microglia functions that promote AD. Successful completion of this work will depend on extensive collaborations with members of the CureAlz Neuroinflammation Consortium. These studies are expected to enable better understanding of how noncoding changes in DNA influence the risk of AD, and may lead to identification of new therapeutic targets.

Integrating Functional Maps to Discover MicroRNAs in Alzheimer's Disease

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

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

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

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

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

JOSEPH R. ECKER, PH.D., The Salk Institute

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

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

CIRCUITS (Collaboration to Infer Regulatory Circuits and to Uncover Innovative Therapeutic Strategies) Consortium Production Group

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

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

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

Here, we seek to overcome this limitation by directly profiling changes in the circuitry of neurons and other brain cell types during Alzheimer's disease, and how genetic variants are affecting that circuitry. In the first funding period of the award, we generated thousands of transcriptional and epigenomic maps of gene

expression and control region activity across individuals at single-cell resolution. We integrated the resulting datasets to decipher the mechanistic basis of genetic variants associated with disease, and to discover new therapeutic targets, and the pathways and cell types where they act.

In the next period of the award, we expand these studies with a spatiotemporal single-cell map of disease progression across brain regions and disease stages, detailed analyses of genetic effects by APOE and other strong-effect variants on gene expression at single-cell resolution, a high-resolution characterization of microglia subtypes, and integration of common, rare and somatic mutations to predict target genes, regulatory regions and regulators, which we systematically perturb using highly parallel reporter assays.

TRANSLATIONAL RESEARCH

Single Nucleus RNA Sequencing Analysis of ACE1 R1284Q Knockin Mice

GENEWIZ

ROBERT VASSAR, PH.D., Northwestern University

LEAH CUDDY, PH.D., Northwestern University

The gene for angiotensin converting enzyme (ACE1) recently was shown to be a genetic risk factor for Alzheimer's disease (AD). Our collaborators, Dr. Rudolph Tanzi and his group, discovered mutations in the ACE1 gene that are associated with AD in families. One of these mutations was introduced into mice by genetic "knockin" (KI) technology. We analyzed the effects of the ACE1 KI mutation on the brain and its functions, and the memory performance of mice. We discovered that the ACE1 KI mutation caused the hippocampus, a part of the brain important for memory, to degenerate in an age- and sex-associated manner, in that females were affected more severely than males, like in human AD. Moreover, the ACE1 KI showed impaired memory performance and electrical activity in the brain. Brain inflammation also was increased in the ACE1 KI mice. Drugs that block the ACE1 pathway were able to prevent the degeneration of the hippocampus

in ACE1 KI mice. Finally, when crossed to mice that develop the AD hallmark amyloid plaque pathology, hippocampus degeneration was accelerated in ACE1 KI mice. Our results strongly suggest that the ACE1 pathway in the brain plays an important role in AD. However, very little is known about the ACE1 pathway in the central nervous system. In this project, we will use a technique called single nucleus RNA sequencing, an unbiased systems biology approach, to determine the genes that are turned on or turned off in different cell types of the hippocampus during early, middle and late stages of degeneration in ACE1 KI mice compared with wild-type mice. These data will allow us to define the ACE1 pathway in the brain that is important for the degeneration of the hippocampus caused by the ACE1 KI mutation, information we anticipate will be valuable for the design of therapies to block brain degeneration in AD.

ABCA7 Loss of Function in Aging and Alzheimer's Disease

TAKAHISA KANEKIYO, M.D., PH.D., Mayo Clinic

GUOJUN BU, PH.D., Mayo Clinic

Alzheimer's disease is the most common cause of memory loss or dementia in the aging population, characterized by brain deposition of toxic molecules, amyloid beta and tau. While diverse genetic and environmental factors contribute to neuronal damages in the disease, accumulating evidence has indicated that microglia plays a critical role in the pathogenic mechanisms. Thus, better understanding of interaction between neurons and microglia in AD is necessary to explore the complex pathogenesis of age-related cognitive decline and AD. Recently, we revealed that deficiency of ATP-binding cassette transporter A7 (ABCA7), which is one of the AD risk genes, causes abnormal phenotypes in microglia as well as neurons in cell models and mice. Since ABCA7 is abundantly expressed in neurons and microglia in the brain,

our overall goals are to explore potential impacts of ABCA7 deletion in those cell types on AD-related phenotypes. To do this, we will use newly generated microglia- or neuron-specific ABCA7 knockout mice with or without the background of amyloid pathology. We also aim to identify novel cell-specific pathways through nontargeted approaches. Furthermore, we will examine ABCA7 function using a mono- or co-culture system of neurons and microglia from human-induced pluripotent stem cells, where the ABCA7 gene is deleted by CRISPR/Cas9. Therefore, our study will give us unique opportunities to determine the roles of ABCA7 depending on brain cell types in both physiological and pathological conditions, and to identify novel targets to develop effective therapeutic interventions for age-related cognitive decline and AD.

The NEDD4-1 and PKCa Connection in Alzheimer's Disease

GENTRY PATRICK, PH.D., University of California, San Diego

Synapses, the point of contact and communication between two neurons, are susceptible to damage by a pathological protein cleavage byproduct of the amyloid precursor protein (APP) called amyloid beta that accumulates in the brains of individuals who have Alzheimer's disease. Specifically, synapses are removed, and the communication between the synapses that remains is weakened in part by the removal of a particular type of glutamate neurotransmitter receptors, called AMPA receptors. We discovered that a protein called NEDD4-1 is responsible for the degradation of AMPA receptors from synapses that facilitate normal learning and memory. We have shown that, in response to elevated amyloid beta levels, NEDD4-1 inappropriately eliminates AMPA receptors in cell culture models of

AD; we intend to determine whether this holds true in mouse models. Furthermore, we find this appears to involve an aberrant signaling pathway involving PKCa previously known to operate downstream of amyloid beta to negatively affect synapses. We have proposed innovative strategies to uncover the functional relationship between NEDD4-1 and PKCa in AD. Many therapeutic strategies for AD are focused on reducing amyloid beta levels or on inactivating amyloid beta directly. However, identifying new molecules that mediate the pathogenic effects of amyloid beta is another area with significant promise. Thus, if achieved, our proposal would deliver NEDD4-1 as a new and potential therapeutic target to mitigate the effects of amyloid beta at synapses.

Understanding and Mimicking the Biological Effects of the Phospholipase C-gamma-2 P522R Variant That Protects Against Alzheimer's Disease

RIK VAN DER KANT, PH.D., Amsterdam University Medical Center
PHILIP SCHELTENS, M.D., PH.D., Amsterdam University Medical Center

No drugs that can prevent or revert Alzheimer's disease currently exist. Genetic studies recently have discovered that people with a genetic variant in the Phospholipase C-gamma-2 (PLC-gamma-2) gene—the "P522R" variant—are protected from Alzheimer's disease and other dementias. The PLC-gamma-2 enzyme plays a role in brain immune cells, but exactly how the P522R variant protects against dementia in these cells is not known. Here we will use novel stem cell techniques to study how the PLC-gamma-2 P522R variants affect the function of human brain immune cells (also known as microglia).

We also will compare the effect of PLC-gamma-2 P522R with other PLC-gamma-2 mutations that are known to cause immune disease. Our goal is to establish what is unique about PLC-gamma-2 P522R that drives the protective effect of this mutation against dementias. This research will help provide insight into the role of PLC-gamma-2 in Alzheimer's disease and other dementias. The knowledge gained from our proposal can directly be applied to discover novel drugs that mimic the protective effect of the P522R variant for the treatment of Alzheimer's disease and other dementias.

SFRP1 as a Therapeutic Target and Diagnostic/Prognostic Factor in Alzheimer's Disease

PAOLA BOVOLENTA, PH.D., CSIC-UAM, Spain
PILAR ESTEVE, PH.D., CSIC-UAM, Spain

There is increasing evidence that Alzheimer's disease not only involves neurons, but also other cell types present in the brain, such as glial cells. Understanding glial cells' contribution to the pathology therefore promises conceptual advances and, at the same time, offers an important window of opportunity for identifying new therapeutic targets. We recently have shown that patients with Alzheimer's disease present a disease-dependent increase in the brain expression of a small glial-derived secreted protein named SFRP1, which interacts with harmful amyloid products (the accumulation of which is thought to be among the culprits of the pathology), and down-regulates an

enzyme that prevents their generation. Studies in mouse models showed that neutralization of SFRP1 activity counteracts several of the pathological traits of the disease. We now wish to obtain preclinical evidence that this strategy is effective against Alzheimer's disease progression—and safe, so that treatment will have no relevant side effects. We also will explore whether the presence of SFRP1 in the serum may be predictive of disease progression. We expect this study will provide the necessary information to translate a novel therapeutic target and possibly an additional diagnostic tool for AD to the clinic.

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
LUCÍA CHÁVEZ-GUTIÉRREZ, PH.D., KU Leuven, Belgium

Genetics and neuropathology of Alzheimer's disease clearly point to the importance for pathogenesis of decreased gamma-secretase-mediated processing of the amyloid precursor protein with consequent increased levels of long, aggregation-prone amyloid beta peptides. Recent research has provided evidence that the disease develops as a vicious cycle of impaired function of gamma-secretase, increased generation of aggregation-prone amyloid beta and accumulation of uncleaved gamma-secretase substrates with compromise of multiple cell-signaling pathways. Nevertheless, the nature of the most toxic amyloid beta species, as well as the details of the molecular and cellular consequences of their altered production, remain unclear. Lack of a thorough understanding of the disease pathomechanisms

hinders therapeutic development. Our novel, exciting data point toward an unexpected mechanism(s) through which amyloid beta peptides contribute to AD pathogenesis. Specifically, we demonstrated that long but not short amyloid beta peptides act as competitive inhibitors of gamma-secretase, and thus lead to failed processing of multiple substrates and consequent dysregulation of multiple cell-signaling cascades. In addition, we determined that peptides generated from APP via a nonamyloidogenic pathway possess much less inhibitory potency. These discoveries, defining the most pathogenic products of the gamma-secretase-mediated proteolysis and pointing toward the cell-signaling pathways impaired in the disease, define promising targets for the novel AD therapeutics.

In Vivo Characterization of a Loss-of-Function GGA3 Rare Variant Associated with Alzheimer's Disease

GIUSEPPINA TESCO, M.D., PH.D., Tufts University School of Medicine

We have identified a novel genetic mutation in a gene called GGA3. This mutation increases the risk of developing Alzheimer's disease. GGA3 is essential for the transport of BACE1, a key enzyme in AD, in neurons. We discovered that the absence of GGA3 is toxic for neurons. More importantly, this AD-linked GGA3 mutation produces a toxic effect similar to the

one observed when GGA3 is completely absent in neurons. Our data indicate this new genetic mutation makes neurons sick because GGA3 has lost its ability to transport BACE1. These findings are important for the development of personalized therapies for subjects carrying this specific mutation.

