Cure Alzheimer's FUND
targeting breakthrough research

2021 ANNUAL REPORT

———

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 2021

Dear Friends,

The uppermost question in all our minds is always, "How much progress are we making in finding a cure for Alzheimer's disease?" We will address that question below, but we first must thank all of our wonderful supporters who have made Cure Alzheimer's fund so successful over the years.

Our sincere thanks go to:

- Our 24,000 donors who, in 2021, contributed to the foundation a total of more than $28 million in new funding, an all-time record.

- Our 102 researchers who have generated 77 very promising research projects in 2021—again, an all-time record (individual details included elsewhere in this Annual Report).

- The members of our newly formed Board of Trustees, who are committing their time and resources to our mission and are helping to support our operating expenses.

- The wonderful staff of Cure Alzheimer's Fund, led by Tim Armour, our CEO. They have managed the foundation with great skill and dedication through the COVID years.

- And all of you for making it possible for **Cure Alzheimer's Fund to continue to receive the top ratings for charitable foundations by rating organizations,** including Charity Navigator and GuideStar.

With great sadness we note the passing of two giant contributors to Alzheimer's research. Jerry Rappaport, our dear friend and husband of Co-Founder and Director Phyllis Rappaport, was an advocate for Alzheimer's research and provided us with knowledge, advice and support. We also lost an extraordinary scientist and member of our Research Leadership Group, Dr. Steven Wagner, a co-developer of the gamma secretase modulator (described later in this letter) with Dr. Rudy Tanzi. Jerry and Steve are remembered within the pages of this Annual Report.

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.

PROGRESS TOWARD FINDING A CURE

Great progress was made in 2021 in unraveling the complexity of the disease, but the cure or preventive still proves elusive. But as you will see, we are gaining on it with good results. Following is a small sampling of some of our important breakthroughs.

NEW ALZHEIMER'S GENES

Fifteen new genes associated with Alzheimer's disease (AD) were identified by Dr. Rudy Tanzi and his lab using whole genome sequencing data from more than 20 Alzheimer's patients and families. This is in addition to nearly 100 genes discovered earlier, enabling us to maintain our leadership as one of the top sources in the world of information on the genomics of Alzheimer's disease. This database provides an important tool for researchers as they investigate the relationships among genes and groups of genes (such as those researchers working within consortia, described below).

FIVE DIFFERENT CONSORTIA, ANALYZING ALZHEIMER'S PATHOLOGY AS A SYSTEM OR SERIES OF SYSTEMS

The cause of Alzheimer's disease is not a single gene, nor genes, as was earlier thought. Genes and noncoding DNA operate within an entire system of relationships and forms of communication. When those systems become unbalanced for one reason or another, Alzheimer's disease may occur. We are funding five different consortia, made up of truly outstanding researchers, focusing on understanding the major systems that underlie the workings of the brain in order to identify major flaws in those systems that may lead to AD. More details of those consortia are contained in the body of this document.

BRAIN MENINGEAL LYMPHATIC SYSTEM

Dr. Jony Kipnis of Washington University School of Medicine in St. Louis showed that boosting the brain's drainage system—the meningeal lymphatics—improves microglial clearance of amyloid beta plaques and reduces dangerous side effects of anti-amyloid immunotherapy in a mouse model of AD. Such clearance is very important, for if amyloid is not cleared, it remains in the brain and begins to clump into toxic deposits and also generates tau tangles. Understanding how clearance works may enable us to create potential new therapies to facilitate clearing for those with deficient clearing mechanisms.

APOE3-JACKSONVILLE

A rare variant of APOE3 studied by Dr. Guojun Bu of the Mayo Clinic Jacksonville, now identified as APOE3-Jacksonville, has been shown to dramatically reduce the risk of developing Alzheimer's disease. The protective mechanism differs from that of another positive variant, APOE3 Christchurch, being studied by Dr. David Holtzman of Washington University. Both provide possibilities for future therapeutic intervention.

INFLAMMATORY ASTROCYTE SIGNALING

Astrocytes normally nourish neurons but are toxic to them under certain conditions. In a breakthrough discovery after years of searching, the lab of Dr. Shane Liddelow of New York University Langone Health identified the long-sought chemical signal by which astrocytes induce the death of nearby injured nerve cells and contribute to neurodegeneration. Therapies that take advantage of our knowledge of how the signaling works may help delay onset of Alzheimer's disease in older patients.

> "Therapies that take advantage of our knowledge of how the signaling works may help delay onset of Alzheimer's disease in older patients."

REPURPOSING FOR AD OF EXISTING DRUGS ORIGINALLY DEVELOPED FOR OTHER ILLNESSES

The original Alzheimer's in a Dish™ modeling of AD has progressed significantly to enable scientists to now confirm the importance of amyloid beta, tau pathology and neuroinflammation as the primary pillars of Alzheimer's pathology. The newest versions of this model also have provided ways to screen existing drugs for their potential therapeutic effects. The highest potential repurposing compounds identified and validated in all of these screens now successfully have been moved into discussions within the CureAlz Fund Alzheimer's Clinical Task Force Accelerating Successful Trials (ACTFAST), to focus on repurposing and combining drugs and natural products selected for their ability to reduce amyloid beta, tau pathology and neuroinflammation.

GAMMA SECRETASE MODULATORS (GSMs)

Developed by Drs. Rudy Tanzi and Steven Wagner, thanks to early CureAlz support, this ingenious small molecule approach to Alzheimer's prevention has received sufficient funding from the National Institutes of Health to support a Phase 1 safety trial. By subtly changing the binding of the gamma secretase complex to the amyloid precursor protein, this drug tilts amyloid production toward shorter lengths of the protein. While it has been well known that longer lengths of amyloid ($A\beta42$ in particular) are associated with AD risk and progression, new research published in 2021 suggests that the shorter length ($A\beta38$) encouraged by the GSM may be protective. The GSM thus may someday be part of a prevention strategy in which people at high risk of AD start taking it in midlife to prevent the development of the amyloid pathology that starts the AD cascade.

AMYLYX PHARMACEUTICALS, WITH A DRUG FOR BOTH ALZHEIMER'S AND ALS

Amylyx is a small biotech company whose founders as undergraduates at Brown University first came to Dr. Rudy Tanzi for "proof of concept" of an innovative idea for a combination drug to fight Alzheimer's disease. Against all odds, that drug has proved to be a viable candidate for both AD and ALS, and has been the basis of the formulation of a company, Amylyx. Amylyx is now preparing a Phase 3 clinical trial for ALS to follow up on positive clinical results from its Phase 2 ALS trial. Although its Phase 2 Alzheimer's trial was too small to allow clinical benefit to be assessed, the data indicated beneficial changes across a number of important cellular stress points, neuroinflammation and AD pathology biomarkers, setting the stage for an eventual follow-on Phase 3 AD trial.

"The GSM thus may someday be part of a prevention strategy in which people at high risk of AD start taking it in midlife to prevent the development of the amyloid pathology that starts the AD cascade."

EMERGING DRUGS FROM OTHER PROVIDERS

In 2021, the U.S. Food and Drug Administration (FDA)—for the first time since approving Namenda (2003) and Aricept (2004), drugs that treat only symptoms—granted accelerated approval to a drug created by Biogen on the basis of predicted clinical benefit from amyloid reduction. The FDA's decision on Aduhelm, called "aducanumab" during development, went through human trials and showed that it was highly effective at removing amyloid from the brain. However, only slight slowing of cognitive decline was demonstrated in only one of its Phase 3 trials. As a consequence, the Centers for Medicare & Medicaid Services decided to limit its coverage—a highly controversial decision. More on the issues surrounding this drug can be found elsewhere in this Annual Report.

Aduhelm works by generating antibodies specifically designed to trigger the brain's immune system to attack and remove amyloid proteins in the brain. There are several companies working on similar products for both amyloid and tau.

WE CLOSE WITH GRATITUDE

We express our tremendous gratitude to our donors who have funded this innovative research, and to our colleagues on the Board of Directors and the Trustees of Cure Alzheimer's Fund who fund all operating expenses of the foundation, thereby **permitting every dollar of donor contributions to go 100% into research**. And of course we give thanks to the researchers who have pledged their professional and, in many cases, their personal lives to slow, stop or even reverse Alzheimer's disease, and to our staff who are all making this splendid foundation function so effectively.

Sincerely,

Jeff Morby
Co-Chairman

Henry McCance
Co-Chairman

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

Prodigy.
Champion.
Visionary.

Celebrating the life of a dear friend and Boston legend.

Jerry Rappaport earned his reputation by transcending standards. He graduated Harvard Law School at just 21 years old. He redesigned Boston's cityscape and ignited renewal with the Charles River Park project. He advocated for emerging leaders in public policy, medical research and the arts. And he touched our hearts with his energy and commitment to help us eradicate Alzheimer's disease.

Jerry lost his mother to Alzheimer's, which was an experience that impacted him in several significant ways. After her passing, Jerry and his wife, Phyllis, made a commitment to help others by supporting the search for a cure.

We are forever grateful to Jerry for all he accomplished—for his family, for his city, and for those of us fortunate to have known him. Thank you, Jerry, for inspiring us all to reach higher than we believe might be possible.

Cure Alzheimer's FUND

The World Loses an Exceptional Researcher and Cure Alzheimer's Fund Loses a Dear Friend

On March 12, 2022, at the age of 64, Dr. Steven Wagner lost his four-month battle with heart disease.

Steve developed a passion for science and medicine at a very young age. After obtaining postgraduate degrees in microbiology and molecular genetics, Steve started his career studying Alzheimer's disease (AD) at the Salk Institute for Biological Studies. As a member of the team that identified amyloid precursor protein (APP), which has a pivotal role in the pathology of Alzheimer's disease, he established his importance in the field of AD research early in his career.

An extremely warm individual who made those around him feel special, Steve was genuine in his personal goal: to find a cure for Alzheimer's disease. He was a valued member of the Cure Alzheimer's Fund Research Leadership Group whose contributions were immense.

"When it came to actually translating scientific research into new therapies that might help patients or even end Alzheimer's disease, once and for all, Steve was second to none," said his friend and colleague, Dr. Rudy Tanzi. Dr. Tanzi continued, "In 2000, Steve and I co-founded a company to develop a drug that is now one of the field's greatest hopes for stopping Alzheimer's disease. After 20 years of hard work, led by Steve, a drug will enter human clinical trials in the fall of 2022. When we finally beat Alzheimer's disease, Steve will have played a major role."

Friends and Colleagues: Cure Alzheimer's Fund researchers, from left, Sam Sisodia, Rudy Tanzi, Steve Wagner, David Holtzman, Guojun Bu, Bob Vassar and Yueming Li celebrated Wagner's 60th birthday in Chicago in 2018. (Photo courtesy of Rudy Tanzi)

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 disease 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*

ADUHELM:
The Drug Approved in 2021
to Treat Alzheimer's Disease

On July 7, 2021, the U.S. Food and Drug Administration (FDA) approved Biogen's drug Aduhelm for the treatment of Alzheimer's disease (AD) under its accelerated approval program.

On May 3, 2022, Biogen announced it was shutting down the commercialization unit supporting Aduhelm, effectively removing it from the market.

Although the failure of Aduhelm is a terrible disappointment to the AD community, the circumstances also can demonstrate important progress in AD drug development, and remind us how vital the fundamental research supported by Cure Alzheimer's Fund is to achieving better therapies faster.

The following is a summary of the complicated events leading to the decision to remove Aduhelm from the market.

Aduhelm is the brand name for aducanumab, a monoclonal antibody designed to bind to aggregated forms of amyloid beta in the brain to trigger their degradation and removal by the brain's immune system. Patients receive Aduhelm via intravenous infusion once a month in specialized medical settings, and imaging is required to monitor for potentially dangerous common side effects. The annual total cost of Aduhelm treatment, even after Biogen reduced the price of the drug itself, was estimated at approximately $75,000. At the time of approval, it was as yet unknown how long a patient would need to keep taking Aduhelm or how to determine, other than for safety concerns, that they could or should cease treatment on the basis of the drug's biological or cognitive effects.

The approval of Aduhelm marked the first new drug for AD to reach the market in 18 years; it was the first drug ever designed to change the course of the disease, not just treat symptoms. Although there was no evidence that Aduhelm would stop or reverse clinical symptoms of Alzheimer's disease, the small slowing of cognitive decline achieved by a subset of its trial participants in one of its two Phase 3 clinical trials was the first cognitive benefit ever achieved in an FDA-approved Phase 3 trial of a disease-modifying AD drug.

The FDA awarded accelerated approval to Aduhelm because, it explained, it expected the drug's well-demonstrated ability to reduce levels of aggregated amyloid in the brain would yield cognitive clinical benefit to patients. Because Aduhelm's Phase 3 clinical

trials did not unequivocally achieve these benefits for participants, the drug did not meet the FDA's usual standards for unconditional approval. The accelerated approval program is designed to allow drugs to reach the market quickly that have demonstrated they affect a surrogate biomarker in a way that scientific evidence strongly suggests will lead to clinical benefit to patients. The program is controversial, particularly because the FDA has little power to enforce the requirement that companies selling drugs under accelerated approvals perform a post-marketing clinical trial to prove their long-term clinical benefit. This means some drugs marketed under accelerated approval continue to be prescribed to patients without confirmatory data or even in the face of negative trial results.

During its decision-making process, the FDA tasked a standing external advisory group of experts to discuss and assess data presented by Biogen and FDA officials. The experts agreed the data did not provide sufficient evidence of clinical efficacy to justify approval of Aduhelm. However, with its award of accelerated approval, the FDA for the first time officially endorsed the amyloid cascade hypothesis, which holds that the accumulation of amyloid beta in the brain triggers a range of changes and pathologies that together drive neurodegeneration that eventually manifests as clinical cognitive symptoms. Amyloid accumulation starts and triggers most of its consequences before clinical symptoms of Alzheimer's disease develop. Using reduction of amyloid as a surrogate biomarker for efficacy against the underlying disease will allow drugs to be assessed for their ability to prevent Alzheimer's cognitive decline, not just react to it.

Many major medical centers and health insurers announced they would not offer or cover Aduhelm after it was approved. After months of analysis and a public notice and comment period, Medicare determined it would limit coverage of anti-amyloid immunotherapies like Aduhelm to participants in clinical trials. It asserted in its decision that whether removing amyloid beta will actually yield clinical benefits remains controversial. This conflict between the FDA and Medicare, Medicare's perceived usurpation of the role of the FDA to determine drug efficacy, and concerns that Medicare's decision was driven by budget concerns rather than value to patients, generated significant public debate. With low sales and no reimbursement possible through the program that covers the vast majority of American seniors, Biogen announced in May 2022 it was ending commercialization of Aduhelm, effectively withdrawing it from the market.

Many Alzheimer's, dementia, and geriatrics advocacy and research organizations lobbied the FDA and Medicare for or against Aduhelm's approval and coverage. Cure Alzheimer's Fund did not lobby the FDA or Medicare because our affiliated scientists were divided, and we believe the FDA's and Medicare's decisions should be driven by rigorous scientific assessment rather than by the loudest voices in the debate. CureAlz is eager for the data from other anti-amyloid immunotherapy clinical trials that are expected to read out in the next 12 to 18 months.

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

- Biological research materials: new animal and cellular models, and human samples

- Epigenetic factors

TRANSLATIONAL RESEARCH

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

- Novel Alzheimer's disease genes

- Amyloid precursor protein (APP) and amyloid beta

- Tau

- Apolipoprotein E (APOE)

- Immune response in Alzheimer's disease

- Alternative neurodegenerative pathways

DRUG DISCOVERY AND ENABLING TECHNOLOGIES

In the third phase of the research, potential therapeutics and approaches are sought to leverage the identified opportunities for intervention. This includes:

- Drug screening and lead drug evaluation projects

- Drug delivery and enabling technologies

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 2021, a total of 98 high-impact science papers made possible by support from Cure Alzheimer's Fund were published in the world's leading science journals.

Nature Aging

Enhanced Epigenetic Profiling of Classical Human Monocytes Reveals a Specific Signature of Healthy Aging in the DNA Methylome

Vishwa Deep Dixit

Alzheimer's Research & Therapy

The Molecular Tweezer CLR01 Improves Behavioral Deficits and Reduces Tau Pathology in P301S-tau Transgenic Mice

Gal Bitan

Journal of Alzheimer's Disease

Thrombin Signaling Contributes to High Glucose-Induced Injury of Human Brain Microvascular Endothelial Cells

Paula Grammas

Cell Stem Cell

Deconstructing Stepwise Fate Conversion of Human Fibroblasts to Neurons by MicroRNAs

Andrew S. Yoo

Genetic Epidemiology

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

Christoph Lange

Journal of Neurochemistry

Using Stable Isotope Labeling to Advance Our Understanding of Alzheimer's Disease Etiology and Pathology

Jeffrey N. Savas

The Lancet Respiratory Medicine

Assessing the Importance of Interleukin-6 in COVID-19

Cheryl L. Wellington

Nature Protocols

Nuclei Isolation of Multiple Brain Cell Types for Omics Interrogation

Christopher K. Glass

Cell

Functional Characterization of the Dural Sinuses as a Neuroimmune Interface

Jonathan Kipnis

Genes & Development

Cell of All Trades: Oligodendrocyte Precursor Cells in Synaptic, Vascular, and Immune Function

Li-Huei Tsai

Current Opinion in Neurology

The Role of Innate Immune Genes in Alzheimer's Disease

Ana Griciuc and Rudolph E. Tanzi

Journal of Proteome Research

Enrichment of Neurodegenerative Microglia Signature in Brain-Derived Extracellular Vesicles Isolated from Alzheimer's Disease Mouse Models

Tsuneya Ikezu

Nature Aging

A Neuronal Blood Marker is Associated With Mortality in Old Age

Tony Wyss-Coray and Mathias Jucker

Life

Evidence of the Cellular Senescence Stress Response in Mitotically Active Brain Cells—Implications for Cancer and Neurodegeneration

Miranda E. Orr

Neurobiology of Aging

Age, Sex, and Cerebral Microbleeds in EFAD Alzheimer Disease Mice

Caleb E. Finch

Journal of Experimental Medicine

Preclinical Validation of a Potent γ-secretase Modulator for Alzheimer's Disease Prevention

Brian P. Head, William C. Mobley, Gopal Thinakaran, Rudolph E. Tanzi and Steven L. Wagner

Neurology Genetics

African Americans Have Differences in CSF Soluble TREM2 and Associated Genetic Variants

Krista L. Moulder, David M. Holtzman and John C. Morris

Scientific Reports

Population Imaging Discrepancies Between a Genetically-Encoded Calcium Indicator (GECI) Versus a Genetically-Encoded Voltage Indicator (GEVI)

Srdjan D. Antic

Alzheimer's Research & Therapy

Development of a Novel, Sensitive Translational Immunoassay to Detect Plasma Glial Fibrillary Acidic Protein (GFAP) After Murine Traumatic Brain Injury

Cheryl L. Wellington

Life

The Cellular Senescence Stress Response in Post-Mitotic Brain Cells: Cell Survival at the Expense of Tissue Degeneration

Miranda E. Orr

Cell Reports

The AD Tau Core Spontaneously Self-Assembles and Recruits Full-Length Tau to Filaments

Anthony W.P. Fitzpatrick and Leonard Petrucelli

Molecular Neurodegeneration

Plaque Associated Microglia Hyper-Secrete Extracellular Vesicles and Accelerate Tau Propagation in a Humanized APP Mouse Model

Tsuneya Ikezu

Alzheimer's & Dementia

Whole-Genome Sequencing Reveals New Alzheimer's Disease-Associated Rare Variants in Loci Related to Synaptic Function and Neuronal Development

Christoph Lange, Winston Hide, Lars Bertram and Rudolph E. Tanzi

Journal of Experimental Medicine

An APP Ectodomain Mutation Outside of the Aβ Domain Promotes Aβ Production in Vitro and Deposition in Vivo

Rudolph E. Tanzi and Sangram S. Sisodia

Frontiers in Neuroscience

ABCA7 Regulates Brain Fatty Acid Metabolism During LPS-Induced Acute Inflammation

Guojun Bu and Takahisa Kanekiyo

Neuron

Selective Removal of Astrocytic APOE4 Strongly Protects Against Tau-Mediated Neurodegeneration and Decreases Synaptic Phagocytosis by Microglia

Oleg Butovsky, Jason D. Ulrich and David M. Holtzman

Alzheimer's & Dementia

Molecular Imaging of NAD(+)-Dependent Deacetylase SIRT1 in the Brain

Rudolph E. Tanzi

Biological Psychiatry

Transcriptome-wide Association Study in Frontotemporal Dementia Identifies New Disease Loci by In Silico Analysis

Christina M. Lill

Nature Immunology

Microglia Use TAM Receptors to Detect and Engulf Amyloid β Plaques

Greg Lemke

Cell Reports Medicine

Soluble Interleukin-6 Receptor in the COVID-19 Cytokine Storm Syndrome

Cheryl L. Wellington

Current Opinion in Neurobiology

A Current View on Tau Protein Phosphorylation in Alzheimer's Disease

Eckhard Mandelkow

The Journal of Neuroscience

Continuous Monitoring of Tau-Induced Neurotoxicity in Patient-Derived iPSC-Neurons

Bradley T. Hyman

Journal of the American Geriatrics Society

White Matter Hyperintensities and Cognition Across Different Alzheimer's Biomarker Profiles

Richard B. Lipton and Ali Ezzati

Nature Communications

Generation of a Humanized Aβ Expressing Mouse Demonstrating Aspects of Alzheimer's Disease-like Pathology

Frank M. LaFerla

Nature

Meningeal Lymphatics Affect Microglia Responses and Anti-Aβ Immunotherapy

David M. Holtzman and Jonathan Kipnis

Cerebral Circulation — Cognition and Behavior

Dabigatran Reduces Thrombin-Induced Neuroinflammation and AD Markers in Vitro: Therapeutic Relevance for Alzheimer's Disease

Paula Grammas

Brain

On the Intersection Between Systemic Infection, Brain Vascular Dysfunction and Dementia

Berislav V. Zlokovic

Cell Reports

Axonal Generation of Amyloid-β From Palmitoylated APP in Mitochondria-Associated Endoplasmic Reticulum Membranes

Mehdi Jorfi, Dora M. Kovacs and Rudolph E. Tanzi

Acta Neuropathologica Communications

Genome-wide Analysis Identifies a Novel LINC-PINT Splice Variant Associated with Vascular Amyloid Pathology in Alzheimer's Disease

Takahisa Kanekiyo and Guojun Bu

Science Advances

Aging-Associated Deficit in CCR7 is Linked to Worsened Glymphatic Function, Cognition, Neuroinflammation, and β-Amyloid Pathology

Jonathan Kipnis

Biomolecules

Mechanisms That Activate 26S Proteasomes and Enhance Protein Degradation

Alfred L. Goldberg

Science Translational Medicine

PAC1 Receptor-Mediated Clearance of Tau in Postsynaptic Compartments Attenuates Tau Pathology in Mouse Brain

Karen E. Duff and Natura Myeku

Current Issues in Molecular Biology

Isoform-Specific Effects of Apolipoprotein E on Markers of Inflammation and Toxicity in Brain Glia and Neuronal Cells in Vitro

Paula Grammas

Alzheimer's & Dementia

Inhibition of Tau Aggregation with BSc3094 Reduces Tau and Decreases Cognitive Deficits in rTg4510 Mice

Eckhard Mandelkow and Eva-Maria Mandelkow

Current Opinion in Neurobiology

Three-Dimensional Chromatin Organization in Brain Function and Dysfunction

Li-Huei Tsai

Journal of Proteome Research

Levetiracetam Treatment Normalizes Levels of Presynaptic Endocytosis Machinery and Restores Nonamyloidogenic APP Processing in App Knock-in Mice

Jeffrey N. Savas

Scientific Reports

Menopause Impacts Human Brain Structure, Connectivity, Energy Metabolism, and Amyloid-Beta Deposition

Lisa Mosconi

Nature Aging

APOE4 Accelerates Advanced-Stage Vascular and Neurodegenerative Disorder in Old Alzheimer's Mice Via Cyclophilin A Independently of Amyloid-β

Berislav V. Zlokovic

Science Advances

Following Spatial Aβ Aggregation Dynamics in Evolving Alzheimer's Disease Pathology by Imaging Stable Isotope Labeling Kinetics

Frances A. Edwards

STAR Protocols

Generation and Validation of APOE Knockout Human iPSC-Derived Cerebral Organoids

Takahisa Kanekiyo and Guojun Bu

eLife

Ketogenic Diet Restrains Aging-induced Exacerbation of Coronavirus Infection in Mice

Vishwa Deep Dixit

Molecular Psychiatry

BACE1 Controls Synaptic Function Through Modulating Release of Synaptic Vesicles

Riqiang Yan

Alzheimer's & Dementia

Plasma IL-12/IFN-γ Axis Predicts Cognitive Trajectories in Cognitively Unimpaired Older Adults

Rudolph E. Tanzi

BMJ Open

Cohort Profile: Follow-up of a Berlin Aging Study II (BASE-II) Subsample as Part of the GendAge Study

Lars Bertram

Science Advances

The CCL2-CCR2 Astrocyte-Cancer Cell Axis in Tumor Extravasation at the Brain

Roger D. Kamm

Circulation Research

Cerebrovascular Anomalies: Perspectives from Immunology and Cerebrospinal Fluid Flow

Jonathan Kipnis

Journal of Alzheimer's Disease

Urban Air Pollution Nanoparticles from Los Angeles: Recently Decreased Neurotoxicity

Caleb E. Finch

Movement Disorders

MicroRNAs as Molecular Biomarkers for Parkinson's Disease Progression

Christina M. Lill

Translational Psychiatry

An Increase in VGF Expression Through a Rapid, Transcription-Independent, Autofeedback Mechanism Improves Cognitive Function

Stephen R. Salton

Nature

Astrocytic Interleukin-3 Programs Microglia and Limits Alzheimer's Disease

Ana Griciuc, Se Hoon Choi, Mehdi Jorfi, Matthias Nahrendorf, Rudolph E. Tanzi and Filip K. Swirski

Molecular Neurodegeneration

Knock-in Models Related to Alzheimer's Disease: Synaptic Transmission, Plaques and the Role of Microglia

John Hardy, Bart De Strooper and Frances A. Edwards

Chemical Science

Monitoring Phagocytic Uptake of Amyloid β Into Glial Cell Lysosomes in Real Time

Shane A. Liddelow

Neurobiology of Aging

Vascular Endothelial Growth Factor Associated Dissimilar Cerebrovascular Phenotypes in Two Different Mouse Models of Alzheimer's Disease

Erin H. Norris and Sidney Strickland

Journal of Magnetic Resonance Imaging

Editorial for 'MRI-Based Investigation of Association Between Cerebrovascular Structural Alteration and White Matter Hyperintensity Induced by High Blood Pressure'

Berislav V. Zlokovic

Journal of Alzheimer's Disease

A Novel Inhibitor Targeting NLRP3 Inflammasome Reduces Neuropathology and Improves Cognitive Function in Alzheimer's Disease Transgenic Mice

George S. Bloom

Nature Neuroscience

Neuroinflammatory Astrocyte Subtypes in the Mouse Brain

Shane A. Liddelow

Nature Metabolism

Exercise Hormone Irisin is a Critical Regulator of Cognitive Function

Se Hoon Choi, Rudolph E. Tanzi and Christiane D. Wrann

Acta Neuropathologica

Apolipoprotein E Regulates Lipid Metabolism and Alpha-synuclein Pathology in Human iPSC-Derived Cerebral Organoids

Takahisa Kanekiyo and Guojun Bu

Aging and Disease

Proteomic Profiling of Extracellular Vesicles Separated from Plasma of Former National Football League Players at Risk for Chronic Traumatic Encephalopathy

Tsuneya Ikezu

Aging and Disease

Enrichment of Phosphorylated Tau (Thr181) and Functionally Interacting Molecules in Chronic Traumatic Encephalopathy Brain-Derived Extracellular Vesicles

Tsuneya Ikezu

Cell Metabolism

IL-33 Causes Thermogenic Failure in Aging by Expanding Dysfunctional Adipose ILC2

Vishwa Deep Dixit

Nature Communications

Microglia Have a Grip on Brain Microvasculature

Berislav V. Zlokovic

Lab on a Chip

Patterning of Interconnected Human Brain Spheroids

Mehdi Jorfi, Rudolph E. Tanzi, Doo Yeon Kim and Daniel Irimia

Science Translational Medicine

Wolframin-1-Expressing Neurons in the Entorhinal Cortex Propagate Tau to CA1 Neurons and Impair Hippocampal Memory in Mice

Tsuneya Ikezu

Molecular Cell

Lipid Metabolism in Sickness and in Health: Emerging Regulators of Lipotoxicity

Anna Greka

Frontiers in Cell and Developmental Biology

Tau and Membranes: Interactions That Promote Folding and Condensation

Eckhard Mandelkow

Nature Reviews Neurology

The Case for Low-Level BACE1 Inhibition for the Prevention of Alzheimer Disease

Randall J. Bateman, Bart De Strooper, Christian Haass, Riqiang Yan and Robert Vassar

Science Translational Medicine

APOE3-Jacksonville (V236E) Variant Reduces Self-Aggregation and Risk of Dementia

Ronald C. Petersen, John D. Fryer and Guojun Bu

Nature

Neurotoxic Reactive Astrocytes Induce Cell Death Via Saturated Lipids

Shane A. Liddelow and Ben A. Barres

Neuronal Signaling

Conventional Protein Kinase C in the Brain: Repurposing Cancer Drugs for Neurodegenerative Treatment?

Alexandra C. Newton

Cellular and Molecular Life Sciences

The Molecular Identity of the TLQP-21 Peptide Receptor

Stephen R. Salton

Acta Neuropathologica Communications

Anatomic Survey of Seeding in Alzheimer's Disease Brains Reveals Unexpected Patterns

Marc I. Diamond

Science

CD4(+) T Cells Contribute to Neurodegeneration in Lewy Body Dementia

Tony Wyss-Coray

Journal of Medicinal Chemistry

Visualization of Receptor-Interacting Protein Kinase 1 (RIPK1) by Brain Imaging with Positron Emission Tomography

Rudolph E. Tanzi

Alzheimer's Research & Therapy

Gut-Microbiota-Microglia-Brain Interactions in Alzheimer's Disease: Knowledge-Based, Multi-Dimensional Characterization

P. Murali Doraiswamy

Frontiers in Neuroscience

Studying Synaptically Evoked Cortical Responses Ex Vivo With Combination of a Single Neuron Recording (Whole-Cell) and Population Voltage Imaging (Genetically Encoded Voltage Indicator)

Srdjan D. Antic

Acta Neuropathologica Communications

P62 Accumulates Through Neuroanatomical Circuits in Response to Tauopathy Propagation

Karen E. Duff

Brain Communications

Leveraging Machine Learning Predictive Biomarkers to Augment the Statistical Power of Clinical Trials with Baseline Magnetic Resonance Imaging

Ali Ezzati

Neurology

Association of Reproductive History With Brain MRI Biomarkers of Dementia Risk in Midlife

Lisa Mosconi

Science Translational Medicine

MEF2 is a Key Regulator of Cognitive Potential and Confers Resilience to Neurodegeneration

Manolis Kellis and Li-Huei Tsai

Alzheimer's & Dementia

Predictive Value of ATN Biomarker Profiles in Estimating Disease Progression in Alzheimer's Disease Dementia

Ali Ezzati and Richard B. Lipton

Alzheimer's & Dementia

ARMADA: Assessing Reliable Measurement in Alzheimer's Disease and Cognitive Aging Project Methods

Bruno Giordani

The FEBS Journal

Untangling Senescent and Damage-Associated Microglia in the Aging and Diseased Brain

Darren J. Baker

Nature

Single-Cell Delineation of Lineage and Genetic Identity in the Mouse Brain

Shane A. Liddelow

Frontiers in Cell and Developmental Biology

Presynaptic Autophagy and the Connection With Neurotransmission

Patrik Verstreken

Cell Reports Medicine

Can Prehospital 'Plasma Supplement' Neutralize the Systemic Storm in Severe Trauma?