Mechanisms of Tau Propagation Across the Plasma Membrane

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

Diseases such as Alzheimer's disease (AD) are progressive and appear to involve brain networks. We have proposed that pathological tau assemblies, which underlie dementia in AD, move from cell to cell to cause pathology to spread through the brain. The mechanism by which tau binds the cell surface to enter and corrupt normal tau on the inside could be an important place to block the disease. We have worked on this question for approximately 10 years and have identified the "receptor" to which tau binds on the cell surface, as well as critical cellular enzymes required to modify this receptor so that it can bind tau. In the first component of this work, we will test in animal models whether reduction of a specific enzyme, NDST1, which

is critical to modify the surface receptor, will prevent cells from developing tau pathology. If this line of work is successful, it immediately will suggest important new drug development strategies. The second line of work will determine how pathological tau directly translocates across the plasma membrane. This process, which is implied strongly by our prior work, breaks certain fundamental rules of biochemistry. Specifically, it is unclear how proteins such as tau, especially in large assemblies, could cross the lipid bilayer that makes up the cell membrane. We will use advanced biochemical and imaging approaches to confirm this mechanism and identify factors that play a fundamental role.

Reversal of Tau Pathology by an Adenosine A1 Receptor Antagonist

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

ECKHARD MANDELKOW, PH.D., DZNE, Germany

ANJA SCHNEIDER, M.D., DZNE, Germany

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, protein clumps (amyloid plaques and neurofibrillary tangles) build up in the brain. The currently available drugs can only modestly slow down the 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 that already have become demented. The likely reason is that the accumulation of clumped tau protein turns down energy production

in neurons, and this is reversed by a specific blocker of ADORA1, rolofylline (Dennissen et al., 2016). We want to test this idea in different model systems: transgenic mice expressing a disease-causing mutation of tau protein, organotypic slices derived from these mice, and organoid slices developed from induced pluripotent stem cells (iPSC) from a human patient with tau pathology. The experiments are designed to reveal the mechanism by which the drug works, how the communication between neurons in the brain is affected by the energy crisis provoked by toxic tau protein, and how the ADORA1 blocker resolves the crisis by enhancing neuronal activity. We hope this leads to a new avenue for treatment of patients with Alzheimer's disease.

Investigating the Role of Tau Protein in Neuronal Senescence Induction and Maintenance

MIRANDA E. ORR, PH.D., Wake Forest School of Medicine

Advanced age is the greatest risk factor for developing Alzheimer's disease and related dementias. Evidence suggests that these diseases begin decades prior to noticeable symptoms. A better understanding of how the brain changes with age may provide clues into how/why these diseases begin and progress. We discovered that the abnormal brain cells that closely track with memory loss and disease in Alzheimer's disease display characteristics of a stress response common to aging, called cellular senescence. Senescent cells accumulate in many tissues during aging, and contribute to disease and dysfunction. In Alzheimer's disease brain tissue, we find that the senescent cells are neurons, the brain cells important for making, storing and retrieving memories—and many of these contain large deposits of tau protein. All neurons normally contain tau protein; however, abnormal forms of tau protein accumulate in many brain diseases. Tau aggregates, called neurofibrillary tangles, closely correlate with dementia and cell death. Similar to senescent cells, neurons

with neurofibrillary tangles display signs of damage and stress, but they do not die. Also, like senescent cells, their survival comes with a tradeoff: they become toxic to surrounding healthy cells. Risk factors that increase cellular senescence in other tissues include advanced age and insulin resistance/diabetes; these risk factors also cause neurons to become senescent in the brain. We have found that regardless of the stressor, senescent neurons rely on tau to execute the stress response. Therefore, the objective of this project is to better understand how tau proteins guide neurons to become senescent in response to stress. This is important because senescent cells contribute to disease and dysfunction. A better understanding of how, why and when neurons become senescent may lead to drug therapies that interrupt the toxic process. Moreover, some of these therapies may be most useful in midlife, when risk factors are evident but neurons still are healthy. This approach may reduce the risk for developing Alzheimer's disease in later life.

Assessing the Added Diagnostic Value of Peripheral Apolipoprotein E Protein Levels in Current Blood-Based Biomarker Assays for Central Nervous System Amyloidosis

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

An accurate blood-based test for preclinical Alzheimer's disease would revolutionize the clinical diagnosis of dementia and accelerate the development of effective AD treatments. Currently, amyloid PET scans and cerebrospinal fluid biomarkers are used in research, clinical trials and clinical practice to detect brain amyloidosis. Clinical utility of these biomarkers ultimately is limited by their cost, availability and

perceived invasiveness. Apolipoprotein E (APOE) is the most significant genetic risk factor for AD and a molecular component of the amyloid plaques that are the hallmark of AD pathology. The current study will assess the diagnostic value of incorporating blood APOE protein measurements into an already high-performing blood-based biomarker assay.

Counteracting Pathogenic Events in Alzheimer's Disease with Peripheral or Central Apolipoprotein E

GUOJUN BU, PH.D., Mayo Clinic

Alzheimer's disease (AD) as the leading cause of dementia has become a growing epidemic in our aging society. While aging promotes AD development, a gene called apolipoprotein E (APOE) is the strongest genetic risk factor for AD. The goal of our study is to address how a specific gene variant called APOE4 drives up the risk, and how we can target this protein for the development of new therapy. Interestingly, APOE 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. Using a new set of animal models and blood transfusion studies, we have shown that blood APOE4 impairs brain functions and increases AD pathology by injuring blood vessels, whereas blood APOE2 and APOE3 have beneficial effects on brain functions. In addition, a recent finding

identified a mutant form of APOE (named Christchurch) that can protect an individual from neurodegeneration and AD development. Our hypothesis is that changing a person's APOE form from toxic APOE4 to APOE2 (or protective APOE variants) will benefit brain functions and reduce AD pathologies. This will be pursued on two tracks: firstly, we will test whether delivery of APOE2, APOE3 or protective APOE variants into APOE4 Alzheimer's animals through peripheral bloodstream can improve inflammatory responses, blood vessel integrity, memory performance and AD-related pathways, including the clearance of amyloid beta, which forms the amyloid plaques thought to be the central driver of AD development. Secondly, we will examine how delivery of APOE2, APOE3 or protective APOE variants directly into the brain of APOE4 Alzheimer's mice impacts brain functions and AD-related pathways. Our findings not only will inform strategies to target APOE4, but also will explore an opportunity to treat AD in an individualized manner through precision medicine.

The Role of Apolipoprotein E 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 a healthy brain and is prone to dysregulation in an Alzheimer's disease (AD) brain. We previously discovered a new role of apolipoprotein E (APOE) in the microglial phenotype switch during neurodegeneration. However, there is a lack of understanding in how human APOE allele variants, specifically APOE4 allele, regulate microglia in AD. APOE4 is the major genetic risk factor for sporadic late-onset AD, with women being more affected than

men. The functional mechanisms underlying the genetic association of APOE4 with AD remain elusive. Our preliminary data demonstrate a negative role of the APOE4 allele in regulating microglia response to neurodegeneration by employing novel tools, including new mouse models and techniques to specifically target APOE in microglia. These findings provide new directions to target APOE4 signaling to restore microglial functions in AD. This follow-on proposal is to understand the role of human APOE variants in neurodegeneration in microglia as well as peripheral immune cells, including neutrophils and monocytes, and to validate our findings in human AD cohort with different APOE alleles.

Sex Matters: Understanding the Influence of Sex and Apolipoprotein E (APOE) Genotype on Hippocampal Plasticity and Cognition

LIISA GALEA, PH.D., University of British Columbia

This research centers on how sex and genetics influence brain health and cognitive decline in a model of Alzheimer's disease (AD) risk. Although sex differences exist in many brain diseases, research targeting sex as a factor in brain health has been scarce. Here we will examine how biological sex and genotype influences the plasticity of an area of the brain called the hippocampus, which is one of the first regions affected by AD.

The hippocampus is an important area for learning and memory, and shows a great deal of capacity to change (plasticity) in adulthood. One of the unique characteristics of this plasticity in the hippocampus is adult neurogenesis (the birth of new brain cells in the adult). Recent evidence indicates that

neurogenesis in the hippocampus is decreased with AD. Furthermore, inflammation appears to contribute to AD, particularly signs of inflammation in the brain, called neuroinflammation. Females show reduced neurogenesis and increased neuroinflammation that may be related to the greater lifetime risk of females to develop AD. An understanding of how neurogenesis is regulated and how inflammation in the brain is involved may provide clues for devising new therapeutic treatments for AD. We have found that biological sex influences neurogenesis in the hippocampus, and now will examine how genetic differences that increase susceptibility to AD influence this plasticity. Further, we will determine whether we can manipulate this process to improve memory and reduce neuropathology associated with AD.

Understanding the Effect of Apolipoprotein E on Tau-Mediated Neurodegeneration

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

The apolipoprotein E (APOE) gene is the strongest genetic risk factor for Alzheimer's 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. We have preliminary data that APOE produced by a particular cell type in the brain called astrocytes is intervening APOE4-mediated brain injury. One goal of the current grant is to better characterize how APOE4 derived from astrocytes is

leading to tau-mediated brain injury via another glial cell type called microglia. Recently, we have found that specific types of lipids and cholesterol accumulate in microglial cells in the presence of APOE4 and tau pathology. We think this lipid accumulation may be detrimental to the brain. A second goal of this grant is to better characterize these APOE4-mediated changes in lipids and cholesterol as well as to determine whether decreasing this lipid/cholesterol accumulation will ameliorate tau-mediated brain injury.