Zhen Zhao and Berizlav V. Zlokovic

Brain

APOE4 Derived from Astrocytes Leads to Blood-Brain Barrier Impairment

Bradley T. Hyman

Acta Neuropathologica

CSF P-tau Increase in Response to Aβ-type and Danish-type Cerebral Amyloidosis and in the Absence of Neurofibrillary Tangles

Mathias Jucker

2021 Events to Facilitate Research Collaboration

Throughout 2021, Cure Alzheimer's Fund (CureAlz) held a number of online events to facilitate collaboration among our funded researchers and dissemination of our research findings to the broader community. Each meeting includes an area of focus for presentations and open discussion. Below are short summaries of many of our meetings.

RESEARCH LEADERSHIP GROUP (RLG) ANNUAL MEETING

This full-day meeting, held in February 2021, 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 QUARTERLY MEETINGS

Throughout the year the RLG meets to discuss the projects in process and provide updates on findings and progress.

RESEARCH STRATEGY COUNCIL (RSC)

The role of the RSC 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, review the entire research portfolio to ensure that CureAlz is supporting investigations into the most important issues in Alzheimer's disease, and that our funding mechanisms accelerate the path to patients.

CONSORTIA MEETINGS

Each of the consortia funded by CureAlz—the CIRCUITS Consortium, the Brain Entry & Exit Consortium, the AD4 Consortium, the Neuroimmune 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.

Cure Alzheimer's Fund: Our Consortia

Cure Alzheimer's Fund historically has supported innovative research projects with grants at the $100,000 to $300,000 level that have the potential to add significant new understanding of Alzheimer's disease (AD) pathology to the field. While CureAlz continues to support these new high-risk, high-potential stand-alone efforts, advances in understanding Alzheimer's disease have warranted larger-scale investigations within specific areas of the science. The consortia model provides for these initiatives with an expanded level of collaboration.

ALZHEIMER'S DISEASE DRUG DISCOVERY AND DEVELOPMENT (AD4) CONSORTIUM

Thousands of drugs have been determined by the U.S. Food and Drug Administration to be safe for humans. These drugs have well-developed clinical profiles but have never been assessed for potential benefit against Alzheimer's disease. Repurposing such drugs offers significant time and cost advantages over developing a new drug from scratch, a process that for neurology drugs is estimated to take several billion dollars and 15 years. The AD4 Consortium has been testing large libraries of such drugs and natural products—which already are being safely consumed—for their ability to reduce Alzheimer's disease pathology in human-derived cell culture systems that mimic the brain environment. The consortium now also is assessing high-potential combinations of such repurposed drugs for synergistic effects.

FLEMING APOE CONSORTIUM

Carriers of different variants of the apolipoprotein E (APOE) gene face very different lifetime risk of sporadic Alzheimer's disease, and a wealth of data has identified differential impact of the variants on amyloid plaque accumulation and clearance, tau tangle formation and neuroinflammation, non-AD hallmarks of aging and the porosity of the blood-brain barrier. Yet the mechanisms by which these effects arise are not fully understood. The Fleming APOE Consortium brings together experts across various dimensions of AD to integrate their work toward diagnostics and therapeutics targeting APOE's myriad roles.

BRAIN ENTRY & EXIT CONSORTIUM

The brain is a remarkable but fragile organ with limited ability for self-renewal following injury; it also has a very high metabolism, using approximately 20% of all energy consumed by the body and producing significant waste. Consequently, it has evolved a complex system of barriers to control the entry and exit of materials to maintain its delicate healthy balance. The CureAlz Brain Entry & Exit Consortium investigates how each component of the brain's entry and exit structures, and the cerebrospinal fluid that flows through the brain, function together to maintain health. Restoration of a single disrupted pathway may be to the benefit of all routes, offering an attractive therapeutic intervention to prevent or rescue widespread functional impairment.

COLLABORATION TO INFER REGULATORY CIRCUITS AND UNCOVER INNOVATIVE THERAPEUTIC STRATEGIES (CIRCUITS) CONSORTIUM

We have long known that advancing age and genetics are the strongest risk factors for late-onset Alzheimer's disease. What science has recognized only in the last two decades, however, is that the two interact—and their impact must be understood together. Although the genes we inherit from our parents do not change, and every cell carries the same DNA, the way and amounts that our DNA is translated into proteins differs in different cells, and changes throughout our life. Some of our DNA encodes regulatory factors that in turn affect how other parts of our DNA are read and decoded into proteins. CIRCUITS is investigating how the expression of regulatory genes differs over our lifespan, in health and disease, at different stages of disease, and in different cell types and brain regions.

NEUROIMMUNE CONSORTIUM

The researchers in the Neuroimmune Consortium are building the first comprehensive map of immune and neural cell state changes in Alzheimer's disease. Microglia and astrocytes, the primary agents of the brain's immune response, dramatically change their shape, behavior and signaling depending on their local environment in the brain, which in turn affects the behavior and state of the neurons they support. Understanding what triggers these changes and identifying patterns of responses that can be observed with imaging or fluid biomarkers could yield diagnostics for different stages of disease and windows for intervention. To achieve this map of the location and progression of microglial and astrocyte activation states—neuroinflammation—in the Alzheimer's brain, the team is integrating protein and gene expression data tied to spatial and disease progression information through imaging clinical histories, and biochemical assessment using new computational tools. This map and the tools used to build it will be shared across the Alzheimer's disease field to accelerate research beyond this consortium.

For complete details about each of our consortia, please visit: **www.CureAlz.org/The-Research/Consortia/**.

Our Researchers

This gallery features researchers who received funding in 2021, as well as the members of our Research Leadership Group and Research Strategy Council.
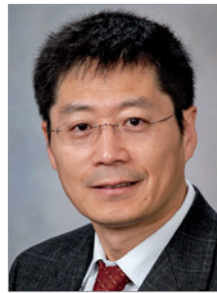

RANDALL BATEMAN, M.D.

Washington University School of Medicine in St. Louis

Charles F. and Joanne Knight Distinguished Professor, Neurology; Director, Dominantly Inherited Alzheimer Network (DIAN) and DIAN Trials Unit (DIAN-TU)

Research Leadership Group

GUOJUN BU, PH.D.

Mayo Clinic

Mary Lowell Leary Professor of Medicine; Chair, Department of Neuroscience; Associate Director, Center for Regenerative Medicine

Research Leadership Group

LARS BERTRAM, M.D.

University of Lübeck, Germany

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

OLEG BUTOVSKY, PH.D.

Brigham and Women's Hospital

Associate Professor of Neurology, Harvard Medical School, Ann Romney Center for Neurologic Diseases, Department of Neurology
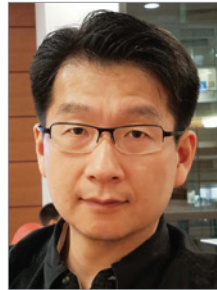
Research Leadership Group

GEORGE S. BLOOM, PH.D.

University of Virginia

Professor of Biology, Cell Biology, and Neuroscience

SE HOON CHOI, PH.D.

Massachusetts General Hospital

Assistant Professor of Neurology, Harvard Medical School; Faculty, Henry and Allison McCance Center for Brain Health

MATHEW BLURTON-JONES, PH.D.

University of California, Irvine

Associate Professor, Neurobiology and Behavior; Faculty, UC Irvine Institute for Memory Impairments and Neurological Disorders (UCI MIND)

Research Leadership Group

MARCO COLONNA, M.D.

Washington University School of Medicine in St. Louis

Robert Rock Belliveau Professor of Pathology and Immunology

Research Leadership Group

LAURA M. COX, PH.D.

Brigham and Women's Hospital

Assistant Professor, Neurology, Ann Romney Center for Neurologic Diseases, Harvard Medical School

KAREN DUFF, PH.D.

University College London, England

Centre Director, Dementia Research Institute of UK

Research Leadership Group

RICHARD DANEMAN, PH.D.

University of California, San Diego

Associate Professor, Departments of Neurosciences and Pharmacology

JOSEPH R. ECKER, PH.D.

The Salk Institute

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

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

VIB-KU Leuven Center for Brain & Disease Research, Belgium

Director, Dementia Research institute of the UK; Professor and VIB researcher at KU Leuven, Belgium, and UCL, London, England
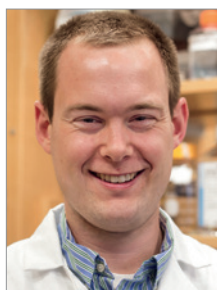
Research Leadership Group

FRANCES EDWARDS, PH.D.

University College London, England

Professor of Neurodegeneration

MARC DIAMOND, M.D.

University of Texas Southwestern Medical Center

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

Research Leadership Group

WILLIAM EIMER, PH.D.

Massachusetts General Hospital

Instructor in Neurology, Harvard Medical School; Faculty, Henry and Allison McCance Center for Brain Health

MURALI DORAISWAMY, M.B.B.S.

Duke University

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

Research Leadership Group

CALEB FINCH, PH.D.

University of Southern California

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

Research Leadership Group

JOHN D. FRYER, PH.D.

Mayo Clinic

Associate Professor of Neuroscience

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

Icahn School of Medicine
at Mount Sinai

*Endowed Chair in Alzheimer's Disease Research;
Professor of Neurology and Psychiatry; Director,
Mount Sinai Center for Wellness and Cognitive
Health; Director, Mount Sinai NFL Center for
Neurological Care*

Research Leadership Group

CHARLES GLABE, PH.D.

University of California, Irvine

Professor, Molecular Biology and Biochemistry

Research Leadership Group

TERESA GOMEZ-ISLA, M.D.

Massachusetts General Hospital

*Associate Professor of Neurology, Harvard Medical
School; Assistant Neurologist*

ANA GRICIUC, PH.D.

Massachusetts General Hospital

Assistant Professor of Neurology

VINCE GROPPI, PH.D.

Oricula Therapeutics

Co-Founder and Chief Executive Officer

Research Strategy Council

JAIME GRUTZENDLER, M.D.

Yale School of Medicine

*Dr. Harry M. Zimmerman and Dr. Nicholas and Viola
Spinelli Professor of Neurology and Neuroscience;
Vice-Chair for Research, Neurology; Director, Center
for Experimental Neuroimaging*

CHRISTIAN HAASS, PH.D.

DZNE, Germany

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

Research Leadership Group

JOHN HARDY, PH.D.

University College London, England

*Chair, Molecular Biology of Neurological Disease,
UCL Queen Square Institute of Neurology*

WINSTON HIDE, PH.D.

Beth Israel Deaconess Medical Center

*Associate Professor, Department of Pathology,
Harvard Medical School; Director, Noncoding
RNA Core*

DAVID M. HOLTZMAN, M.D.

Washington University School of Medicine in St. Louis

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

Research Leadership Group

RICHARD L. HUGANIR, PH.D.

Johns Hopkins University School of Medicine

Bloomberg Distinguished Professor of Neuroscience and Psychological and Brain Sciences; Director, Department of Neuroscience; Co-Director, Brain Science Institute
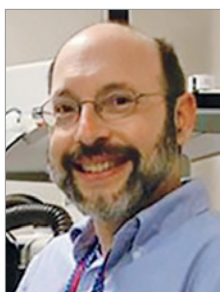
Research Leadership Group

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

Massachusetts General Hospital

John B. Penney, Jr., Professor of Neurology, Harvard Medical School; Director, MassGeneral Institute for Neurodegenerative Disease (MIND)

Research Leadership Group

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

Mayo Clinic

Director, Molecular NeuroTherapeutics Laboratory; Professor, Department of Neuroscience

NANCY IP, PH.D.

Hong Kong University of Science and Technology (HKUST)

Vice-President for Research and Development; The Morningside Professor of Life Science; Director, State Key Laboratory of Molecular Neuroscience

Research Leadership Group

RUDOLF JAENISCH, M.D.

Massachusetts Institute of Technology

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

ROGER D. KAMM, PH.D.

Massachusetts Institute of Technology

Cecil and Ida Green Distinguished Professor of Biological and Mechanical Engineering

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

Mayo Clinic

Assistant Professor of Neuroscience

MANOLIS KELLIS, PH.D.

Massachusetts Institute of Technology

Professor, Computer Science; Head, MIT Computational Biology Group; Member, Broad Institute
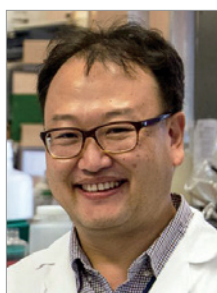
DOO YEON KIM, PH.D.

Massachusetts General Hospital

Associate Professor of Neurology, Harvard Medical School; Faculty, Henry and Allison McCance Center for Brain Health

JONATHAN KIPNIS, PH.D.

Washington University School of Medicine in St. Louis

BJC Investigator; Alan A. and Edith L. Wolff Distinguished Professor of Pathology and Immunology; Professor of Neurology, Neuroscience and Neurosurgery; Director, Center for Brain Immunology and Glia (BIG)

Research Leadership Group

DEEPAK KUMAR VIJAYA KUMAR, PH.D.

Massachusetts General Hospital

Instructor in Neurology; Faculty, Henry and Allison McCance Center for Brain Health

BRUCE LAMB, PH.D.

Indiana University School of Medicine

Executive Director, Paul and Carole Stark Neurosciences Research Institute

Research Leadership Group

CHRISTOPH LANGE, PH.D.

Harvard T.H. Chan School of Public Health

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

Research Leadership Group

JOHN S. LAZO, PH.D.

University of Virginia

Harrison Distinguished Professor, Departments of Pharmacology and Chemistry; Associate Director for Basic Research, University of Virginia Cancer Center; Director, Fiske Drug Discovery Laboratory

Research Leadership Group

CYNTHIA A. LEMERE, PH.D.

Brigham and Women's Hospital

Associate Professor of Neurology; Scientist, Ann Romney Center for Neurologic Diseases, Harvard Medical School

Research Leadership Group

YUEMING LI, PH.D.

Memorial Sloan Kettering Cancer Center

Head, Laboratory of Biochemistry and Molecular Pharmacology

Research Leadership Group

SHANE A. LIDDELOW, PH.D.

Neuroscience Institute at NYU Langone Health

Assistant Professor, Department of Neuroscience and Physiology; Assistant Professor, Department of Ophthalmology

Research Leadership Group

ENG H. LO, PH.D.

Massachusetts General Hospital

Professor of Neurology and Radiology, Harvard Medical School

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

Stanford University School of Medicine

Nancy Friend Pritzker Professor in Psychiatry and Behavioral Sciences; Deputy Director, Wu Tsai Neurosciences Institute; Director, Nancy Pritzker Laboratory

Research Leadership Group

FREDERICK R. MAXFIELD, PH.D.