Toward Developing High-Density Lipoprotein Enriched in Apolipoprotein E as a Potential Biomarker and Therapeutic Targeting Vascular Contributions to Alzheimer's Disease

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

A major genetic risk factor for sporadic Alzheimer's disease (AD) is a gene called apolipoprotein E (APOE), which codes for the APOE protein. The version of the APOE gene that confers higher AD risk makes the protein APOE4, while the normal version makes APOE3, and the protective version makes APOE2. Exactly how the different versions of this gene/protein contribute to AD is not known. The APOE protein is made both in the brain and outside the brain, but the "brain" and "blood" pools of APOE are separated because APOE does not cross the blood-brain barrier. Importantly, most patients with AD have problems with the blood vessels in their brain, including cerebral amyloid angiopathy (CAA), which is the deposition of amyloid beta—the main component of the hallmark AD plaques—in the brain's blood vessels. With support from the BrightFocus Foundation, the Weston Brain Institute and Cure Alzheimer's Fund, we have developed an advanced model of bioengineered human cerebral blood vessels. Using this model, we discovered that circulating high-density lipoprotein (HDL; the "good cholesterol") on the "blood" side, particularly HDL containing APOE (HDL-E), can help remove amyloid beta that gets stuck in the vessel wall as well as reduce vascular inflammation—two key pathological features of AD. We now seek to understand how the different versions of APOE protein affect this process from both the "blood" and "brain" sides. As astrocytes are the main cell type in the brain that make APOE, we will engineer

vessels with astrocytes on the "brain" side that make either APOE2, APOE3 or APOE4 to study how the version of astrocyte APOE affects amyloid beta deposition and vascular inflammation from the "brain" side. We also will isolate HDL-E from healthy people with different versions of the APOE gene to study how circulating HDL-E carrying different versions of the APOE protein affects the same processes from the "blood" side. We then will combine these two approaches to determine whether circulating HDL-E carrying APOE2 or APOE3 on the "blood" side can compensate for the negative effects of APOE4 on the "brain" side. If so, this could open up new ways to treat or prevent vascular components of AD, as HDL-based therapies that can work from the inside of the vessel may not need to enter the brain to be effective. Important new areas of study for the upcoming CureAlz funding period are to establish methods to measure HDL-E in human blood samples, determine whether HDL-E levels are lower in patients with the risk version of APOE and learn whether reduced levels of HDL-E are related to CAA. Developing peripheral treatments that may promote vascular health in the context of AD is especially timely, given that drugs like aducanumab are promising but can have some adverse effects on the cerebral vessels. This new work has the potential to set the stage for safer and/or broader use of new AD drugs expected to hit the market.

Regulation by Apolipoprotein E of Selective Neuronal Vulnerability to Alzheimer's Disease

JEAN-PIERRE ROUSSARIE, PH.D., The Rockefeller University

Apolipoprotein E (APOE), the most important genetic predisposition factor for Alzheimer's disease (AD), long has been known for its effect on the formation of amyloid plaques, and more recently for its importance in glial cell activation. There is evidence for another role of APOE on neuron function independent of amyloid plaques. Since some neurons are more vulnerable than others to neurodegeneration, we ask in this proposal whether APOE also could modulate their vulnerability. Our aim is to both better understand the role of APOE in AD, as well as the vulnerability of specific neurons. The most vulnerable neurons of the brain are the ones from the layer II of the entorhinal cortex (ECII), which are crucial for new memory formation. Their early degeneration hinders the ability to form new memories at the onset of

the disease. We previously compared the full inventory of all proteins present in these ECII neurons in mice with different alleles of human APOE: the risk allele, the neutral one and the protective one. Preliminary experiments now indicate that the human risk allele of APOE is putting ECII neurons in an increased vulnerability state compared with the neutral or the protective alleles of APOE. We want to pinpoint more precisely the molecular events that occur in vulnerable neurons in the presence of the risk allele of APOE to understand how these events could lead to the death of the neurons. Proteins that make ECII neurons more vulnerable, and that are modulated by APOE, could represent new drug targets to prevent ECII neurons from degenerating, and thereby halt the progression of the disease.

Examining the Role of Human Microglia in the Transition Between Parenchymal and Vascular Amyloid Beta Pathology

MATHEW BLURTON-JONES, PH.D., University of California, Irvine

Alzheimer's disease (AD) is the leading cause of age-related dementia, affecting more than 5 million people in the United States alone. Unfortunately, current therapies are largely palliative, and thus there is an urgent need to improve our understanding of the mechanisms that drive the development and progression of AD. Recent genetic studies have provided strong evidence that microglia, the primary immune cell of the brain, play a critical role in this disease. Yet precisely how microglia influence the accumulation of amyloid beta, the pathology that underlies the initial development of AD, remains unclear. In recent studies, we have found that microglia help to determine whether amyloid beta accumulates within the extracellular space as amyloid plaques, or within the blood vessels of the brain as cerebral amyloid angiopathy (CAA). This distinct localization

appears to be very important in the progression of AD, as CAA occurs in greater than 80% of AD patients and is associated with a more rapid decline in cognitive function and earlier mortality. To further understand how microglia influence CAA, we will collaborate closely with the other members of the CureAlz Neuroinflammation Consortium to examine the impact of genetic changes in human microglia on multiple aspects of AD neuropathology. Using both mouse models and stem cell-derived human microglia, we will determine how two key AD risk genes—APOE and TREM2—influence the development of AD pathology, and neuronal and cognitive function. Our studies will, therefore, provide crucial insight into the functional genetics that underlie AD, and hopefully uncover important new information that can be used to guide the development of therapies.

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 (AD) 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 odds of developing Alzheimer's disease and its associated progression.

Here we focus on a set of genes, called the MS4As, that seems to have a surprising degree of influence on a given person's chances of developing Alzheimer's disease later in life. Interestingly, these genes seem to act in a subset of glial cells called microglia, rather than neurons, consistent with microglia playing an important role in disease initiation or progression. In order to make the link between the MS4As and Alzheimer's disease, we propose 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 that will help us to build new drugs that target the 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 develop Alzheimer's disease. Our experiments also may identify a new set of promising targets that could be the substrate for future drug development.

Role of Secreted Protein Acidic and Rich in Cysteine (SPARC) in Immunometabolic Control of Age-Related Inflammation

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

Inflammation associated with aging is an important trigger for Alzheimer's disease (AD) development. There is growing evidence that age-related inflammation mediated via the activation of the NLRP3 inflammasome is an important mechanism for loss of cognition and memory, and development of AD. Studies from our lab have identified that the NLRP3 inflammasome controls the development of inflammation-associated degenerative diseases during aging. Consistent with our data, independent studies also have demonstrated increased activation of the NLRP3 inflammasome in AD in humans, and that genetic loss of NLRP3 protects against dementia in the amyloid precursor protein/PS1 mouse model of AD. This proposal is based on our findings that 14% caloric restriction, or CR (from

the CALERIE-II study) in healthy humans lowers a matricellular protein called SPARC. To determine whether SPARC is a driver of CR's salutary effects on reducing inflammation, we pursued this protein to understand its function in macrophages, the major cell type that is a source of inflammatory cytokines in aging. SPARC is a 32kDa calcium-binding matricellular protein. To determine whether reduction in SPARC as caused by CR lowers inflammation, we have created microglia and tissue resident macrophage-specific SPARC-deficient mice. Given our preliminary data that SPARC can control inflammation, we hypothesize that downregulation of SPARC in tissue resident macrophages and microglia will protect against inflammasome activation, age-related astrogliosis, and loss of memory and cognition.

VGF-Derived Peptide Therapy for Alzheimer's Disease: Studies of Mouse and Human TLQP-21 and its Receptor, C3aR1

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

The VGF (nonacronymic) gene encodes a neuronal and neuroendocrine protein precursor that is post-translationally processed with cell- and tissue-type specificity into multiple bioactive peptides. These peptides are secreted and are involved in numerous physio/pathological functions, including reproduction, depression, obesity, memory and also neurodegenerative diseases, in particular Alzheimer's disease (AD). Recent studies conducted by the NIH Accelerating Medicines Partnership for Alzheimer's

Disease (AMP-AD) consortium have further identified reduced VGF levels in the brains of AD subjects that correlate with stage of disease. Druggability of the VGF pathway is of intense interest in many fields. We propose to use recombinant mouse models of AD and a humanized VGF receptor to determine the efficacy of human VGF and one of its neuroactive peptides, TLQP-21, in prevention and amelioration of the "AD phenotype" in these mice.

Investigating the Contribution of Astrocytic-Dependent Inflammation on Amyloid-Induced Tau Pathology

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

An emerging pathophysiological mechanism influencing Alzheimer's disease (AD) is neuroinflammation, characterized by elevated levels of pro-inflammatory molecules, reactive astrocytes and microglia that span across the course of the disease, potentially influencing disease progression. The role of astrocytes and their contribution to AD development and progression has remained mostly unexplored. In the proposed studies,

we aim to determine the influence of astrocytic-dependent inflammation on progressing tau pathology in the presence of plaque burden. Additionally, we aim to identify a mechanism by which astrocytes expressing apolipoprotein E4 display neurotoxicity. These studies will clarify the therapeutic potential of reactive astrocytes and potentially provide new therapeutic targets.

Discovery and Development of Chemical Probes to Elucidate MS4A Protein Function

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

Genome-wide association studies (GWAS) in Alzheimer's disease (AD) suggest that studying the immune system of the brain may provide insights into disease resilience, onset and progression. Many think the brain immune system is likely the next target for drugs to treat this intractable disease. Currently though, there are huge knowledge gaps that exist in our understanding of brain immune system function in AD and its relationships to classic AD pathology (e.g., amyloid plaques and neurofibrillary tangles). In many cases, the basic tools—including chemical probes—needed to more fully study AD-implicated proteins simply do not exist. Chemical probes enable functional modulation of systems at all levels of study—cell, organoid, tissue, animal and human—and are the basis of drug development efforts;

thus, it is imperative that we develop a chemical probe development strategy that can keep pace with the rate of vulnerable gene/protein elucidation. Here, we propose development and testing of a platform technology that could be generalized to identify hits and develop chemical probes for GWAS-implicated proteins. We focus our initial effort on MS4A protein, the function of which is not fully elucidated, and yet which appears to influence the risk of developing AD, and is the subject of other protocol and technology development within the CureAlz Neuroinflammation Consortium. Through the development of this discovery platform, we will provide MS4A modulators (e.g., antagonists and agonists) that facilitate the study of the receptor system, and also provide hits for drug development.

Investigation of Alzheimer's Disease Risk Alleles in Astrocytes—Focus on Cholesterol Transport and Microglia Interactions

SHANE A. LIDDELOW, PH.D., Neuroscience Institute at NYU Langone Health

The brain is composed of many different cells that are tightly interconnected during health and disease. Astrocytes are integral to the normal function of the healthy brain—providing nutrients to neurons and microglia. In the AD brain, we identified that microglia become reactive and release factors that cause astrocytes to become reactive, ultimately leading to neuron death. The activation of microglia is, in part, due to a lack of release of cholesterol from astrocytes (which normally provide cholesterol to maintain microglia in a healthy state). Two risk alleles for AD, clusterin (CLU) and apolipoprotein E (APOE), are involved

in this cholesterol transport, are highly expressed by astrocytes and are integral for normal brain health. Here we will investigate the role of AD-associated mutations in CLU and APOE and determine how they change the function of astrocytes and, in turn, how this affects microglia. These studies will connect the whole genome studies of AD risk factors with known astrocyte-microglia function, providing understanding of this glial-immune axis important for the health of neurons. We predict these results will provide insights and novel targets for future therapy development.