Weill Cornell Medical College

Chairman and Professor of Biochemistry; Vladimir Horowitz and Wanda Toscanini Horowitz Distinguished Professor in Neuroscience

JOSEPH PARK, PH.D.

Massachusetts General Hospital

Instructor in Neurology

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

University of California, San Diego

Associate Dean of Neurosciences Initiatives; Distinguished Professor of Neurosciences; Executive Director, Down Syndrome Center for Research and Treatment; Florence Riford Chair of Alzheimer's Disease Research

Research Leadership Group

GENTRY PATRICK, PH.D.

University of California, San Diego

Professor in the Neurobiology Section of the Division of Biological Sciences

JOHN MORRIS, M.D.

Washington University School of Medicine in St. Louis

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

Research Strategy Council, Chair

STEVEN M. PAUL, M.D.

Karuna Therapeutics

Chairman of the Board, President and Chief Executive Officer; Director, Foundation for the National Institutes of Health (FNIH); Former Scientific Director, National Institute of Mental Health (NIMH/NIH)

Research Strategy Council

NANDA KUMAR NAVALPUR SHANMUGAM, PH.D.

Massachusetts General Hospital

Research Associate, Massachusetts General Hospital; Instructor, Harvard Medical School; Faculty, Henry and Allison McCance Center for Brain Health

RONALD C. PETERSEN, M.D., PH.D.

Mayo Clinic

Director, Alzheimer's Disease Research Center and Study of Aging; Professor of Neurology

Research Leadership Group

ALEXANDRA NEWTON, PH.D.

University of California, San Diego

Professor of Pharmacology

LEONARD PETRUCELLI, PH.D.

Mayo Clinic

Chair and Professor, Department of Neuroscience

ANDREAS R. PFENNING, PH.D.

Carnegie Mellon University

Assistant Professor, Computational Biology

JEFFREY N. SAVAS, PH.D.

Northwestern University

Assistant Professor of Behavioral Neurology, Medicine and Pharmacology

CHRISTIAN PIKE, PH.D.

University of Southern California

Professor of Gerontology

ELIZABETH R. SHARLOW, PH.D.

University of Virginia

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

LUISA QUINTI, PH.D.

Massachusetts General Hospital

Instructor in Neurology

SUBHASH SINHA, PH.D.

Weill Cornell Medicine

Assistant Professor of Research Neuroscience

KAREN REEVES, M.D.

AZTherapies

President and Chief Medical Officer

Research Strategy Council

SANGRAM SISODIA, PH.D.

University of Chicago

Thomas Reynolds Sr. Family Professor of Neurosciences; Professor, Departments of Neurobiology and Neurology; Director, Center for Molecular Neurobiology

Research Leadership Group

JEAN-PIERRE ROUSSARIE , PH.D.

Boston University School of Medicine

Assistant Professor, Anatomy and Neurobiology

HERMANN STELLER, PH.D.

The Rockefeller University

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

BETH STEVENS, PH.D.

Boston Children's Hospital

Associate Professor of Neurology, Harvard Medical School; Research Associate, F.M. Kirby Neurobiology Center; Investigator, Howard Hughes Medical Institute (HHMI); Member, Broad Institute

Research Leadership Group

ROBERT VASSAR, PH.D.

Northwestern University

Scientific Director of Behavioral Neurology, Department of Neurology; Davee Professor of Alzheimer Research; Professor of Neurology and Cell and Developmental Biology

Research Leadership Group

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

Stanford University School of Medicine

Professor, Departments of Molecular and Cellular Physiology and of Neurosurgery; Avram Goldstein Professor Investigator, Howard Hughes Medical Institute (HHMI)

Research Leadership Group

STEVEN L. WAGNER, PH.D.

University of California, San Diego

Professor in Residence, Neurosciences; Director of Neurodegenerative Research, Department of Neurosciences

Research Leadership Group

(Deceased March 2022)

FILIP SWIRSKI, PH.D.

Icahn School of Medicine at Mount Sinai

Arthur and Janet C. Ross Professor of Medicine (Cardiology); Professor of Diagnostic, Molecular and Interventional Radiology; Director, Cardiovascular Research Institute

WILMA WASCO, PH.D.

Massachusetts General Hospital

Associate Professor of Neurology, Harvard Medical School; Associate Geneticist

RUDOLPH TANZI, PH.D.

Massachusetts General Hospital

Vice Chair of Neurology; Director, Genetics and Aging Research Unit; Co-Director, Henry and Allison McCance Center for Brain Health; Co-Director, MassGeneral Institute for Neurodegenerative Disease (MIND); Joseph P. and Rose F. Kennedy Professor of Neurology, Harvard Medical School

Research Leadership Group, Chair
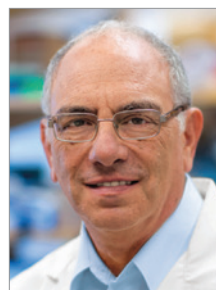
HOWARD L. WEINER, M.D.

Brigham and Women's Hospital

Robert L. Kroc Professor of Neurology, Harvard Medical School; Chief, Division of Multiple Sclerosis and Neuro-Immunology, Department of Neurology; Co-Director, Ann Romney Center for Neurologic Diseases

LI-HUEI TSAI, PH.D.

Massachusetts Institute of Technology

Director, The Picower Institute for Learning and Memory; Picower Professor of Neuroscience, Department of Brain and Cognitive Sciences; Senior Associate Member, Broad Institute; Co-Director, Alana Down Syndrome Center

Research Leadership Group

CHERYL WELLINGTON, PH.D.

University of British Columbia, Canada

Professor, Department of Pathology and Laboratory Medicine

Research Leadership Group

STEPHEN T.C. WONG, PH.D.

Houston Methodist Research Institute

John S. Dunn, Sr. Distinguished Endowed Chair, Biomedical Engineering; Professor of Radiology, Pathology, Laboratory Medicine, Neurology, and Neurosciences; Associate Director, Translational Research; Chief, Medical Physics and Chief Research Information Officer, Houston Methodist Hospital; Founding Director, Chao Center for BRAIN

Research Leadership Group

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

Massachusetts General Hospital

Assistant Professor in Medicine, Affiliate of the Harvard Stem Cell Institute Cardiovascular Research Center; Faculty, Henry and Allison McCance Center for Brain Health

TONY WYSS-CORAY, PH.D.

Stanford University School of Medicine

D.H. Chen Professor, Neurology & Neurological Sciences

Research Leadership Group

WEIMING XIA, PH.D.

Boston University School of Medicine

Professor, Pharmacology and Experimental Therapeutics

RIQIANG YAN, PH.D.

University of Connecticut Health Center

Professor and Chair, Department of Neuroscience

Research Leadership Group

ANDREW S. YOO, PH.D.

Washington University School of Medicine in St. Louis

Associate Professor, Developmental Biology

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 Biophysics

Research Leadership Group

New Researchers

This gallery features researchers who received funding from Cure Alzheimer's Fund for the first time in 2021.

NICOLA J. ALLEN, PH.D.

Salk Institute for Biological Studies

Associate Professor

JOEL BLANCHARD, PH.D.

Icahn School of Medicine at Mount Sinai

Assistant Professor of Neuroscience

BÉRÉNICE A. BENAYOUN, PH.D.

University of Southern California

Assistant Professor, Gerontology

MICHAEL BONAGUIDI, PH.D.

University of Southern California

Assistant Professor of Stem Cell & Regenerative Medicine and Gerontology

HELENE BENVENISTE, M.D., PH.D.

Yale School of Medicine

Professor of Anesthesiology

DANIEL BOS, M.D., PH.D.

Erasmus University Medical Center, The Netherlands

Clinical Epidemiologist and Associate Professor, Department of Radiology and Nuclear Medicine and the Department of Epidemiology

RAJA BHATTACHARYYA, PH.D.

Massachusetts General Hospital

Instructor of Neurology, Harvard Medical School; Faculty, Henry and Allison McCance Center for Brain Health

COLETTE CYWES-BENTLEY, PH.D.

Brigham and Women's Hospital

Scientist, Division of Infectious Diseases; Assistant Professor of Medicine, Harvard Medical School

GEERT JAN BIESSELS, M.D., PH.D.

UMC Utrecht Brain Center, The Netherlands

Professor of Neurology

SANDRO DA MESQUITA, PH.D.

Mayo Clinic

Assistant Professor of Neuroscience

FRANCESCO DI VIRGILIO, M.D.

University of Ferrara, Italy

Professor of Clinical Pathology

CHARLES L. GREENBLATT, M.D.

Hebrew University, Israel

Professor Emeritus, Faculty of Medicine

LI GAN, PH.D.

Weill Cornell Medicine

Director, Helen and Robert Appel Alzheimer's Disease Research Institute; Burton P. and Judith B. Resnick Distinguished Professor in Neurodegenerative Diseases

Research Leadership Group

ANNA GREKA, M.D., PH.D.

Brigham and Women's Hospital

Associate Professor of Medicine, Harvard Medical School

DAVID GATE, PH.D.

Northwestern University Feinberg School of Medicine

Assistant Professor of Neurology

SEIKO IKEZU, M.D.

Mayo Clinic

Associate Consultant I, Department of Neuroscience

ALISON GOATE, D.PHIL.

Icahn School of Medicine at Mount Sinai

Jean C. and James W. Crystal Professor and Chair, Department of Genetics and Genomic Sciences; Director, Ronald M. Loeb Center for Alzheimer's Disease; Professor of Neuroscience; Professor of Neurology

LANCE A. JOHNSON, PH.D.

University of Kentucky

Assistant Professor, Department of Physiology

OFER N. GOFRIT, M.D., PH.D.

Hadassah Medical Organization, Israel

Professor

MEHDI JORFI, PH.D.

Massachusetts General Hospital

Investigator, Genetics and Aging Research Unit, Henry and Allison McCance Center for Brain Health; Instructor in Neurology, Harvard Medical School

BENJAMIN Y. KLEIN, M.D.

Hebrew University, Israel

Senior Scientist, Biochemical Cellular Studies

CAMERON McALPINE, PH.D.

Icahn School of Medicine at Mount Sinai

Assistant Professor, Cardiovascular Research Institute and the departments of Medicine and Neuroscience

VIJAY K. KUCHROO, D.V.M., PH.D.

Brigham and Women's Hospital

Samuel L. Wasserstrom Professor of Neurology, Harvard Medical School; Senior Scientist, Brigham and Women's Hospital; Co-Director, Center for Infection and Immunity, Brigham Research Institutes

JOSH MORGANTI, PH.D.

University of Kentucky

Assistant Professor, Department of Neuroscience

MARIA K. LEHTINEN, PH.D.

Boston Children's Hospital

Associate Professor, Department of Pathology, Harvard Medical School

LIISA MYLLYKANGAS, M.D., PH.D.

Helsinki University Hospital, Finland

Group Leader, Consultant Neuropathologist and Clinical Instructor, University of Helsinki
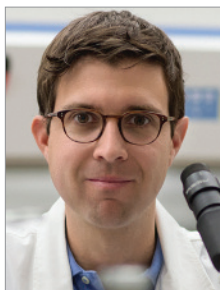
JOHN R. LUKENS, PH.D.

University of Virginia

Associate Professor, Department of Neuroscience and the Center for Brain Immunology and Glia (BIG)

JULIA NEITZEL, PH.D.

Harvard T.H. Chan School of Public Health

Postdoctoral Scientist

EDOARDO MARCORA, PH.D.

Icahn School of Medicine at Mount Sinai

Associate Professor of Neuroscience and Genetics and Genomic Sciences

GERALD B. PIER, PH.D.

Brigham and Women's Hospital

Professor of Medicine, Microbiology and Immunology, Harvard Medical School; Microbiologist

PAOLA PIZZO, BC.S., PH.D.

University of Padova, Italy

Associate Professor of General Pathology

LAURA SANTAMBROGIO, M.D., PH.D.

Weill Cornell Medicine

Associate Director, Precision Immunology, Englander Institute of Precision Medicine; Professor, Radiation Oncology; Professor, Physiology and Biophysics

KAI SCHLEPCKOW, PH.D.

DZNE, Germany

Postdoctoral Fellow, German Center for Neurodegenerative Diseases

RAMON SUN, PH.D.

University of Kentucky
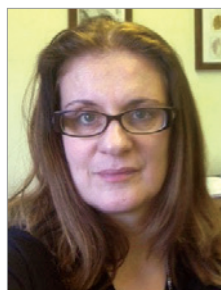
Assistant Professor, Department of Neuroscience

ALLEN TANNENBAUM, PH.D.

State University of New York at Stony Brook

Distinguished Professor of Computer Science and Applied Mathematics & Statistics

HUIZHONG W. TAO, PH.D.

University of Southern California

Professor of Physiology and Neuroscience

MEIKE VERNOOIJ, M.D., PH.D.

Erasmus University Medical Center, The Netherlands

Neuroradiologist, Head and Neck Radiologist; Professor of Population Imaging at the Departments of Radiology and Nuclear Medicine and Epidemiology

PATRIK VERSTREKEN, PH.D.

VIB-KU Leuven Center for Brain & Disease Research, Belgium

Director; Professor, Department of Neurosciences, KU Leuven

FRANK WOLTERS, M.D., PH.D.

Erasmus University Medical Center, The Netherlands

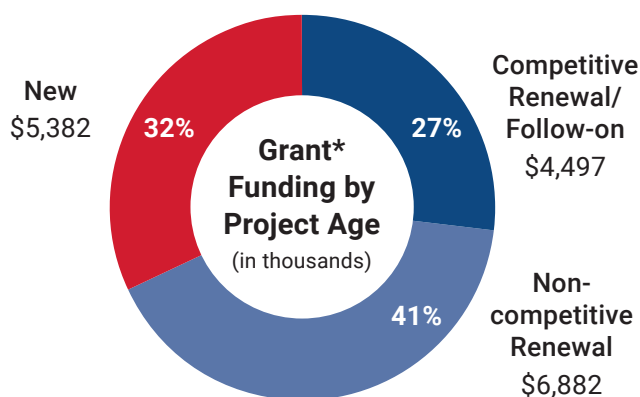*Assistant Professor; Clinical Epidemiologist*

HUI ZHENG, PH.D.

Baylor College of Medicine

Huffington Foundation Endowed Chair in Aging; Director, Huffington Center on Aging; Professor, Departments of Molecular and Human Genetics

Research Leadership Group

2021 Funded Research

Cure Alzheimer's Fund spent **$17.5 million to support 77 research projects** across our four research areas of focus. Visit **CureAlz.org/the-research** to read about all of our current research projects.

Grant* Funding by Project Age
(in thousands)

- New $5,382 — 32%
- Competitive Renewal/Follow-on $4,497 — 27%
- Non-competitive Renewal $6,882 — 41%

Number of New Investigators and Projects

	Number	% of Total
New Named Investigators*	40	39%
New Projects	31	40%
New Institutions*	7	18%

* Excludes Brain Donor Project Grant and Taconic Spending

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	**$244,496**
The Alzheimer's Genome Project™ Rudolph Tanzi, Ph.D., Massachusetts General Hospital	**$1,495,000**
BIOMARKERS, DIAGNOSTICS, AND STUDIES OF RISK AND RESILIENCE	
Understanding Human Brain Resilience to Alzheimer's Pathology Teresa Gomez-Isla, M.D., Massachusetts General Hospital	**$300,000**
BIOLOGICAL RESEARCH MATERIALS: NEW ANIMAL AND CELLULAR MODELS, AND HUMAN SAMPLES	
Targeted Recruitment of Underrepresented Americans for Brain Donation Registration Brain Donor Project	**$35,050**
Neuronal Subtype-Specific Modeling of Alzheimer's Disease by Direct Neuronal Reprogramming of Patient Fibroblasts Andrew S. Yoo, Ph.D., Washington University School of Medicine in St. Louis	**$172,500**
Genes to Therapies™ (G2T) Research Models and Materials Taconic Biosciences	**$669,601**
EPIGENETIC FACTORS	
Characterizing Epigenetic Biomarkers of Human Cognitive Aging Lars Bertram, M.D., University of Lübeck, Germany	**$245,350**
Impact of 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	**$422,500**
A Unified Approach to Actionable Alzheimer's Disease Signatures Winston Hide, Ph.D., Beth Israel Deaconess Medical Center	**$249,026**
Interpreting Alzheimer's Disease-Associated Genetic Variation at Enhancer Regions Andreas R. Pfenning, Ph.D., Carnegie Mellon University	**$200,000**
Collaboration to Infer Regulatory Circuits and Uncover Innovative Therapeutic Strategies—Production Group Manolis Kellis, Ph.D., and Li-Huei Tsai, Ph.D., Massachusetts Institute of Technology	**$550,000**

Project/Researcher	Distribution Amount
TRANSLATIONAL RESEARCH	
STUDIES OF NOVEL ALZHEIMER'S DISEASE GENES	
The Role of Clusterin in Tau Pathology John D. Fryer, Ph.D., Mayo Clinic	$172,500
Functional Basis for Novel Protein Kinase C-eta K56R Mutation in Alzheimer's Disease Alexandra Newton, Ph.D., University of California, San Diego	$172,500
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
Genes to Therapies™ (G2T), Alzheimer's Disease Drug Discovery and Development (AD4), ACTFAST and General Scientific Support Wilma Wasco, Ph.D., Massachusetts General Hospital	$172,500
STUDIES OF AMYLOID PRECURSOR PROTEIN (APP) AND AMYLOID BETA	
Interrogating Levetiracetam's Impact on Amyloid Pathology and Presynaptic Proteostasis in Knock-In Mouse Models with Humanized Amyloid Beta Jeffrey N. Savas, Ph.D., Northwestern University	$164,314
Effects of Depalmitoylation and ACAT Inhibition on Axonal Amyloid Beta Generation Via MAM-Associated palAPP Raja Bhattacharyya, Ph.D., and Rudolph Tanzi, Ph.D., Massachusetts General Hospital	$172,500
Air Pollution and Alzheimer's Disease Risk Interact With Premature Aging of Neural Stem Cells and Apolipoprotein E Alleles Caleb Finch, Ph.D., and Michael Bonaguidi, Ph.D., University of Southern California	$257,679
The NEDD4-1 and PKCa Connection in Alzheimer's Disease Gentry Patrick, Ph.D., University of California, San Diego	$172,500
STUDIES OF TAU	
Mechanisms of Tau Propagation Across the Plasma Membrane Marc Diamond, M.D., University of Texas Southwestern Medical Center	$250,000
Influence of Plaque Vicinity on Microglial and Astrocyte Gene Expression; Role of Human Tau and TREM2 Frances Edwards, Ph.D., and John Hardy, Ph.D., University College London, England	$172,289
Patient-Based Structural and Functional Biology of Tauopathies Leonard Petrucelli, Ph.D., Mayo Clinic	$172,500
STUDIES OF APOLIPOPROTEIN E (APOE)	
Establishing the Molecular and Cellular Mechanisms and Biomarkers of APOE4-Mediated Susceptibility to Tau-Related Cognitive Impairments Joel Blanchard, Ph.D., Icahn School of Medicine at Mount Sinai	$172,500
Counteracting Pathogenic Events in Alzheimer's Disease with Peripheral or Central Apolipoprotein E Guojun Bu, Ph.D., Mayo Clinic	$250,000
The Role of APOE in Microglia Regulation in Neurodegeneration Oleg Butovsky, Ph.D., Brigham and Women's Hospital	$250,000
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
Protection Against APOE4 With Longevity-Promoting Interventions Christian Pike, Ph.D., Caleb Finch, Ph.D., and Bérénice A. Benayoun, Ph.D., University of Southern California	$191,008
Apolipoprotein E and Immunometabolism in Alzheimer's Disease Lance A. Johnson, Ph.D., Ramon Sun, Ph.D., and Josh Morganti, Ph.D., University of Kentucky	$172,500

Project/Researcher	Distribution Amount
Cellular and Molecular Studies of Apolipoprotein E Regulation of Blood-Brain Barrier, Synaptic and Neuronal Functions and Protection Strategies in Mouse Models With and Without Alzheimer's Pathology Berislav V. Zlokovic, M.D., Ph.D., University of Southern California	**$250,000**
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, Canada	**$249,550**
Regulation by Apolipoprotein E of Selective Neuronal Vulnerability to Alzheimer's Disease Jean-Pierre Roussarie, Ph.D., Boston University School of Medicine	**$250,000**
STUDIES OF THE IMMUNE RESPONSE IN ALZHEIMER'S DISEASE	
The Role of MGnD-Neurodegenerative CLEC7A+ Microglia in an Alzheimer's Disease Mouse Model Oleg Butovsky, Ph.D., Brigham and Women's Hospital	**$172,500**
The Role of Astrocyte-Secreted Insulin-Like Growth Factor Binding Protein 2 (IGFBP2) in the Progression of Alzheimer's Disease Nicola J. Allen, Ph.D., Salk Institute for Biological Studies	**$172,500**
Tau and Amyloid Beta are Innate Immune Antimicrobial Peptides in the Brain William Eimer, Ph.D., Massachusetts General Hospital	**$172,500**
Understanding the Role of Natural Amyloid Beta-Specific B Cell Responses in Alzheimer's Disease Progression Marco Colonna, M.D., Washington University School of Medicine in St. Louis	**$172,500**
Systems Integration and Therapeutics Translation in Alzheimer's Disease Alison Goate, D.Phil., and Edoardo Marcora, Ph.D., Icahn School of Medicine at Mount Sinai	**$172,500**
Understanding the Mechanism Underlying Vaccination for Alzheimer's Disease Charles L. Greenblatt, M.D., and Benjamin Y. Klein, M.D., Hebrew University of Jerusalem, Israel, and Ofer N. Gofrit, M.D., Ph.D., Hadassah Medical Organization, Israel	**$229,425**
T Cell Epigenetics in Alzheimer's Disease David Gate, Ph.D., Northwestern University Feinberg School of Medicine	**$172,500**
Revealing New Genes and Pathways at the Intersection of Lipotoxic and Genetic Risk for Alzheimer's Disease Anna Greka, M.D., Ph.D., Brigham and Women's Hospital, and Beth Stevens, Ph.D., Boston Children's Hospital	**$172,500**
The Neuroprotective Glial Barrier: A Multicellular Reaction with Therapeutic Potential in Alzheimer's Disease Jaime Grutzendler, M.D., Yale School of Medicine	**$172,500**
Signaling Function of TREM2 Cleavage Products, Which are Affected by Agonistic Antibodies to the Stalk Region Christian Haass, Ph.D., and Kai Schlepckow, Ph.D., DZNE, Germany	**$172,500**
Contribution of Skull Bone Marrow-Derived Cells to Alzheimer's Disease Jonathan Kipnis, Ph.D., Washington University School of Medicine in St. Louis	**$172,500**
Role of Checkpoint Molecule TIM-3 in Regulating Microglia in Alzheimer's Disease Vijay K. Kuchroo, D.V.M., Ph.D., Brigham and Women's Hospital	**$172,500**
Neuroinflammation Contributions to Alzheimer's Disease: Role of the Choroid Plexus Maria K. Lehtinen, Ph.D., Boston Children's Hospital, and Liisa Myllykangas, M.D., Ph.D., Helsinki University Hospital, Finland	**$172,500**
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**
The Role of Interferon-Induced Transmembrane Protein 3 (IFITM3) and Gamma-Secretase in Microglia Yueming Li, Ph.D., Memorial Sloan Kettering Cancer Center	**$172,500**
The Role of Astrocyte-Derived Toxic Lipids Mediating Degeneration in Alzheimer's Disease Shane A. Liddelow, Ph.D., Neuroscience Institute at NYU Langone Health	**$174,754**
Targeting a Master Innate Immune Adaptor Molecule in Alzheimer's Disease John R. Lukens, Ph.D., University of Virginia	**$172,500**

Project/Researcher	Distribution Amount
STUDIES OF THE IMMUNE RESPONSE IN ALZHEIMER'S DISEASE (continued)	
Extracellular ATP Is a Key Factor in Promoting Alzheimer's Disease Neuroinflammation Paola Pizzo, Bc.S., Ph.D., University of Padova, Italy, and Francesco Di Virgilio, M.D., University of Ferrara, Italy	$172,500
Elucidating the Role of Soluble Epoxide Hydrolase and Arachidonic Acid Metabolism in Neuroinflammation and Alzheimer's Disease Hui Zheng, Ph.D., Baylor College of Medicine	$167,920
Role of Microglia in Degradation and Trimming of Alzheimer's Amyloid Beta Frederick R. Maxfield, Ph.D., Weill Cornell Medical College	$172,500
STUDIES OF ALTERNATIVE NEURODEGENERATIVE PATHWAYS	
Glymphatic-Lymphatic Coupling in Alzheimer's Disease Helene Benveniste, M.D., Ph.D., Yale School of Medicine, and Allen Tannenbaum, Ph.D., State University of New York at Stony Brook	$164,730
Human 3D Neurovascular Interaction and Meningeal Lymphatics Models with Application to Alzheimer's Disease Se Hoon Choi, Ph.D., Massachusetts General Hospital, and Roger D. Kamm, Ph.D., Massachusetts Institute of Technology	$215,000
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
Disentangling the Role of Intracranial Arteriosclerosis in Alzheimer's Disease Daniel Bos, M.D., Ph.D., Meike Vernooij, M.D., Ph.D., Frank Wolters, M.D., Ph.D., Erasmus University Medical Center, The Netherlands, Geert Jan Biessels, M.D., Ph.D., UMC Utrecht Brain Center, The Netherlands, and Julia Neitzel, Ph.D., Harvard T.H. Chan School of Public Health	$172,052
Harnessing Meningeal Lymphatics and Immunity to Alleviate APOE4-Induced Brain Dysfunction Sandro Da Mesquita, Ph.D., Mayo Clinic	$172,500
Identifying the Blood-Brain Barrier Changes During Alzheimer's Disease Richard Daneman, Ph.D., University of California, San Diego	$172,500
Crosstalk of Central Nervous System Barriers and Clearance Routes in Homeostasis and Alzheimer's Disease Jonathan Kipnis, Ph.D., Washington University School of Medicine in St. Louis	$250,000
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
Investigating Bone Marrow Hematopoiesis as the Link Between Sleep Fragmentation and Vascular Inflammation in AD Cameron McAlpine, Ph.D., and Filip Swirski, Ph.D., Icahn School of Medicine at Mount Sinai	$172,500
Effects of Cerebrovascular Insufficiency and Exercise on the Alzheimer's Disease Brain Vasculome Eng H. Lo, Ph.D., Massachusetts General Hospital	$170,907
Immunotherapies Targeting the Microbiota to Prevent Cognitive Decline in Alzheimer's Disease Gerald B. Pier, Ph.D., Colette Cywes-Bentley, Ph.D., and Cynthia A. Lemere, Ph.D., Brigham and Women's Hospital	$178,612
Lymphatics and Central Nervous System Fluid Homeostasis Laura Santambrogio, M.D., Ph.D., Weill Cornell Medicine	$172,500
Neural Synaptic Circuit Changes During Alzheimer's Disease Progression Huizhong W. Tao, Ph.D., University of Southern California	$172,500
Targeting the Microbiome and Innate Immunity in Alzheimer's Disease Howard L. Weiner, M.D., and Laura M. Cox, Ph.D., Brigham and Women's Hospital	$172,500

Project/Researcher	Distribution Amount
DRUG DISCOVERY AND ENABLING TECHNOLOGIES	
DRUG SCREENING AND LEAD DRUG EVALUATION PROJECTS	
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	$197,500
Development of Human cGAS Inhibitors to Treat Alzheimer's Disease Li Gan, Ph.D., and Subhash Sinha, Ph.D., Weill Cornell Medicine	$250,000
Stimulating Synaptic Proteasome Activity for the Treatment of Alzheimer's Disease Hermann Steller, Ph.D., The Rockefeller University	$172,500
Uncovering the Molecular Mechanism of Selected Drug Candidates Derived from Systematic Alzheimer's Drug Repositioning Stephen T.C. Wong, Ph.D., Houston Methodist Research Institute	$225,000
Targeting Microglial TSG101 for Synaptic Protection and Cognitive Enhancement in Alzheimer's Disease Seiko Ikezu, M.D., and Tsuneya Ikezu, M.D., Ph.D., Mayo Clinic	$172,500
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	$230,590
Targeting Tauopathies With Antisense Oligonucleotides to Synaptogyrin-3 Patrik Verstreken, Ph.D., VIB-KU Leuven Center for Brain & Disease Research, Belgium	$129,375
Blocking Synaptotoxicity in Alzheimer's Three-Dimensional Models Weiming Xia, Ph.D., Boston University School of Medicine	$197,500
DRUG DELIVERY AND ENABLING TECHNOLOGIES	
Development of a Multicellular Brain Model to Study Brain-Vascular-Peripheral Immune Cells Crosstalk in Alzheimer's Disease Mehdi Jorfi, Ph.D., Joseph Park, Ph.D., and Rudolph Tanzi, Ph.D., Massachusetts General Hospital	$172,500
PRECLINICAL AND CLINICAL DRUG DEVELOPMENT AND TRIALS	
PRECLINICAL DRUG DEVELOPMENT	
Continuing Studies of the Effects of GSM 776890 Administration on Amyloid Species and Microgliosis in Older Alzheimer's Model Mice Steven L. Wagner, Ph.D., University of California, San Diego	$291,374
CLINICAL TRIALS	
PEGASUS Clinical Study of AMX0035 in Alzheimer's Disease AMYLYX	$78,234

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

The development of a new statistical methodology that makes more efficient use of whole genome sequencing data led to the discovery of a new disease region for Alzheimer's disease (AD) that replicated in independent studies, and additional sex-specific risk loci that suggest a genetic basis to the sex differences in AD. Our new polygenic risk scores for AD provide a better individual risk prediction for the disease.

The Alzheimer's Genome Project™

RUDOLPH TANZI, PH.D., Massachusetts General Hospital

The Alzheimer's Genome Project™ (AGP) is aimed at identifying and characterizing novel Alzheimer's disease (AD) genes using an extensive genetic 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 both common and rare genomic variants and gene mutations associated with AD. We currently analyze WGS and WES datasets from more than 30,000 individuals in AD families and case-control cohorts. 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 three-dimensional cell culture models (Alzheimer's in a Dish™). The most promising AD-associated functional variants are also shared with Cure Alzheimer's Fund investigators and the greater AD research community. Our overarching goals are to elucidate the genetic basis of AD to better understand and treat this disease, and to better predict AD risk, age at onset, resilience to AD, and the sex- and ethnicity-specific effects on all of these factors.