Understanding the Consequences of Noncoding Alzheimer's Disease Risk Alleles on Microglia Function

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

Alzheimer's disease (AD) is the health challenge of our generation. The majority of AD cases are of late onset and result from the interaction of many genes and nongenetic risk factors, of which the most important is aging. Emerging genetic studies of late-onset AD implicate the brain's resident immune cells, microglia, in the pathogenesis of AD. In fact, more than half the risk genes associated with late-onset AD are selectively expressed in microglia and peripheral myeloid cells, two cell types associated with the brain's immune system;

yet, we know shockingly little about their biology and 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 they also can promote detrimental forms of neuroinflammation leading to inappropriate and damaging synapse loss—one of the earliest changes in the AD brain, and the strongest correlate of cognitive decline.

Senescent Cells and Alzheimer's Disease

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

The relationship between organismal aging and debilitating chronic diseases, including Alzheimer's disease (AD), is clearly linked. One potential culprit driving age-associated pathologies are senescent cells (SnCs), which are characterized by a permanent cell cycle arrest. These cells accumulate with advancing age and at sites of dysfunction in a number of age-related diseases. This association led to the hypothesis that SnCs actively drive tissue deterioration and are not simply innocent bystanders in these conditions. A proposed mechanism behind this dynamic process is the acquisition of a senescence-associated secretory phenotype, or SASP, where SnCs produce and secrete a variety of growth factors, matrix metalloproteinases, chemokines and pro-inflammatory cytokines. Many recent studies, including

those from my laboratory, have demonstrated that SnCs shorten life and actively drive age-related pathology, including neurodegeneration, in mice. In addition to neurofibrillary tangles and amyloid beta plaques, Alzheimer's disease patients exhibit increased indicators of cellular senescence. Recently, we have demonstrated that treating mice to prevent accumulation of SnCs led to attenuation of tau-dependent degeneration and cognitive loss. As pharmacological modulation of SnCs appears to be on the horizon, it is imperative to determine whether removal of SnCs from established AD patients has beneficial impacts. We first will test this using mouse model systems with degeneration. Additionally, we will explore whether SnCs are a common occurrence in AD mouse models.

Gut Microbiota, Endothelial Dysfunction and Tau-Mediated Cognitive Impairment

GIUSEPPE FARACO, M.D., PH.D., Weill Cornell Medicine
COSTANTINO IADECOLA, M.D., Weill Cornell Medicine

Bacteria colonizing the mucosal surfaces of our body have a profound effect on the cells of the immune system. In particular, due to the abundance of immune cells in the gut, gut bacteria can influence the immune system of the entire body. Therefore, alterations in gut bacteria can result in dysregulation of immune cells that can cause damage to other organs, including the brain. Indeed, alterations in the gut flora have been implicated in the brain pathology underlying Alzheimer's disease (AD), but how that happens has not been elucidated. A certain class of gut immune cells (Th17 lymphocytes) are particularly sensitive to gut bacteria and play a major role in autoimmune diseases by producing the harmful cytokine IL-17. IL-17 also can result in the accumulation

of the protein tau in the brain, a major culprit in AD. Therefore, this proposal will test the hypothesis that changes in gut bacteria that promote proliferation of Th17 cells in the gut lead to an increase in circulating IL-17 that causes cognitive impairment by promoting accumulation of tau in the brain. To this end, we will colonize the gut of mice with bacteria that activate the proliferation of Th17 cells (segmented filamentous bacteria) to determine whether the increase in IL-17 in the blood will lead to tau accumulation in the brain. The results of these studies will provide a direct link between gut bacteria and tau pathology, and may open new avenues for the treatments of AD and related tauopathies based on modulation of the gut flora.

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

Alzheimer's disease (AD) and associated dementia caused by neurological impairment have become an increasing health burden. Exercise has been shown in animal models and clinical studies in humans to be neuroprotective in AD. The mechanisms by which exercise protects the brain are diverse and complex. We found that exercise increases a hormone called fibronectin-domain III containing 5 (FNDC5) and its

secreted form, irisin. In our pilot studies, we also found that irisin reduces amyloid beta pathology and cell loss in our cell culture system. This research will test the hypothesis that the novel exercise hormone irisin is neuroprotective in AD; we already have been testing our hypothesis in our cell culture and animal models of AD. Our study will provide a potential promising way to generate novel therapeutic targets for AD.

Characterizing Gut Microbiome Synergy With Emphasis on Mycobiome and Its Impact on Alzheimer's Disease (AD) Pathology in AD Mouse Models

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

NANDA KUMAR NAVALPUR SHANMUGAM, PH.D., Massachusetts General Hospital

WILLIAM EIMER, PH.D., Massachusetts General Hospital

RUDOLPH TANZI, PH.D., Massachusetts General Hospital

Microorganisms of the gastrointestinal (GI) tract include bacteria, fungi, viruses and parasites that are collectively referred to as the “microbiota” or “microbiome.” While the bacteria or bacteriome remains the most explored area, the ecological niche occupied by other groups, especially the fungi or mycobiome, cannot be ignored. More than a century ago, Nobel laureate Elie Metchnikoff proposed and postulated that the good bacteria of the gut, famously referred to as probiotics, benefit the host in many ways, including mitigation of stress-related anxiety and delaying senility in humans. This is the basis of fecal transplantation that involves administration of the microbiome from healthy subjects to diseased individuals. Based on our previous findings, there appears to be a synergistic association between the bacteriome and mycobiome, the dynamics of which is dependent on numerous factors such as antibiotic usage, stress, infection, and other metabolic and

environmental factors. In this study we propose aims to address this area, with emphasis on how some of the above factors induce changes in microbiome profile and how that impacts the brain in Alzheimer's disease (AD), using mouse models. The research strategies were designed based on recent accumulating evidence that demonstrate a link between central nervous system (CNS) disorders and the gut microbiome. In this study we will continue working on our previous aims, include additional ones based on our earlier findings, and use AD mouse models to investigate the impact of gut microbes on the brain during early and late stages of AD. Identifying specific genus and species of fungi and bacteria that emerge post treatment, and whether their presence mitigates or accelerates CNS insult, will be the main focus of our proposed goals. Findings are likely to provide better understanding toward designing novel strategies for early treatment of AD.

Microbes and Alzheimer's Disease: Metagenomics on Saliva, Cerebrospinal Fluid, Blood and Brain

NANDA KUMAR NAVALPUR SHANMUGAM, PH.D., Massachusetts General Hospital

WILLIAM EIMER, PH.D., Massachusetts General Hospital

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

RUDOLPH TANZI, PH.D., Massachusetts General Hospital

Brain health in the elderly is of special significance since age is associated with increased likelihood of neurodegenerative diseases that cause memory impairment, behavioral and learning deficits. The protein amyloid beta, found in the brain, plays an important physiological role in neuronal function, but an excess of the protein due to aging and disease can damage the central nervous system and impair normal brain function. Though the extracellular deposition of amyloid beta is a signature pathology of Alzheimer's disease (AD), the signaling events that trigger aggregation and plaque deposits in the brain are not clear. Research studies from our laboratory and others have studied amyloid beta extensively and discovered a novel role for the protein as an antimicrobial protein—

an innate immune peptide that is part of a defense system against pathogens and microbes. Further, data from our lab and the literature also indicate the presence of numerous microbes in the brain of aged healthy controls and AD patients who have an altered microbial pattern. Our proposal aims to investigate whether the brain can be a niche for microbes. Additionally, we would like to characterize different sources of both control and AD postmortem samples to explore how microbes can penetrate the brain. Findings from this project will serve as translational research for the increasingly aged population and will help in determining disease-modifying therapies for age-related neurological problems of those who suffer from dementia.

Effect of Gut Microbiome Dysbiosis on Neuroinflammation and Amyloid Beta Deposition: A Longitudinal Micro-PET Study in Alzheimer's Transgenic Mice

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

Alzheimer's disease (AD) remains the most common form of dementia, affecting 50 million people worldwide. Recent studies from our laboratory established a clear role for the gut microbiome in the pathology of AD. These studies also suggested rampant neuroinflammation in the AD brain, triggered by imbalances in gut-microbiome diversity. However, the exact mechanism through which the gut microbiome exerts its effect on the AD brain remains unknown. Our lack of knowledge in this area can be attributed partly to the absence of quantifiable brain imaging data from microbiome-perturbed animal models of AD. In this proposal, we intend to image brains of normal and AD mice treated with antibiotics using noninvasive Positron

Emission Tomography (PET) to study the effects of the gut microbiome on neuroinflammation in AD. We will perform serial PET imaging using brain permeable radiotracers to monitor the amount and location of neuroinflammation and amyloid beta deposition in age- and sex-matched mouse models. Using this imaging strategy, we also will quantify the direct effects of gut-microbial metabolites (e.g., short-chain fatty acids (SCFA)) and fecal microbiome transplantation (FMT) on the progression of AD. The proposed PET imaging study is anticipated to provide new insights into the molecular mechanisms of gut-brain communication that may lead to the development of new therapeutic approaches for treating AD.

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

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

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

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

DRUG DISCOVERY AND ENABLING TECHNOLOGIES

Adult Human iNeurons: A Next-Generation Drug Screening Platform for Alzheimer's Disease

GEORGE S. BLOOM, PH.D., University of Virginia

JOHN S. LAZO, PH.D., University of Virginia

ELIZABETH R. SHARLOW, PH.D., University of Virginia

The multitude of failed drug trials for Alzheimer's disease (AD) emphasizes the urgent need for a better understanding of how normal neurons (nerve cells) in the brain are converted into AD neurons, and how to identify drugs that can block this conversion. To that end, we have defined and are continuing to explore many AD-like features of cultured mouse neurons that have been exposed to small aggregates (oligomers) of amyloid beta. Importantly, amyloid beta oligomers are the soluble building blocks of the poorly soluble amyloid plaques that accumulate in the AD brain, and are far more toxic than the plaques themselves. The AD-like properties of mouse neurons exposed to amyloid beta oligomers include "cell cycle reentry," which precedes most neuron death in human AD; impaired function of mitochondria, the "power plants" of the cell; cellular senescence; and neuronal DNA damage. It follows naturally that drugs that block these neuronal

responses to toxic amyloid beta oligomers might have prophylactic potential for AD. To take our basic science findings to the next step, we will develop and optimize neuron cultures that more faithfully mimic human AD and can be rapidly screened for drug testing. More specifically, we will refine a system in which cultured adult human neurons (iNeurons) are used in place of mouse neurons, and the iNeurons will be grown in three-dimensional matrices instead of on flat, two-dimensional surfaces. Importantly, the adult human neurons will not be obtained from brain tissue, but instead will be differentiated in culture from fibroblasts, which are common cells found throughout the body and are easily and painlessly acquired, and could position the platform for future "personalized medicine" usage. We anticipate initiating pilot drug screening studies near the end of year 1, and continuing those studies on a grander scale during year 2.

Modulating CD33 Function and Neuroinflammation as a Therapeutic Approach for Alzheimer's Disease

ANA GRICIUC, PH.D., Massachusetts General Hospital

One of the regulators of amyloid beta clearance in Alzheimer's disease is a microglial receptor called CD33. Through an unbiased high-throughput screen of a natural product library, we identified natural products that increase amyloid beta uptake and clearance. We also identified FDA-approved medications that increase amyloid beta uptake and maintain microglia in an anti-inflammatory state in the brain. Here, we will screen the natural product library for modulation of levels of

pro-inflammatory mediators in microglia. We also will investigate the effects of FDA-approved medications on amyloid beta uptake and inflammation in a microglial cell line stably expressing human CD33. To assess the impact of the most promising hits on tau clearance, we will set up a tau uptake assay in microglia. The development of effective anti-inflammatory medications and CD33 inhibitors should facilitate Alzheimer's disease therapeutics targeting neuroinflammation.

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

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

Alzheimer's disease is thought to be caused by an excess of the peptide amyloid beta. This peptide greatly impacts synapses, leading to their inability to function normally. This is achieved, at least in part, by driving the loss of an important synaptic protein, PSD-95. This project seeks to leverage recent findings from our laboratory indicating that synapses can be protected

from amyloid beta by increasing the amount of PSD-95 at synapses. The most exciting finding is that this can be achieved pharmacologically, using drugs that are being developed for human use. These studies should provide important preclinical data, paving the way for human trials with these drugs.

Virtual High-Throughput Screening for CD33 Inhibitors

SUBHASH SINHA, PH.D., Weill Cornell Medicine

Alzheimer's disease (AD) is an age-related disease of the central nervous system. Its prevalence has become a major concern in both developed and developing countries. There are 5.4 million AD patients in the United States; 96% of them are age 65 and older, but no disease-modifying drug is available except a few that treat the symptoms only. Accumulation of neurotoxic forms of amyloid beta and tau protein in the brain is the major hallmark of AD; together, they cause toxicity to neurons and their death. Microglia are the

brain's housekeeping cells, mediating the degradation of accumulated amyloid beta, tau protein and other debris. Microglia express a cell surface protein, CD33, which has been implicated in late-onset AD. The CD33 protein reduces the ability of microglia to capture and degrade accumulated amyloid beta and tau protein when the former is expressed at a high level in microglia. It is argued that: 1) reducing the expression of CD33 protein in microglia, or 2) inhibiting binding of CD33 protein to agonists (molecules that will increase CD33

activity) expressed on the surface of the same cells or interacting cells will have a favorable response. Because CD33 has been a therapeutic target for treating acute myeloid leukemia, a form of blood cancer, the majority of work has focused on antibody therapy. A relatively high molecular weight synthetic compound has also been developed as a mild CD33 inhibitor and further formulated as microparticles that enhance the uptake and degradation of amyloid beta in microglia cells. However, due to the large molecular weight of the antibody as well as of the synthetic inhibitor, in both

original and formulated forms, they cannot penetrate the blood-brain barrier (BBB) and cannot be used in patients. A long-term goal of our study is to develop small-molecule CD33 inhibitors that can penetrate and accumulate in the brain. In this application, we will perform in silico screening to identify hit inhibitors of the CD33 protein and also build tool compounds and reagent and assay capabilities to study CD33-targeted drug development. At the end of the proposed study, we also anticipate having identified sets of hit inhibitors of the CD33 protein for further development.

Small Molecule Activators of Phospholipase C-gamma-2 as Novel Therapeutics for Alzheimer's Disease

QISHENG ZHANG, PH.D., University of North Carolina

JOHN SONDEK, PH.D., University of North Carolina

KENNETH PEARCE JR., PH.D., University of North Carolina

Current drugs used to treat Alzheimer's disease (AD) ameliorate the symptoms of the disease but do not slow or reverse disease progression. Part of the reason for this has been a lack of knowledge on specific and actionable biological molecules that contribute to the disease and that can be targeted with drugs. In recent years, several large genomics studies of tens of thousands of patients with AD have provided new insights into the causes of the disease, leading to several new potential targets for drug treatment. One of the most promising targets to arise from these studies is Phospholipase C-gamma-2, abbreviated as PLC-gamma-2. A natural variant of PLC-gamma-2 harboring a single substitution (P522R) of one residue out of more than 1,200 that make up the protein provides protection from Alzheimer's disease. Protection is robust, reproducible and, perhaps most

promising of all, patients with mild cognitive impairment that express PLC-gamma-2 (P522R) show slower cognitive decline relative to noncarriers.

PLC-gamma-2 (P522R) is more active than its more frequent, wild-type counterpart, and it generally is accepted that protection from AD arises from this increased activity. We intend to recapitulate this increased activity for wild-type PLC-gamma-2 using small molecules. We have developed a high-throughput screen that allows us to search a large collection of small molecules for activators of PLC-gamma-2. We will carry out this screen for more than 100,000 compounds and optimize compounds that activate PLC-gamma-2. These optimized compounds will serve as the initial leads for further work to develop drugs to treat Alzheimer's disease.

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

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

In fiscal year 2020, we focused on identifying molecular mechanisms related to six confirmed screening hits and predicting more candidates based on such mechanisms. Specifically, our collaborators in the Tanzi lab and the Kim lab successfully confirmed six primary hits through secondary screening and toxicity tests, and we were able to identify significantly changed pathways potentially related to the p-tau clearance ability of each hit. We were able to carry out in-depth pathway analysis for these six confirmed cases and identified four subclusters potentially bearing different mechanisms of p-tau clearance. One of the subclusters was used as bait in our in silico predictions and generated 33 candidates, three

of which were validated previously in the Alzheimer's in a Dish™ (ADiD) model as being able to clear p-tau. Next year, we will continue working on validating the predictions in this list of 33 candidates, and also perform additional in silico predictions from other confirmed hits. We also will generate single cell RNA-seq data to study the effect of three to five confirmed hits on different cell types within the ADiD model. This analysis will facilitate the effort to understand how different types of cells in the brain microenvironment talk to each other, and how such communications are altered in the AD brain. Ultimately, such in-depth and systematic understanding on neuronal-glia crosstalk will open the door for novel therapeutics.

High-Throughput Drug Screening for Alzheimer's Disease Using Three-Dimensional Human Neural Culture Systems

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

LUISA QUINTI, PH.D., Massachusetts General Hospital

Alzheimer's disease (AD) has become a significant public health problem, but there is currently no cure for the disease. We pioneered a novel three-dimensional (3D) Alzheimer's in a Dish™ model that can revolutionize AD drug screening. This ongoing project will identify and validate novel AD drug candidates using our 3D AD cellular model as a drug screening platform. We will

continue to validate and identify AD drug candidates from natural products and microglial-modulating drugs in this period. This year, we will start a pilot drug screening to identify neuroprotective drugs against pathogenic amyloid accumulation and oxidative stress. This study's goal is to find novel AD drug candidates directly applicable to human clinical trials.

Proteomics of Alzheimer's Disease Three-Dimensional Cultures

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

The goal of this proposed project is to understand the composition of different proteins in a three-dimensional model of Alzheimer's disease (AD) brain and the responses of these proteins to drugs that will be repurposed and tested for potential therapeutic use for

AD. We will focus on specific groups of proteins involved in inflammation and their relationship to AD pathological proteins. The proposed research will provide critical information about potential AD therapeutics and their effectiveness in the model system.

Novel Entry Routes for Therapeutic Biologicals to the Brain

MAARTEN DEWILDE, PH.D., KU Leuven, Belgium

BART DE STROOPER, M.D., PH.D., VIB-KU Leuven, Belgium

The blood-brain barrier (BBB) is a vital barrier between the bloodstream and the brain. This barrier tightly controls which molecules can enter the brain. As a consequence of this barrier, the majority of currently available drugs cannot enter the brain. Importantly, to treat Alzheimer's disease, drugs need to reach the brain. Our laboratory has

been validating an innovative methodology to discover and validate novel ways to deliver drugs over the BBB. The aim of this project is to implement this methodology in our drug discovery campaign and deliver novel tools to the community to advance treatments for neurological disorders like Alzheimer's disease.

PRECLINICAL AND CLINICAL DRUG DEVELOPMENT AND TRIALS

Comprehensive Analyses of Chronic Efficacy Studies with GSM 776890 for Submission of the Pre-IND Brochure to the FDA Prior to Pre-IND Meeting and IND Filing for the SAD/MAD Phase I Safety/Toxicity and Ultimately for Phase II and Phase III Efficacy Clinical Trials to Support the NDA

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

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that affects patients over a period of decades. Researchers at the University of California, San Diego and Massachusetts General Hospital have developed a potential treatment that they will test for its ability to slow down the course of the

disease or prevent it from occurring. The studies in this grant will be conducted using an AD transgenic mouse model that closely mimics the human disease in many aspects. Studies will be carried out over six months to a year, thus mimicking the human treatment course for a disease-modifying or preventive-treatment study.

PEGASUS Clinical Study of AMX0035 in Alzheimer's Disease

AMYLYX

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

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

Improving Alzheimer's Disease Clinical Trials' Design by Machine Learning Models

ALI EZZATI, M.D., Albert Einstein College of Medicine

RICHARD B. LIPTON, M.D., Albert Einstein College of Medicine

Despite the high burden of Alzheimer's disease (AD) and increased efforts in research, the success rate of the pharmaceutical randomized clinical trials (RCTs) for dementia drugs has been abysmally low in the last two decades. This is thought to be partly due to clinical heterogeneity and difficulty in predicting which person will have cognitive decline during the one to five years of follow-up in a clinical trial. One strategy to improve design of clinical trials and boost their power is using predictive models that effectively can estimate probability of disease progression and cognitive decline. In recent years, innovative machine learning techniques

have been used increasingly in pharmaceutical research and development for prediction of clinical outcomes and response to treatments in various fields of medicine. However, to date, such techniques have not been used in design or conduct of AD trials. This project aims to develop a machine learning platform that can be practically used in design and conduct of future clinical trials. We will use advanced machine learning and deep learning methods and data from previously completed RCTs for treatment of mild to moderate AD to develop precise models that can predict disease progression and rate of cognitive decline.

2020 Events to Facilitate Research Collaboration

Throughout 2020, Cure Alzheimer's Fund (CureAlz) held a number of online events, some closed and some open to the scientific public, to facilitate collaboration among our funded researchers and dissemination of our research findings to the broader community. Each meeting included an area of focus for presentations and open discussion. Below are short summaries of many of our meetings.