BIOMARKERS, DIAGNOSTICS, AND STUDIES OF RISK AND RESILIENCE

Understanding Human Brain Resilience to Alzheimer's Pathology

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

Not everyone with a significant burden of classic Alzheimer's disease (AD) neuropathological changes (e.g., plaques and tangles) experiences comparable cognitive decline or has the typical tissue responses of neuronal and synaptic derangement. Identifying predictive markers of such natural protection and understanding the underlying mechanisms involved may hold key clues to developing novel cognitive-sparing therapies in the elderly. This project will take advantage of a large collection of deeply characterized brains from cognitively intact individuals whose brains are free of Alzheimer's pathology (e.g., plaques and tangles), cognitively intact individuals before death whose postmortem exam demonstrates robust amounts of plaques and tangles ("resilient"), and individuals with well-established dementia that meet pathological criteria for Alzheimer's disease. We will use a new and revolutionary technique to expand and image the brain—with unprecedented resolution and speed—using lattice light-sheet microscopy along with a pioneering expansion microscopy process. This technique will allow us, for the first time, to visualize and analyze in the human brain the changes that take place in synapses in the setting of plaques and tangles that may be responsible for the opposite cognitive fate of resilient individuals and demented Alzheimer's patients. We propose to test the novel idea that an aberrant microglial inflammatory response triggered by the mislocalization and accrual of toxic soluble phospho-tau species within synapses is responsible for the loss of synapses and the subsequent impairment of brain function in Alzheimer's disease. The information derived from this project has the potential to help identify novel molecular targets that may guide the discovery of better disease-modifying treatments for Alzheimer's disease directed at protecting the integrity of synapses and brain function, as well as the design of novel surrogate *in vivo* markers able to more precisely identify who among asymptomatic elderly individuals who harbor plaques and tangles in their brains will develop clinical symptoms of dementia and in what time frame. This information may provide guidance on the need and optimal timing for personalized preventive intervention.

BIOLOGICAL RESEARCH MATERIALS: NEW ANIMAL AND CELLULAR MODELS, AND HUMAN SAMPLES

Targeted Recruitment of Underrepresented Americans for Brain Donation Registration

BRAIN DONOR PROJECT

The Brain Donor Project (BDP) has helped more than 12,000 individuals make plans to donate their brains when they die since the website launched in October 2016. Donors come from all over the United States, range in age from prenatal to 104 years old and represent more than 100 categories of brain disease. This success has been achieved largely by engaging dozens of patient advocacy and disease-based research groups as well as end-of-life professionals by offering a variety of outreach vehicles. Much has been invested in maximizing the BDP's online presence to optimize its appearance in digital searches. This work and our relationship as the intake arm of the National Institutes of Health NeuroBioBank (NBB) positions us as an ideal partner to lead—with the proper partner organizations and individuals—a robust effort to effectively invite understudied people to donate their brains when they die. We are anxious to put all of these assets toward advancing the complete science of brain disease.

Neuronal Subtype-Specific Modeling of Alzheimer's Disease by Direct Neuronal Reprogramming of Patient Fibroblasts

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

My laboratory studies genetic networks underlying neurogenesis and develops cell fate reprogramming approaches using microRNAs (miR-9/9* and miR-124) to generate human neurons by directly converting (reprogramming) adult fibroblasts. The primary purpose of developing the direct neuronal conversion approaches is to establish a patient neuron-based platform to model and study adult-onset disorders such as Alzheimer's disease (AD) and Huntington's disease. With support from Cure Alzheimer's Fund (CAF), we have successfully addressed several vital considerations for modeling neurodegenerative disorders. One question relates to the age information stored in the original fibroblasts when cells transition to neurons via direct reprogramming. We previously carried out in-depth analyses of age-associated marks, including DNA-methylation-based epigenetic clock analysis, transcriptome, miRNA profiles and cellular properties (reactive oxygen species, DNA damage and telomere lengths) in human neurons converted from fibroblasts across the age spectrum. We learned that the age information stored in the starting fibroblasts propagated during neuronal conversion, resulting in neurons that reflect fibroblast donors' age, a feature highly instrumental to modeling adult-onset neurodegenerative disorders. Extending these findings, our goals pertinent to the CAF grant have been to

leverage direct neuronal reprogramming as a system to model AD.

Neurodegenerative disorders often affect different subtypes of neurons differentially. It is critical to have control for what types of neurons can be generated by direct neuronal reprogramming. Toward this goal, we have carried out studies to dissect mechanisms underlying how miR-9/9* and miR-124 (miR-9/9*-124) elicit reprogramming of human fibroblasts to neurons. Supported by CAF, we previously performed genomic analyses of changes in chromatin accessibility in response to miR-9/9*-124. We learned that miR-9/9*-124 led to an extensive reconfiguration of the chromatin state poised to receive inputs from subtype-defining transcription factors. In a recently published study (a new publication for the current round of progress report), we conducted a follow-up study in which we looked into cellular dynamics of reprogramming cells at a single-cell resolution. Our findings indicated that the miRNA-mediated neuronal conversion occurs through distinct steps where miR-9/9*-124 orchestrate the erasure of fibroblast identity first, followed by the adoption of the neuronal identity in sequence. During the later stage of miRNA-induced neuronal state, subtype-defining transcription factors promote the maturation of converting neurons into a specific neuronal subtype. This study provides us with fundamental insights into how neuron-specific degenerative phenotypes may arise during the neuronal conversion of patient fibroblasts.

Taking our experiences in modeling Huntington's diseases with patient-derived striatal medium spiny neurons (MSNs), we are actively pursuing AD-modeling studies using fibroblast samples from familial and late-onset AD patients. We hope to submit three manuscripts for publication within this year based on the results we have so far. One study relates to our current AD modeling using miRNAs and NeuroD2 and MYT1L TFs, which produce glutamatergic cortical neurons; i) directly converting familial AD fibroblast samples generates neurons that display extracellular amyloid beta accumulation, ii) reprogrammed familial AD neurons show increased tau phosphorylation that appears to underly insoluble form of tau, and iii) most importantly, familial AD neurons display spontaneous neurodegeneration as cells acquire the neuronal identity.

We are currently extending these studies to fibroblast samples obtained from late-onset AD patients. Another study extends our expertise in subtype-specific neuronal reprogramming, in which we developed miRNA-based reprogramming methods specific for serotonergic neurons and upper-layer cortical neurons. Finally, we are in the process of preparing a manuscript that describes the tau isoform expression in human neurons reprogrammed from adult fibroblasts. Based on the results obtained, reprogrammed neurons from adult fibroblasts express tau 3R and 4R isoforms at a ratio similar to what is detected in the human adult brain, both transcriptionally and protein level-wise.

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/knock-out, conventional/

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

EPIGENETIC FACTORS

Characterizing Epigenetic Biomarkers of Human Cognitive Aging

LARS BERTRAM, M.D., University of Lübeck, Germany

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 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 two phases of the CureAlz-funded 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 third installment of our CIRCUITS consortium contribution, we propose to extend this work by adding genome-wide DNA methylation and micro-RNA (miRNA) measurements in blood at a second timepoint. This will effectively allow us to not only analyze the levels of these two types of molecular markers, but also assess their change over time. We hypothesize that these longitudinal DNAm and miRNA expression data are even more powerful than using cross-sectional data alone to derive informative molecular biomarkers of cognitive aging.

Impact of 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, or sAD) 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, DNAm) changes in AD brains, validating the role of these changes in induced pluripotent stem cell (iPSC)-derived neuronal cells, and investigating the role of microglia, the immune cells of the brain, on AD initiation and progression.

A Unified Approach to Actionable Alzheimer's Disease Signatures

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

Alzheimer's disease (AD) is a complex disease for which no broadly successful treatment exists. Despite enormous investment and even with a controversial recent drug approval, nothing has convincingly slowed the progression of Alzheimer's disease. The first clinical signs of AD dementia present many years after the disease has begun its course. The disease is characterized in the brain by the presence of amyloid plaques and neurofibrillary tangles that associate with inflammation and synaptic loss, yet treatments targeting brain pathology, such as amyloid beta plaques—thought to be responsible for the initiation of the progression of AD—have been failures. The challenge is very similar to the adage that we are trying to describe an elephant by exploring it in a dark room. We need to bring light into the system. More validated, interconnected models of AD are needed. We propose to generate or capture and integrate genetics and gene expression signatures that represent the key aspects of AD initiation and progression. A pathogenesis network map of Alzheimer's disease, relating the key signatures of AD, is proposed. Each mapped signature will result in predicted drugs targeting that aspect of AD. The signatures will be connected in a systems biology framework that will allow, for the first time, molecular aspects of the disease to be integrated with one other. We will test and validate predicted drugs and regulatory programs for the signatures we discover to provide a set of validated, translated signatures of AD.

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

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

Whole-genome sequencing and other studies of Alzheimer's disease (AD) genetics are identifying more and more candidate regions of the genome that influence disease predisposition. However, we still lack an understanding of what these regions are doing in the context of Alzheimer's disease, which involves a complex interplay of different biological processes and cell types. Our approach uses a combination of laboratory and computational research to disentangle this complexity. First, we used epigenetic analysis to find a new network of Alzheimer's-associated genes that only emerge during the course of disease progression in oligodendrocyte cells, which make up the brain's "white matter." Next, we built sophisticated machine learning models that predict how mutations in the human genome influence different cell types. These models demonstrate the importance of the brain immune cells, microglia, as well as peripheral immune cells that circulate in the bloodstream. Finally, we conducted a set of experiments where we synthesized hundreds of fragments of the human genome associated with Alzheimer's disease and studied them in the context of the mouse brain. Our results thus far identified a mutation that is likely to impact the regulation of the gene PTK2B, influencing how sensitive neurons are to the buildup of amyloid protein during Alzheimer's disease. We have shared these resources with consortium collaborators, who are using them to find pathways for potential therapeutics that may be selectively active across different cell types.

Collaboration to Infer Regulatory Circuits and Uncover Innovative Therapeutic Strategies—Production Group

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

Alzheimer's disease (AD) 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 is currently 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 examining how genetic variants are affecting that circuitry. Numerous high-profile attempts and hopes at therapeutics have consistently failed, and it is increasingly thought that the secret to success may be early intervention in pre-symptomatic individuals or those with mild cognitive impairment (MCI). However, such early interventions require detailed knowledge of the genes, pathways and cell types altered during the early stages of MCI and AD progression. To guide targeted therapeutic development that modulates these pathways, and to recognize the progression of Alzheimer's disease at the molecular level across different brain regions and stages, we proposed single-cell profiling to dissect transcriptomic and epigenetic signatures. In addition, we also use contributions of combinations of genetic variants to uncover the expression changes resulting from their joint interactions.

Our ongoing work suggests microglial cells (immune cells in the brain) are likely to yield important insights in early diagnosis and interventions of AD, so we will classify subtypes of microglial cells according to different states, which will guide biomarker development and new therapeutic strategies for early intervention. We also will develop computational tools to systematically search for the candidates from the convergence of common, rare and somatic mutations in AD. Furthermore, we will functionally validate the candidates to support our hypothesis and predictions.

STUDIES OF NOVEL ALZHEIMER'S DISEASE GENES

The Role of Clusterin in Tau Pathology

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

Alzheimer's disease is caused by the accumulation of toxic protein aggregates in the form of extracellular amyloid plaques and intracellular tangles composed of the tau protein. In the current genomic era, several genes have been discovered that are associated with Alzheimer's disease risk. However, for most of these risk genes, we do not know in any detail how they are playing a role in the development of Alzheimer's disease. One of the top genes to emerge from these genetic studies is the clusterin (CLU) gene. Our lab has recently published that CLU plays a critical role in the formation of the extracellular amyloid plaques that form near neurons and also the blood vessels of the brain. We now have new evidence that CLU also might play a role in the formation of the other major pathological hallmark of Alzheimer's disease, the neurofibrillary tau tangles. In this proposal, we will directly test whether CLU influences the ability of the tau protein to accumulate and cause toxicity and behavioral impairments using novel mouse models developed in our lab. We also will employ new cutting-edge technologies to determine how CLU influences tau pathology. The completion of these studies could firmly establish that CLU is an important therapeutic target for the development of both major Alzheimer's disease pathologies.

Functional Basis for Novel Protein Kinase C-eta K56R Mutation in Alzheimer's Disease

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

The proposed research addresses whether aberrant activity of a key information processor in the microglial cells of the brain contributes to the pathogenesis of Alzheimer's disease. This protein, called Protein Kinase C-eta (PKC-eta), "translates" cues to maintain homeostasis in inflammatory signaling. We will analyze genetic mutations identified in the Genes to Therapies™ program by Rudolph Tanzi, Ph.D., to understand how the mutation alters information processing, with the goal of determining whether PKC-eta is a promising new therapeutic target in Alzheimer's disease.

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 (AD) 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 play a critical role in the pathogenic mechanisms. Thus, better understanding of the 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, using 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 neurons and microglia from human induced pluripotent stem cells (iPSCs). Therefore, our study will give us unique opportunities to determine 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.

Genes to Therapies™ (G2T), Alzheimer's Disease Drug Discovery and Development (AD4), ACTFAST and General Scientific Support

WILMA WASCO, PH.D., Massachusetts General Hospital

Dr. Wasco's responsibilities include the following:
- Guiding the group activities of the AD4 Consortium, including assisting with CureAlz proposal and report writing, and organizing regular joint lab meetings.
- Guiding and organizing the group activities of the ACTFAST Task Force.
- Providing scientific oversight to the G2T Taconic development and breeding programs.
- Acting—on an informal and irregular basis—as a scientific adviser to the Cure Alzheimer's Fund foundation.
- Planning virtual and in-person meetings, including the quarterly CureAlz Research Leadership Group meetings/calls.
- Serving as an internal science analyst who can advise CureAlz staff as necessary.

- Serving as a resource for scientific questions that arise during the CureAlz grant application review process, including providing assistance with selecting appropriate reviewers for specific proposals.
- Attending conferences to identify investigators who might be candidates for building the CureAlz pipeline, and facilitating letter of intent invitations when appropriate.
- Providing assistance and support with scientific communications to and from CureAlz researchers.
- Integrating more fully with the overall foundation mission by virtue of attending regular one-on-one and other meetings, and fully using all CureAlz resources in public-facing circumstances.

STUDIES OF AMYLOID PRECURSOR PROTEIN (APP) AND AMYLOID BETA

Interrogating Levetiracetam's Impact on Amyloid Pathology and Presynaptic Proteostasis in Knock-In Mouse Models with Humanized Amyloid Beta

JEFFREY N. SAVAS, PH.D., Northwestern University

Synapse loss represents an important and early feature of Alzheimer's disease (AD) that correlates with the severity of dementia. The mechanisms leading to synaptic dysfunction and loss are not fully understood, but both direct and indirect effects of amyloid beta peptides and tau pathology are recognized as key drivers. Synapses in the entorhinal cortex and hippocampus are selectively affected in the early stages of AD, but the underlying mechanism of this anatomical specificity remains a mystery. Further complicating this mystery, we still do not know whether the initial stages of synaptic dysfunction are triggered by pre- or postsynaptic changes. Our team has recently discovered that there is impaired protein degradation selectively in axon terminals that results in elevated abundance of synaptic vesicle-associated proteins in early stages of AD pathology. Intriguingly, we observe a relationship between these observations and the effects of the atypical antiepileptic drug levetiracetam that is currently the subject of several Phase II clinical trials for AD. Our preliminary studies demonstrated that levetiracetam

selectively normalizes SV endocytosis machinery abundance and restores nonamyloidogenic processing of the amyloid precursor protein (APP), which is anti-correlated to our disease progression observations. Thus, we have uncovered a potential mechanism that may explain the therapeutic benefits of levetiracetam, as well as targets for future therapeutic intervention. To rigorously extend these findings, in Aim 1 we will confirm our preliminary findings in a larger study and characterize the effect of chronic levetiracetam treatment on amyloid beta 42 production, the amyloid plaque load, and the axon terminal proteome in male and female APP knock-in (KI) mice. The goal of Aim 2 is to determine whether levetiracetam acts to slow the production or to enhance the clearance of existing amyloid-associated pathology in APP KI mice. The proposed research will advance our understanding of the critical protein networks that drive synaptic dysfunction in AD, and of promising therapeutic targets that may prevent or treat cognitive impairment in AD.

Effects of Depalmitoylation and ACAT Inhibition on Axonal Amyloid Beta Generation Via MAM-Associated palAPP

RAJA BHATTACHARYYA, PH.D., Massachusetts General Hospital
RUDOLPH TANZI, PH.D., Massachusetts General Hospital

Only 10% of amyloid precursor protein (APP) generates amyloid beta (Aβ), one of the hallmarks of Alzheimer's disease (AD) pathophysiology. Ten percent of total APP is palmitoylated-APP (palAPP), which serves as a better substrate for Aβ generation. We recently reported that nearly all palAPP (more than 70%) resides in the region juxtaposed between the endoplasmic reticulum (ER) and the mitochondria called MAMs (mitochondria-associated ER membranes). We also have demonstrated that the disruption of MAMs in the axons and in neuronal processes leads to reduction in axonal Aβ generation in a 3D cellular model of AD. MAMs are implicated in early-and late-onset AD, but their roles are largely unknown. We propose to demonstrate that small molecule depalmitoylating agents, such as hydroxylamine and its derivatives or inhibitors of MAM-resident ACAT1 enzymes, reduce Aβ generation from axons or from neuronal processes by inhibiting the levels of MAM-associated palAPP (MAM-palAPP). The overarching goal is to generate mechanistic data to develop effective therapeutic strategies against AD by specifically targeting the MAM-palAPP in the axons or in neuronal processes.

Air Pollution and Alzheimer's Disease Risk Interact With Premature Aging of Neural Stem Cells and Apolipoprotein E Alleles

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

Environmental factors in Alzheimer's disease (AD) are poorly defined. Recent epidemiological studies strongly associate elevated air pollution (AirPoll) with increased risks for accelerated cognitive loss and AD. Moreover, carriers of amyloid precursor protein (APP) mutations, which contribute to amyloidosis in familial AD, are more vulnerable to AirPoll. However, it remains unknown how AirPoll and APP risks interact. We propose studies on how neural stem cells (NSC) integrate AirPoll and APP risk in adult mouse brains. NSC proliferation declines during normal aging, but is greater in AD brains. Maintenance of NSC in older ages is hypothesized as critical for resistance to AD-related pathology and cognitive deficits. Our pilot data shows that AirPoll exposure of adult rodents impairs NSC replication. Because brain amyloid peptides increase during normal aging in rodents and humans, we examined possible benefits of BPN-15606, an anti-amyloid drug developed by CureAlz investigators and with CureAlz support. In a pilot study, BPN-15606 protected mouse NSC from loss during AirPoll exposure. We propose further studies with BPN-15606 to identify the relation of early NSC loss to brain amyloid increase during normal aging and the role of amyloid beta in NSC loss. Single-cell studies of NSC messenger RNA response to AirPoll will identify molecular pathways that damage NSC and could identify further targets to protect AD risk from AirPoll. These studies are the first to examine NSC aging at the single-cell level for modulation by AirPoll and environmental interactions with amyloid peptides. The findings could extend the benefits of anti-amyloid drugs and treatments to lowering environmental risks for 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 (AD). Specifically, synapses are removed, and the communication between the synapses that remain 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. However, in response to elevated amyloid beta levels, we have shown that 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 PKC alpha 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 PKC alpha in AD. Many therapeutic strategies for AD are focused on reducing amyloid beta levels or inactivating amyloid beta directly. However, identifying new molecules that mediate the pathogenic effects of amyloid beta is another area that has 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.

STUDIES OF TAU

Mechanisms of Tau Propagation Across the Plasma Membrane

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

The molecular mechanism of progression of neurodegenerative diseases caused by aggregation of the tau protein is not understood. According to a model of prion pathogenesis, once a tau assembly forms in one cell, it can escape that cell and move to an adjacent cell, where it is taken up. Prior to uptake, the tau assembly must bind specialized surface proteins. After binding, the tau enters vesicles within the second cell. However, it is unknown how tau might escape a vesicle to enter the cytosol and serve as a template for its own replication.

We have determined that after binding appropriate surface proteins, tau assemblies—even those that are very large—can directly cross the plasma membrane to enter the cell. This presents a fascinating biophysical problem, since the lipid bilayer of a cell membrane is not thought to be permeable to large protein complexes. Through the study of these molecular mechanisms, we hope to gain insight into why Alzheimer's and related disorders are relentlessly progressive, and also to identify new targets to block this process.

Influence of Plaque Vicinity on Microglial and Astrocyte Gene Expression; Role of Human Tau and TREM2

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

Why do we still have such limited treatments for Alzheimer's disease (AD)? One major reason is that AD mouse models do not cover the important step that leads from increasing amyloid plaques to the development of tau tangles. There have been improvements, and the recently developed "APPKI" mice now model plaque development in a manner much closer to the human disease progression. Our previously funded CureAlz study produced a detailed database of gene expression in these models throughout life and aimed to analyze the effect of bringing the APPKI mice even closer to the human condition by adding normal human tau. We found that the addition of human tau weakened several protective mechanisms in the mouse immune system and accelerated age-related changes likely to decrease the function of mitochondria, the energy-producing engines of the brain. These differences suggest points at which the resistance of humans to the clinical phases of Alzheimer's disease could be improved. Our proposed studies will validate these changes further, both morphologically and functionally.

We also now are looking at these gene expression changes in a regional and cell-specific manner to pinpoint the differences between the effects of mouse and human tau in response to plaques. In addition, we are adding a version of a gene that we know increases the risk of Alzheimer's disease in humans, with the aim of further compromising the mouse immune system and developing a full model of disease in which rising plaque load in the mouse leads to the later clinical phases of the disease. Such a model would provide a leap forward in our analysis of how to prevent this devastating condition.

Patient-Based Structural and Functional Biology of Tauopathies

LEONARD PETRUCELLI, PH.D., Mayo Clinic

We seek to generate models depicting the unique structures characteristic of abnormal forms of tau protein that accumulate in Alzheimer's disease and related disorders. In addition, using new structural models, we have generated novel resources to provide both a greater understanding of key events that drive disease, as well as facilitated testing of potential therapies.

STUDIES OF APOLIPOPROTEIN E (APOE)

Establishing the Molecular and Cellular Mechanisms and Biomarkers of APOE4-Mediated Susceptibility to Tau-Related Cognitive Impairments

JOEL BLANCHARD, PH.D., Icahn School of Medicine at Mount Sinai

APOE4 is the strongest genetic risk factor for Alzheimer's disease (AD) and is also associated with poor recovery from traumatic brain injury (TBI) and increased risk of cognitive impairments following chemotherapy (CBI). Personalized genotyping products are increasingly enabling individuals to identify whether they are carriers of APOE4 or other genetic risk factors for cognitive impairments. However, we have a limited understanding of how APOE4 increases the risk for cognitive impairments. As a result, there currently are no lifestyle or therapeutic interventions to minimize these known genetic risks. Here, we will investigate the relationship of APOE4 with the strongest pathological signature of cognitive impairment, neurofibrillary tangles composed of tau. Although AD, TBI and CBI arise from very different causes, they all exhibit tau pathology, which strongly correlates with cognitive outcomes. Studies have demonstrated that APOE4 clearly increases the severity of tau pathology and cognitive impairments, but the mechanisms are unknown. We reason investigating how APOE4 increases tau pathology in AD, TBI and CBI will uncover genetically informed therapeutic opportunities. To achieve this, we engineer human brain tissue from stem cells. Combining this technology with CRISPR/CAS9 genome editing, we generate genetically identical sets of human brain tissue that differ only by APOE genotype. This enables us to replay the biological events of AD, TBI and CBI in a controlled laboratory setting to determine precisely how APOE4 influences the development of tau pathology. In addition to this, we have developed a novel drug screening platform that employs our engineered human brain tissue. We will deploy this technology to investigate how FDA-approved drugs interact with the human brain and APOE4 to further modulate tau pathology. We expect this to reveal adverse drugs that accelerate the development of tau pathology, and also drugs that reduce or prevent tau pathology that could be repurposed to treat cognitive impairments. By integrating experimental and drug-screening approaches, we will gain an in-depth understanding of the relationship of APOE4 with tau, and uncover ways to modulate this connection that will accelerate our progress toward cures for Alzheimer's disease.

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

GUOJUN BU, PH.D., Mayo Clinic

Alzheimer's disease (AD) is the leading cause of dementia, with apolipoprotein E (APOE) being the strongest genetic risk factor. Our project, part of the APOE Consortium, is to define how the APOE2 gene and two other APOE genetic variants—Christchurch (APOE-Ch) and Jacksonville (APOE-Jac)—protect against AD-like outcomes such as amyloid beta accumulation and vascular impairment. Because APOE protein is present not just in the brain, but also at a high concentration in the blood produced primarily by the liver to transport cholesterol and other lipids, we aim to assess how APOE in the blood or brain contributes to its effects on AD pathways. 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 neutral or beneficial effects on brain functions. Our hypothesis is that enhancing a person's APOE amount with the protective forms, such as APOE2, APOE-Ch or APOE-Jac, will benefit brain functions and reduce AD pathologies. This will be pursued on two tracks: firstly, we will test whether delivery of APOE2, APOE3, APOE3-Ch or APOE3-Jac into Alzheimer's animals through peripheral bloodstream can reduce amyloid and other AD-related harmful effects. Secondly, we will examine these effects upon delivery of these APOE forms directly into the brain of Alzheimer's mice. During the first year of our supported research, we have made significant progress toward our original goals: we found that when delivered to the bloodstream, APOE4 worsens brain amyloid and increases toxicity compared with APOE3, likely by impairing blood vessel function. Next, we found that expressing the APOE-Jac protective variant in the brain reduces brain amyloid beta load and eases the related toxicity. Finally, we found that the APOE-Ch protective variant expressed in human cells has reduced binding to a key cell surface molecule called heparin, suggesting a potential protective mechanism. Our efforts also include building the animal cohorts to carry out the additional *in vivo* studies as planned, as well as exchanging ideas and collaborating with other APOE consortium projects. Successful completion of our proposed studies should provide mechanistic guidance on how to target the beneficial effects of "good" forms of APOE to treat or cure AD.

The Role of APOE in Microglia Regulation in Neurodegeneration

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

Microglia, the primary immune cells and sensors 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. 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 proposal aims to understand the role of human APOE variants in microglia peripheral innate immune cells in neurodegeneration, and to validate our findings in a human AD cohort with different APOE alleles.

Understanding the Effect of Apolipoprotein E on Tau-Mediated Neurodegeneration

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

Alzheimer's disease (AD) is the most important cause of dementia in the United States. It is characterized by the accumulation of two proteins in the brain, amyloid beta (Aβ) and tau. While Aβ accumulation is necessary for the AD process, the accumulation of tau is linked with cognitive decline, as well as nerve cell loss/damage. Utilizing mouse models of this process, we have found that the major genetic risk factor for AD, apolipoprotein E (APOE), is involved in the nerve cell damage, nerve cell loss and cognitive decline linked with tau accumulation in the brain. We now have found that APOE produced by a specific cell type in the brain called astrocytes is key in leading to this nerve cell damage. This provides a novel target for future therapy development. In addition, this APOE-linked process is associated with the buildup of certain types of lipids and cholesterol in the brain. We now are trying to determine ways to get rid of this buildup as a potential therapy to block tau-induced damage in the brain.

Protection Against APOE4 With Longevity-Promoting Interventions

CHRISTIAN PIKE, PH.D., University of Southern California
CALEB FINCH, PH.D., University of Southern California
BÉRÉNICE A. BENAYOUN, PH.D., University of Southern California

Apolipoprotein E (APOE) is the most common genetic risk factor for late-onset Alzheimer's disease (AD) and accelerated cognitive loss: AD risk is reduced by the APOE2 variant and increased by the APOE4 variant. Longevity follows the same pattern, increased by APOE2 and decreased by APOE4, which parallels advanced age as the single greatest risk factor for AD. Indeed, APOE genotype may regulate AD vulnerability in part by affecting aging processes. Consistent with this possibility, recent findings by our research team and others show that APOE4 modifies key outcomes linked with aging and AD risk, including elevated inflammation and metabolic outcomes. We propose studies of new longevity-promoting interventions with the synthetic steroid 17a-estradiol (17aE2) for potential attenuation of senescent changes in the brain and throughout the body that are associated with heightened AD risk. Pilot data with APOE4 mice predict that the benefits of the anti-aging intervention 17aE2 will be most robust for APOE4 and least for APOE2. The proposed studies will establish proof of principle for 17aE2 as an AD therapeutic, with efficacy predicted to be strongest in the APOE4 genotype. Because the majority of those with AD are APOE4 carriers, mitigating its impact would promote brain health throughout life.

Apolipoprotein E and Immunometabolism in Alzheimer's Disease

LANCE A. JOHNSON, PH.D., University of Kentucky
RAMON SUN, PH.D., University of Kentucky
JOSH MORGANTI, PH.D., University of Kentucky

Alzheimer's disease (AD) is characterized by changes in both metabolism and inflammation. Notably, the E4 allele of apolipoprotein E (APOE)—the strongest genetic risk factor for AD—is also associated with both metabolic dysfunction and a heightened pro-inflammatory response. This translational study will use state-of-the-art methods to determine whether E4 drives AD risk by affecting metabolism within microglia, the resident immune cells of the brain. If successful, our studies could provide new therapeutic targets to help "normalize" brain metabolism, thus potentially preventing or delaying the onset of AD in high-risk individuals.

Cellular and Molecular Studies of Apolipoprotein E Regulation of Blood-Brain Barrier, Synaptic and Neuronal Functions and Protection Strategies in Mouse Models With and Without Alzheimer's Pathology

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

Vascular contributions to dementia and Alzheimer's disease (AD) are increasingly recognized. These findings have led to the "neurovascular hypothesis" of AD, which holds that cerebrovascular dysfunction contributes to cognitive decline and dementia in AD. Apolipoprotein E4 (APOE4), the major AD susceptibility gene, exerts strong cerebrovascular toxic effects, including accelerated blood-brain barrier (BBB) breakdown and degeneration of pericytes, the BBB-associated cells that maintain BBB integrity. Recent studies have suggested that BBB breakdown is an early biomarker of human cognitive dysfunction, including the early clinical stages of AD. Our pilot data show that APOE4 compared with APOE3 leads to an early disruption of the BBB molecular composition followed by dysregulation in multiple signaling mechanisms, which precedes synaptic and neuronal dysfunction and behavioral changes in mice. However, how neurovascular APOE derived from the BBB-associated cells—astrocytes and pericytes—regulates the BBB, synaptic and neuronal functions at the cellular, molecular and systems levels, and in an isoform-specific and gender-specific fashion, remains largely unknown. We also do not have an effective APOE-based therapy for AD targeting the cerebrovascular system. To address these questions, we propose to use humanized APOE4 and APOE3 (control genotype) mouse models generated by Cure Alzheimer's Fund that allow cell-specific deletion of APOE from the BBB-associated astrocytes and pericytes. We will use state-of-the-art molecular analyses (e.g., single nuclear RNA sequencing and novel proteomics analysis) of different vascular cell types and neuronal cells to understand at the cellular and molecular level how APOE4 affects BBB, synaptic and neuronal functions. We will cross the APOE4 and APOE3 mouse lines with and without APOE in astrocytes and pericytes to mice that model amyloid (APP/PS-21 mice) and tau (P301S mice) AD pathology. This will allow us to evaluate how neurovascular APOE influences BBB integrity in relation to AD pathology using the same molecular methods as above. Finally, we propose to evaluate whether treatment with the novel drug 3K3A-activated protein, which exerts large-scale protective molecular changes in endothelial barriers and neurons, can alleviate harmful effects of APOE4 on cerebral vasculature and synaptic and neuronal function in mice with or without AD-like pathology. If successful, we expect that the proposed studies will advance our understanding of the pathogenesis of AD at the cellular and molecular level and in an APOE isoform-specific and gender-specific fashion, and will possibly lead to development of new therapeutic approaches for AD.