RESEARCH LEADERSHIP GROUP ANNUAL MEETING

This full-day meeting, held in February 2020, featured presentations related to the subject of neuroinflammation. Each year at this annual meeting, the group also reviews CureAlz's research priorities and identifies emerging areas of interest to pursue.

RESEARCH LEADERSHIP GROUP

In March the Research Leadership Group met again to hear from Darren J. Baker, Ph.D., M.S., and Tony Wyss-Coray, Ph.D., regarding the work taking place in their laboratories, and to discuss current issues in Alzheimer's disease (AD) research.

APOE PUBLIC SEMINAR

Ten projects looking at APOE and its role in AD were presented to a public audience of more than 300 people in an online seminar in May. The projects included the interrelated collaborations of the Fleming APOE Consortium.

RESEARCH STRATEGY COUNCIL

The role of the Research Strategy Council is to provide guidance to Cure Alzheimer's Fund regarding its overall scientific direction and funding efficacy. The members, who have broad experience bringing therapeutics to patients, reviewed the entire research portfolio to ensure that CureAlz is supporting investigations into the most important issues in AD, and that our funding mechanisms accelerate the path to patients.



RESEARCH LEADERSHIP GROUP

This July meeting included a presentation from Robert Vassar, Ph.D., and discussions of recent findings from Oleg Butovsky, Ph.D., Caleb Finch, Ph.D., and Sam Sisodia, Ph.D. The group also discussed priorities in funding, the status of the labs given COVID-19 constraints and other considerations regarding research during the pandemic.

RESEARCH LEADERSHIP GROUP

Featured presenters in the September meeting included Sam Gandy, M.D., Ph.D., and Stephen Salton, M.D., Ph.D. (presenting on behalf of the project with Michelle Ehrlich, M.D.).

CIRCUITS (Collaboration to Infer Regulatory Circuits and to Uncover Innovative Therapeutic Strategies) CONSORTIUM

All CureAlz-funded researchers were invited to a meeting in September to hear eight presentations from the members of the CIRCUITS Consortium.

CONSORTIA MEETINGS

Each CureAlz-convened consortium—the CIRCUITS Consortium, the Berg Brain Entry & Exit Consortium, the Three-Dimensional Drug Screening (3DDS) Consortium, the Neuroinflammation Consortium and the Fleming APOE Consortium—has a regular schedule of meetings to bring lab leaders and personnel together to discuss findings and ensure productive collaboration. In 2020, these schedules were supplemented by combination meetings that brought the Neuroinflammation and CIRCUITS consortia together.

Dear Friends,

We are pleased to report that 2020 was the 16th consecutive record year for funds raised by Cure Alzheimer's Fund (see the chart that follows). Donations for the year totaled \$25.9 million, a modest increase of 2.6% from 2019; those dollars came from 21,000 contributions.



Research spending for 2020 totaled \$16.5 million, including funding 59 projects.

Cure Alzheimer's Fund was not immune to the events of 2020. Despite the uncertainty of the year, CureAlz donors and staff responded strongly, understanding that Alzheimer's disease continues to devastate lives regardless of what else is happening in the world. Our Board in particular assured continued progress with increased generosity not only to support vital research now, but also to invest in our ability to contribute even more to the future. Most other medical research nonprofits saw significant decreases in contributions, while Cure Alzheimer's Fund remained among the few in its segment to enjoy increased support and advance its mission.

We continue to keep our overhead costs low. Since inception through the end of 2020, our Board of Directors has contributed \$50.5 million to support operating expenses totaling \$31.0 million. 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 10th consecutive time, the highest rating the charity watchdog offers.

Research momentum was slowed in the early part of 2020. Researchers with M.D.s went into the clinic to help with COVID-19 support, and other researchers often were locked out of their labs for safety reasons. One result of this was a significant increase in

"no-cost extensions" for research projects that could not be completed under the circumstances. Most of these projects are being extended into 2021, and are being joined by a number of new proposals.

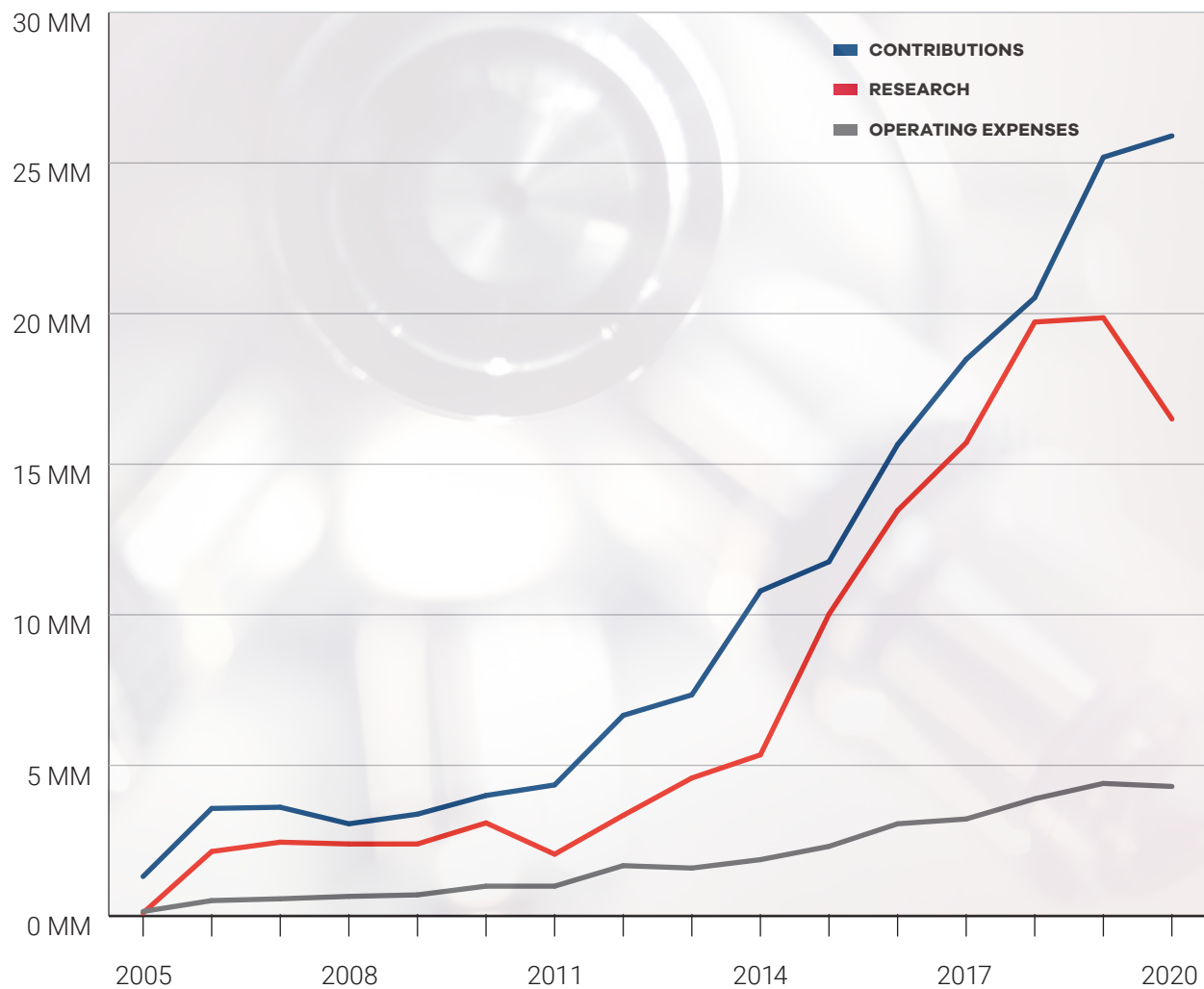
Since our inception in 2004 and through the end of 2020, Cure Alzheimer's Fund has distributed more than \$123 million to 194 researchers around the world. Although the disease is still with us, great progress is being achieved in understanding Alzheimer's. Enthusiasm and optimism about finding the pathways to effective therapies have never been higher.

Our belief in the value of innovative, breakthrough research to unravel the complexities of Alzheimer's pathology is yielding significant contributions to understanding the disease as described elsewhere in this report. The continued generosity of our Board and thousands of donors, the continued commitment and professionalism of the staff, and the extraordinary dedication of the hundreds of researchers focused on ending this disease give us all solid reasons for hope.

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

Sincerely,
Tim Armour
President and CEO

Growth: Inception Through 2020

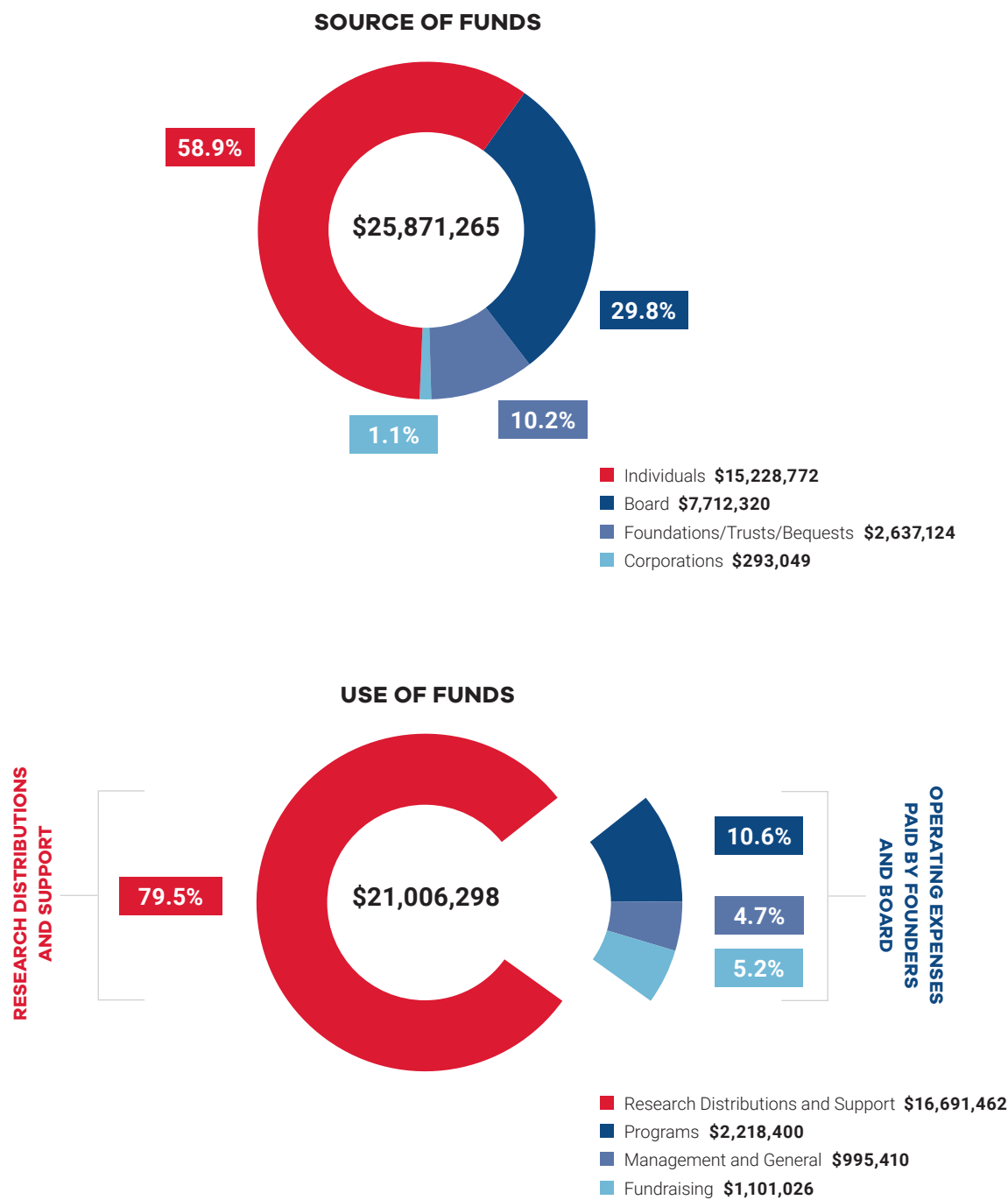


Sixteen Years of Growth:

Cure Alzheimer's Fund's investment in research continues to be driven by strong increases in overall contributions.

2020 Fundraising

In 2020, Cure Alzheimer’s Fund received 20,981 gifts—from individuals, the Board, corporations and foundations—totaling \$25,871,265. Cumulative contributions from inception given by our Founders and Board total \$50,446,418. Cumulative operating expenses from inception paid by the Founders and Board total \$30,947,803.



Source and Use of Funds obtained from internal records.

2020 Financials

(Year ended Dec.31, 2020)

Statement of Financial Position

Assets

Current Assets:

Cash and cash equivalents	\$6,399,792
Contributions receivable	200,001
Pledges receivable, current portion	2,365,000
Investments	6,362,446
Prepaid expenses and other current assets	55,727
Total current assets	<u>15,382,966</u>

Pledges receivable, less current portion, net	1,028,694
Equipment, net	15,382
Total Assets	<u>\$16,427,042</u>

Liabilities and Net Assets

Current Liabilities:

Accounts payable	\$959,088
Accrued expenses	172,501
Deferred revenue	500,000
Total current liabilities	<u>1,631,589</u>

Net Assets:

Without donor restrictions	10,674,191
With donor restrictions	4,121,262
Total net assets	<u>14,795,453</u>

Total Liabilities and Net Assets	<u>\$16,427,042</u>
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Statement of Cash Flows

Cash Flows from Operating Activities

Cash received from:

Contributions	\$26,090,393
Investment income	15,391
Total receipts	<u>26,105,784</u>

Cash paid for:

Research distributions and support	(16,171,932)
Salaries and related expenses	(2,241,550)
Professional fees	(1,114,197)
Gift processing fees	(112,067)
Occupancy expenses	(183,995)
Other expenses	(581,798)
Total expenditures	<u>(20,405,539)</u>
Net cash provided by operating activities	5,700,245

Cash Flows from Investing Activities

Proceeds from sale of investments	70,855
Purchase of investments	(4,168,466)
Net cash provided (used) by investing activities	<u>(4,097,611)</u>

Net Increase in Cash and Cash Equivalents	1,602,634
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Cash and Cash Equivalents, beginning of year	<u>4,797,158</u>
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Cash and Cash Equivalents, end of year	<u>\$6,399,792</u>
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Statement of Activities

Revenue and Support:

Contributions	\$22,874,388
Investment income	24,761
Total revenue and support	<u>22,899,149</u>

Expenses:

Program expenses:

Research distributions and support	16,691,462
Other program expenses	2,218,400
Total program expenses	<u>18,909,862</u>

Management and general	995,410
Fundraising	1,101,026
Total expenses	<u>21,006,298</u>

Change in net assets	1,892,851
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Net Assets, beginning of year	<u>12,902,602</u>
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Net Assets, end of year	<u>\$14,795,453</u>
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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/.

BOARD OF DIRECTORS



JEFFREY L. MORBY

*Co-Chairman, Board of Directors
Founding Board Member
Former Vice-Chairman of Mellon Bank,
Chairman of Mellon Bank Europe
Chairman of the Morby Family
Charitable Foundation*



HENRY F. McCANCE

*Co-Chairman, Board of Directors
Founding Board Member
Chairman Emeritus of Greylock
Partners
Trustee of the McCance Family
Foundation*



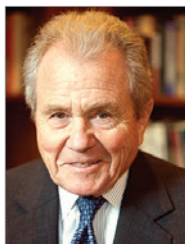
TIM ARMOUR

President and Chief Executive Officer



JACQUELINE C. MORBY

*Founding Board Member
Senior Advisor of TA Associates*



ROBERT F. GREENHILL

*Chairman and Founder
Greenhill & Company*



PHYLLIS RAPPAPORT

*Treasurer
Founding Board Member
Chair of the Phyllis and Jerome Lyle
Rappaport Charitable Foundation
Director of New Boston Fund Inc.*



SHERRY SHARP

*Christian Writer
President and Director of the Rick Sharp
Alzheimer's Foundation*

ADMINISTRATION

JO ANTONELLIS

Controller

TIM ARMOUR

President and Chief Executive Officer

LISA BIDA

Marketing Manager

JOYCE CANTOW

Accounting Assistant II

BARBARA CHAMBERS

*Executive Vice President, Marketing and
Communications*

KYRSTEN CONOVER

Development Associate

INGRID DANKERS

Gift Processing Assistant

KRISTEN HAWLEY

Manager, Meetings and Events

MAHUA HEATH

Senior Philanthropic Advisor

MORGAN HERMAN

Executive Vice President, Development

AMANDA LACEY

Office Manager and Executive Assistant

LAUREL LYLE

*Vice President, Board Relations and
Development Operations*

JESSICA MUTCH

Chief Financial Officer

LAURA PELLETRINO

Development Associate

LISA RAND

Vice President, Marketing and Communications

EMANUELA ZAHARIEVA

RAPPOPORT, PH.D.

Science Writer

CAITLIN SAIA

Research Program Administrator

NIKKI SENGSAVANH

Director, Development Operations

SHARON SEVRANSKY

Coordinator, Development Operations

JOHN SLATTERY

Senior Vice President, Development

MEG SMITH

*Executive Vice President, Research
Management*

CONNOR SWAN

Manager, Leadership Gifts and Heroes Program

CINDY TURNER

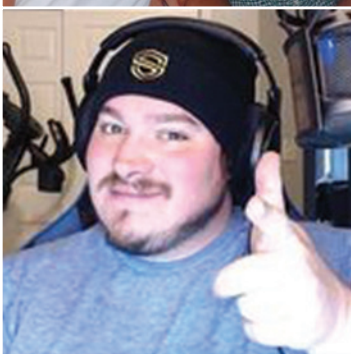
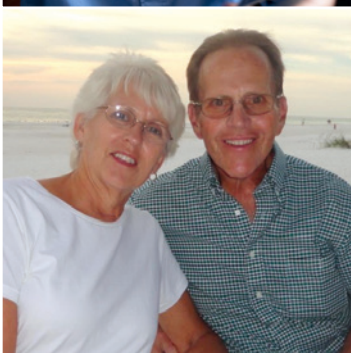
Accounting Supervisor

DOROTHY VACARO

Gift Processing Coordinator

KELLY WESTERHOUSE

Vice President, Leadership Giving



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 **2020 heroes, and share a few of their stories on the following pages.**

Alan Arnette
 alphauprising
 Amelia Pleasant Kennedy
 Axels for Alzheimer's
 Barbara Reed
 Barry Bronstein
 Catherine LaCasce
 Edward E. Zucker, Chestnut Hill Realty
 Crimson Star Emporium
 David K. Johnson Foundation
 Dr. Richard Kelliher
 Drew Houx
 Elijah Henson
 Essex Paddle Tennis Club
 Gabrielle Stern
 John Sharp, Hardenbergh Insurance Group
 Harold Sanditen
 International Association of Fire Fighters (IAFF) Local 792
 International Brotherhood of Magicians Ring 122
 Jason Kollat, Badgunpla
 Jen Noonan, A Token Of
 Jenny Chen
 Jeremy Katz
 Jog Your Memory
 Jonny Gerber (Malingo)
 Katie Wilson, Keller Williams NA
 Lezlee Sabo, My Dance Studio
 Luis Perez and Micah Bolden
 Mahkana
 Maria Vicari
 Maritza Shapiro

MatthewOrMatt
 Michael Makar
 Courtney Vanderlinde Iverson, Morels & Memories—Mushroom Hunt & Alzheimer's Fundraiser
 Nancy Greene, Swimming Miles for Meredith and Alzheimer's Research
 Nikki Patrick, Strengthlets
 Nikki Torchon, CureSong
 Nikki Zazzali, Revive Jewelry
 Pamela Panahon
 Peter Flynn, Friars for Alzheimer's Awareness
 Ria's Hallmark Shop
 Ride for a Reason
 Running 4 Answers
 Samuel Middlehurst, Mongol Rally
 Shelly Mellott, Impact Charms
 SingStrong A cappella Festival
 Skeletora
 Sustainable Sports Foundation, Marin County Half Marathon
 Terry Donoghue
 Viralu
 VitaminAxion
 The Whetton Family
 Whit Collier
 Xinyu (Simon) Wu
 Ziv Bard, magician



Yvette Gonzalez-Nacer

Singer, songwriter and Broadway actress Yvette Gonzalez-Nacer started the charitable foundation Creative Minds Care with the simple desire to live in a world without Alzheimer's disease. Inspired by her grandmother, who had the disease, Yvette established her foundation to raise awareness and donations to fund Alzheimer's research. Leveraging her connections and experience in the arts, Yvette brought together a collective of like-minded individuals for a concert and raised \$50,000 to fund research in the areas of neuroplasticity and neurogenesis.

Ella O'Donnell

Ella, a high school freshman who lives in New Jersey, made tie-dye masks for a special school project. Ella has firsthand experience with the impact of Alzheimer's disease; her grandmother was diagnosed with it a few years ago. She sold the masks and chose Cure Alzheimer's Fund to receive the proceeds to support research. Ella worked on her project for more than 30 hours, made almost 200 masks and raised \$1,500 for Cure Alzheimer's Fund. We applaud Ella's creativity during the COVID-19 pandemic and thank her for helping fund needed research.





Jog Your Memory

In 2014, Jess and Bob Rice created the Jog Your Memory road race to raise funds for Alzheimer's disease research. For its seventh year, they faced a dilemma: how to hold the race during a pandemic. The answer? The former one-day race in Needham, Massachusetts, went virtual for a two-day event in September, and brought together more than 700 runners and walkers from 42 states and six countries. In this incarnation, Jog Your Memory raised \$190,000 for Alzheimer's research and caregiving, and surpassed the \$1 million mark for funds raised since its inception—a spectacular success!



The Whetton Family

Dave Whetton of Caldwell, New Jersey, witnessed the long and difficult decline of his father-in-law due to the effects of Alzheimer's disease, and its impact on his family. Dave, along with his wife, Rita, and their son, Enzo, have become tireless advocates for Alzheimer's awareness and fundraising. The Whettons' first effort to benefit CureAlz was a music trivia night at a local coffeehouse that raised \$1,000 for research. During the pandemic, the Whettons held two virtual Zoom raffles that each raised more than \$2,200. Dave was recognized in 2021 as a New Jersey State Governor's Jefferson Awards Honoree for Volunteer Leadership for his outstanding acts of public service.

Awareness

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

Webinars

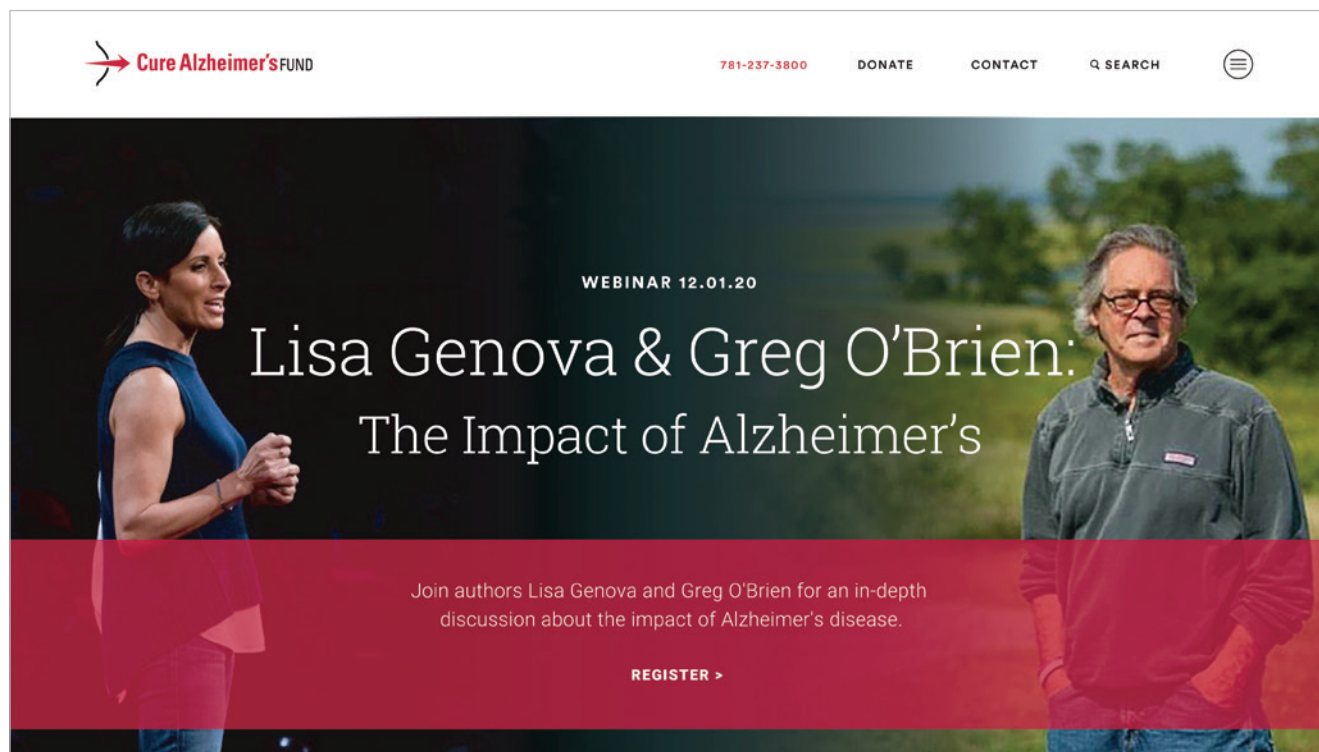
Cure Alzheimer's Fund continued to provide updates on research to audiences throughout 2020 by pivoting to online events. To view a recording of these webinars, visit CureAlz.org/news-and-events/.

CURE ALZHEIMER'S FUND RESEARCH DURING THE COVID-19 PANDEMIC

On April 30, Dr. Rudy Tanzi presented the ways that researchers throughout the world collaborated to understand COVID-19. Many researchers—including those involved with Alzheimer's disease—were able to share findings from their work that provided a more complete analysis of the virus. The update also included an overview of many activities taking place during the early shutdown of funded labs.

A CONVERSATION BETWEEN LISA GENOVA, PH.D., AND GREG O'BRIEN

Good friends Lisa Genova, Ph.D., neuroscientist and author of "Still Alice" and "Remember," and Greg O'Brien, journalist and author of "On Pluto," had an open conversation about the impact of living with Alzheimer's disease. Greg was diagnosed with Alzheimer's disease 11 years ago at the age of 59, and shared his experience with warmth, candor and—at times—raw emotion.



The screenshot shows the Cure Alzheimer's Fund website. The header includes the logo, phone number (781-237-3800), and links for DONATE, CONTACT, and SEARCH. The main content area features a webinar announcement for Lisa Genova & Greg O'Brien: "The Impact of Alzheimer's". The text "WEBINAR 12.01.20" is displayed above the title. Below the title, it says "Join authors Lisa Genova and Greg O'Brien for an in-depth discussion about the impact of Alzheimer's disease." and a "REGISTER >" button.

THE LATEST CLINICAL TRIALS AND THERAPEUTICS FOR ALZHEIMER'S DISEASE

During an update on May 27, Dr. Rudy Tanzi provided information on therapeutics in phase 3 clinical trials, including Aducanumab, GV-971, DIAN-TU, AMX0035 and four others on the horizon.

THE PATHOLOGY OF ALZHEIMER'S DISEASE AND CURRENT RESEARCH

Arbonne is an international organization focused on a holistic approach to health and well-being. On July 15, CureAlz President and CEO Tim Armour was invited to make a presentation about Alzheimer's disease and advancements in research to Arbonne representatives.

2020 ROTARY INTERNATIONAL CONFERENCE

Rotary International has an annual conference with tens of thousands of participants. Its conference shifted to an online event for 2020, and Tim Armour was invited to speak about the progress of research on Alzheimer's disease.

REASONS FOR HOPE: ALZHEIMER'S DISEASE AND CLINICAL TRIALS

In this CureAlz Fund webinar, Dr. Ron Petersen presented the progress that has been made in understanding Alzheimer's disease, current therapeutic approaches and clinical trials. Dr. Petersen was the clinician to President Reagan and country singer Glen Campbell. During the program, he shared footage from the 2014 film documenting Glen Campbell's life with Alzheimer's disease.

VENTURE THERAPY IN ACTION: THE RACE FOR AN ALZHEIMER'S CURE

Cresset Capital invited Henry McCance, Co-Chairman of Cure Alzheimer's Fund, and Dr. Rudy Tanzi to share the story of CureAlz with the organization's wealth managers and clients. Mats Lederhausen, Cresset Advisory Board member and friend of CureAlz, moderated a discussion about the role of venture funding and resulting advances in research on Alzheimer's disease.

First Republic Bank

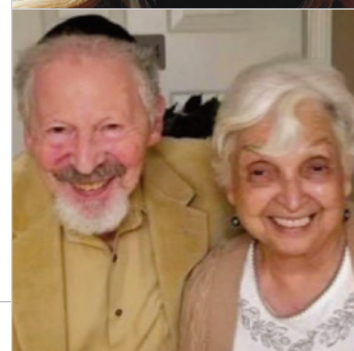
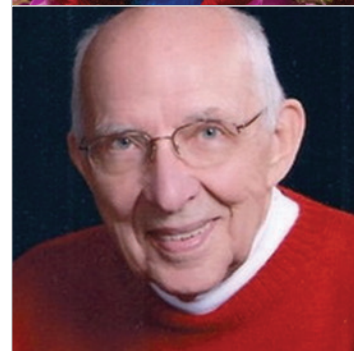
First Republic Bank created a profile of Cure Alzheimer's Fund that was published on its website and featured in its print publication distributed to clients during Alzheimer's Awareness Month in November. The interview with Tim Armour, President and CEO of Cure Alzheimer's Fund, and Barbara Chambers, Executive Vice President, Marketing and Communications, explores the effects of the pandemic on research and the impact on those with the disease and their caregivers. We are thankful to First Republic Bank for helping to bring awareness to the need for increased funding for research into the causes of Alzheimer's disease, which may lead to future therapies.

Holiday Gift Guide

Cure Alzheimer's Fund has the privilege of benefiting from the generous contributions of companies that have chosen to offer a portion of the proceeds from their products to fund our research. For 2020 we produced a holiday gift guide, which featured a selection of these products, including jewelry, cosmetics, wine and personal gifts. We are grateful to the individuals who purchased these items and the businesses that selected our organization to receive these contributions to fund research.

Public Service Announcements

This year, Cure Alzheimer's Fund produced two new public service announcements (PSAs) to share the vital role of scientists and their discoveries in our future solutions for Alzheimer's disease. "Night Sky" and "The Call" combine vivid imagery with compelling storytelling to bring awareness to the work our funded researchers do every day to discover the causes of Alzheimer's disease. The PSAs invite the viewer to be part of the discovery and join the fight, because "research is the only path to a cure." The PSAs were created by the agency Proper Villains on behalf of Cure Alzheimer's Fund, and aired on Comcast and its digital properties throughout New England.



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, Board Relations and Development Operations, at LLyle@CureAlz.org, or call **781-237-3800**. Thank you.



Support Our Research

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

Donor Advised Funds

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

Planned Giving

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

Qualified Charitable Distribution

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

Monthly Giving

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

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

100% of your donation goes directly to research.

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.

RECOGNIZED FOR EXCELLENCE



Cure Alzheimer's Fund has been awarded the highest rating of 4 stars for 10 consecutive years.



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



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



Cure Alzheimer's Fund has been named one of The 50 Best Charities to Give to Right Now.

**Main Office**

34 Washington St., Suite 310
Wellesley Hills, MA 02481
Phone: (781) 237-3800
info@CureAlz.org

CureAlz.org**WomenandAlzheimers.org**

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