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, Canada

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 (Aβ)—the main component of the hallmark AD plaques—in the brain's blood vessels. We are focused on developing advanced bioengineered models of the human cerebral artery and capillary to study how "brain" and "blood" APOE affect vascular factors associated with AD. As the COVID-19 pandemic caused a full research curtailment for this project from March–August 2020 and our institution remains at reduced (30% to 60%) capacity, progress has been slower than anticipated on activities using our established model of the human cerebral artery. Although we published two papers on this model in the past 12 months, we have been unable to make progress on understanding the impact of genetic variation of APOE on vascular effects. We have thus focused our efforts this year on perfecting protocols to produce each relevant vascular cell type from human-induced pluripotent stem cells, with success in generating endothelial cells, pericytes, smooth muscle cells, astrocytes and neurons. Additionally, we have made substantial progress in developing a perfusible capillary model using the Mimetas platform. We also have performed a pilot study that tests a new method to measure blood APOE that resides on high-density lipoprotein (HDL, the "good cholesterol"), which protects from heart disease. HDL typically is measured in blood samples by calculating its cholesterol content; newer methods that measure the APOE content on HDL may be better predictors of cardiovascular disease risk. We now are evaluating two new methods to measure APOE on HDL in AD, including a pilot study of the Denka assay in 61 controls and 300 patients with AD, with data analyses continuing. A new aim focuses on a drug called obicetrapib, which, in a Phase 2 clinical trial called TULIP effectively raised HDL (including APOE-containing HDL), lowered low-density lipoprotein (LDL, the "bad" cholesterol) and reduced major coronary events in 364 patients at risk for heart disease. There is now considerable interest in evaluating obicetrabip to prevent or reverse the vascular contributions to AD, with both clinical and animal model experiments being planned.

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

JEAN-PIERRE ROUSSARIE, PH.D., Boston University School of Medicine

Apolipoprotein E (APOE), the most important genetic predisposition factor for Alzheimer's disease (AD), has long 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 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. We now have data showing that with aging, there is a slightly decreased number of neurons within the most vulnerable neuron population in mice with the risk allele of APOE. We also find that vulnerable neurons show markers of stress. This is pretty remarkable, since this occurs in the absence of any detectable tau or amyloid pathology, demonstrating that the effects of APOE are truly pleiotropic. In an attempt to further characterize the mechanisms by which APOE mediates pathology in vulnerable neurons, we also investigate PTPRD, a gene that is affected by the genotype of APOE and was shown to be tightly genetically associated with neurofibrillary tangle formation. Our data suggest that PTPRD could regulate major tau kinases and could be itself regulated by the synaptic plasticity modulator reelin.

STUDIES OF THE IMMUNE RESPONSE IN ALZHEIMER'S DISEASE

The Role of MGnD-Neurodegenerative CLEC7A+ Microglia in an Alzheimer's Disease Mouse Model

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

Microglia, the primary immune cells and the sensor of the brain, play a pivotal role in the maintenance of brain homeostasis, but lose their functions during the course of aging and neurodegenerative diseases. There is a gap in our knowledge about how microglial function is maintained in healthy brain and is prone to dysregulation in Alzheimer's disease (AD). Recent studies have distinguished and described the microglia phenotype in neurodegenerative diseases. However, whether this

phenotype is beneficial or detrimental in the disease progression still is not understood. This application will investigate the role of neurodegenerative microglia as a potential therapeutic target in AD. We will study the role of disease-associated microglia by employing a novel mouse model created by Cure Alzheimer's Fund, which enables us to target specifically these cells in order to restore microglia-mediated protein clearance and brain function in animal models of AD.

The Role of Astrocyte-Secreted Insulin-Like Growth Factor Binding Protein 2 (IGFBP2) in the Progression of Alzheimer's Disease

NICOLA J. ALLEN, PH.D., Salk Institute for Biological Studies

Identifying new targets to slow or halt the progression of Alzheimer's disease (AD) is an urgent need. Our approach to this is to ask whether nonneuronal cells in the brain, called astrocytes, are contributing to the progression of AD by negatively impacting the neurons they interact with. We identified that in AD, astrocytes upregulate production of a protein called IGFBP2. This protein has also been shown to be increased in patients with AD, as well as other brain disorders, linking it to brain pathology. The role of IGFBP2 is to inhibit growth factor signaling, suggesting its upregulation will have a negative impact on cells in the brain, including neurons. In this project, we ask whether blocking the actions of IGFBP2 is beneficial in AD, examining this in patient samples and mouse models. The outcomes of these experiments will determine whether IGFBP2, a candidate biomarker for cognitive decline and AD, is contributing to AD pathogenesis.

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

WILLIAM EIMER, PH.D., Massachusetts General Hospital

Alzheimer's disease (AD) has long been associated with two proteins: amyloid beta and tau. These are most often observed in the AD brain as amyloid plaques and tau tangles. As such, these proteins have been the primary focus of research groups and pharmaceutical companies searching for a treatment. This line of reasoning is firmly grounded in the idea that the amyloid beta and tau observed in diseased brains are a mistake of the body, resulting in the progression of the disease that leads to neuron loss, memory failure and eventual death. Unfortunately, recent drug trials have failed to halt or slow down AD progression despite successfully removing amyloid beta. Our recent research proposes an alternative: the amyloid beta peptide's previously perceived abnormal properties are consistent with those of antimicrobial peptides (AMPs), and that amyloid beta is an important player in the immune system. AMPs are a family of peptides and proteins that serve as the first line of defense against bacteria, yeast, fungi and viruses. Our findings revealed that aggregation and generation of amyloid are important parts of amyloid beta's role in immunity, mediating the capture and neutralization of pathogens in the brain. In our experiments, genetically modified cells, nematode worms, fruit flies and AD mice expressing human amyloid beta were protected from infection by amyloid-mediated entrapment of the invading pathogens. These findings suggested that an immune response involving amyloid beta may be important to AD pathology.

Our proposal will characterize amyloid beta's role as an AMP by examining its impact at physiological levels on immune system responses in both mouse and a three-dimensional human neural progenitor cell culture system. We will examine whether amyloid beta contributes to neuron death by selectively targeting neurons that already are infected, or whether amyloid beta acts as a signal for microglia to engulf the infected cell. Finally, we will expand our antimicrobial hypothesis by demonstrating that tau is also an AMP. Our preliminary data demonstrate that tau already exhibits some potent anti-bacterial abilities. The field of AD is shifting away from treating amyloid beta as a target for removal, and we think our proposed study solidifies the importance of immune responses and inflammation in AD etiology. We expect these findings to provide important information for current and future AD prevention and treatment therapies.

Understanding the Role of Natural Amyloid Beta-Specific B Cell Responses in Alzheimer's Disease Progression

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

The U.S. Food and Drug Administration recently approved aducanumab, an antibody that promotes clearance of amyloid beta plaques in patients with Alzheimer's disease. Here we propose to study whether Alzheimer's disease is associated with the development of natural antibodies against amyloid beta plaques, whether these antibodies attenuate disease progression and whether their presence can help identify patients who will benefit from antibody therapy.

Systems Integration and Therapeutics Translation in Alzheimer's Disease

ALISON GOATE, D.PHIL., Icahn School of Medicine at Mount Sinai
EDOARDO MARCORA, PH.D., Icahn School of Medicine at Mount Sinai

Human genetic studies conducted by us and others strongly implicate microglia, the brain's "trash collector" cells, as key players in Alzheimer's disease (AD). Here, we propose to integrate genetics and genomics data in order to identify 1) genes that regulate the function of these cells and modulate AD susceptibility, and 2) drugs that boost the ability of these cells to dispose of the waste that accumulates during aging and, in so doing, reduce the risk of developing AD.

Understanding the Mechanism Underlying Vaccination for Alzheimer's Disease

CHARLES L. GREENBLATT, M.D., Hebrew University of Jerusalem, Israel
OFER N. GOFRIT, M.D., PH.D., Hadassah Medical Organization, Israel
BENJAMIN Y. KLEIN, M.D., Hebrew University of Jerusalem, Israel

Evidence is accumulating that vaccination against a variety of different pathogens can reduce risk of Alzheimer's disease (AD). The vaccines now include: the Bacillus Calmette-Guérin (BCG) vaccine, a 100-year-old anti-tuberculosis vaccine; the triple vaccine of childhood (DPT); anti-tetanus or anti-diphtheria vaccination alone; anti-influenza; anti-pneumonia; and possibly anti-shingles, currently "under review." The levels of risk reduction range from 32% to 80%, with BCG offering the best results. These studies have been retrospective, but at least three prospective randomized clinical trials now are under way in Denmark, Greece and the United States. When one considers that all attempts to treat established AD or even to slow its course have failed thus far, a major effort in "prevention" as well as "cure" seems worthwhile. Kelley et al., writing in 2015, found that in the previous five years of treating AD, the cost to the health system and families was more than the burden of cancer and cardiovascular disease together. This proposal is focused on understanding the mechanism of this immune prophylaxis, observed from a number of vaccines, but here focused on BCG. The Hebrew University group has a major program in treating superficial bladder cancer with BCG. These

patients, compared with other individuals with bladder cancer treated by other means, will be followed for their cognition and other co-morbidities, and to assess in detail how their immune systems respond to the vaccine. The aim of this specific project will be to study the cell signaling processes that follow delivery of the vaccine into the bladder. A special emphasis will be on the interaction of the immune system with metabolic changes occurring in the monocyte line. These cells are known to cross the blood-brain barrier and transform to microglia, a critical cellular population that promotes neuronal health.

T Cell Epigenetics in Alzheimer's Disease

DAVID GATE, PH.D., Northwestern University Feinberg School of Medicine

This study will investigate genetic changes to a type of immune cell known as T cells. T cells regulate our immune system's memory. Here, we will study how changes to T cells' genetic structure might influence Alzheimer's disease by promoting brain inflammation. We will study T cells from the blood and the brain's cerebrospinal fluid to better understand their genetic differences using an approach known as epigenetics. Epigenetic changes are important to understand because they influence the types of genes our cells produce, and are thought to be influenced by environmental factors.

Revealing New Genes and Pathways at the Intersection of Lipotoxic and Genetic Risk for Alzheimer's Disease

ANNA GREKA, M.D., PH.D., Brigham and Women's Hospital
BETH STEVENS, PH.D., Boston Children's Hospital

Complex diseases, including Alzheimer's disease (AD), are caused by an interaction of genetic and environmental risk factors. Emerging genetic studies of late-onset AD implicate neuroimmune mechanisms and the brain's resident immune cells, called microglia, in AD pathogenesis. In many cases, genetic risk factors only are revealed by an environmental trigger. One particularly damaging instigator of disease is the overconsumption of dietary lipids, predominantly in the form of triglycerides, that leads to the accumulation of free fatty acids (FFAs) in many organs, including the brain. This byproduct of modern human diets rich in excess lipids causes a detrimental condition known as lipotoxicity.

Historically, studies involving FFAs were limited, because there was no technology available that allowed scientists to study the entire spectrum of dietary FFAs and how they contribute to disease progression. Having built this technology, we now can expose human-derived microglia from individuals with either high or low risk of Alzheimer's disease to a comprehensive library of diverse FFAs. This unique gene by environment analysis will provide insights into mechanisms of disease and will reveal a new way to derive patient risk profiles that go beyond genetics. This experimental approach uses human microglial-like cells differentiated from induced pluripotent stem cells (iMGL) that represent a rigorous model for assessing microglial states and function in human neurological diseases. We will use an array of modern tools such as transcriptomics, engulfment assays, CRISPR knockout screens and inflammation-profiling assays to gain insights into how human microglia respond to a lipotoxic environment. In summary, our work will investigate how excess lipids can affect the health of the brain by exacerbating the genetic risk for Alzheimer's disease.

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

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

Our research group has discovered that microglia play a critical role in compacting and insulating amyloid plaques, which renders them less toxic to adjacent neuronal processes. We propose to use sophisticated live-imaging and high-resolution microscopy combined with molecular manipulations to investigate how microglia interact with astrocytes during the protective encapsulation of amyloid plaques. We hypothesize that coordinated encapsulation by these two glial cells is critical for preventing damage to adjacent axons. We hope this interaction can be exploited therapeutically to diminish the progression of neural dysfunction in Alzheimer's disease.

Signaling Function of TREM2 Cleavage Products, Which are Affected by Agonistic Antibodies to the Stalk Region

CHRISTIAN HAASS, PH.D., DZNE, Germany
KAI SCHLEPCKOW, PH.D., DZNE, Germany

Alzheimer's disease (AD) is an uncurable neurodegenerative disorder that affects elderly people with a very high probability. Current treatment strategies reduce the disease-characterizing amyloid deposits from the brain; however, they fail to stabilize memory. We have developed strategies that allow boosting the protective activity of the brain's immune cells—the microglia. This targets a trigger on the immune cell's surface and turns it on, which in return initiates a defensive genetic program. Induction of this pathway is carefully regulated by cutting the trigger with a scissor-like enzyme, which terminates its activity. We developed a therapeutic antibody, which binds close to the site where the scissor cuts, and thus prevents its access, which leads to a stabilization of the trigger and consequently a boost of the defensive program of microglia. Such protective microglia recognize amyloid plaques more quickly and can rapidly remove them immediately after they are deposited. We think we are providing a very valuable additional strategy to prevent or slow AD. However, we need to know what happens in the brain after prolonged activation of microglia. We cannot exclude that continuous activation of microglia may exhaust these cells and probably even reduce their survival in the long run. We, therefore, want to induce long-lasting maximal stimulation of the trigger by genetically modifying it so that the scissor-like enzyme is not able to cleave it anymore. This would allow us to follow beneficial but also detrimental consequences of long-lasting treatments, which will be required to slow the progression of AD successfully. To follow the consequences in living animals, we are using imaging methods, which we also apply in parallel in humans at our institute to visualize amyloid deposition.

Contribution of Skull Bone Marrow-Derived Cells to Alzheimer's Disease

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

Alzheimer's disease is the most common neurodegenerative disease in America, affecting more than 6 million people and robbing them of their memory and independence as they age. Furthermore, as the population gets older, the number of people with Alzheimer's disease is expected to more than double in the next 30 years. Despite the toll it takes on families and society, treatment options are limited because our understanding of Alzheimer's disease remains incomplete. Alzheimer's disease causes people to lose their memory because the brain cells called neurons die off, causing the brain to shrink. These neurons are thought to die because of runaway inflammation in the brain. We have recently discovered that the skull, containing a rich repertoire of immune cells, supplies these to the brain's borders under normal circumstances and to the brain itself when it is damaged. The immune cells in the skull also receive signals from the brain, meaning that they can respond to changes in the brain. We think that these skull-derived cells are changed by Alzheimer's disease, and they may migrate into the brain to help or cause damage.

Role of Checkpoint Molecule TIM-3 in Regulating Microglia in Alzheimer's Disease

VIJAY K. KUCHROO, D.V.M., PH.D., Brigham and Women's Hospital

Microglia, the primary immune cells and the sensor of the brain, play a pivotal role in the maintenance of brain homeostasis. In the adult and aging brain, many of the phagocytic and proinflammatory functions of microglia are curtailed so that microglia can promote a homeostatic phenotype. But this behavior of microglia comes at a cost, in that homeostatic microglia are not readily able to clear amyloid beta plaques in the aging brain, resulting in the buildup of plaque burden and generation of neurofibrillary tangles, which contribute to the disease pathology observed in Alzheimer's disease (AD). There is a gap in our knowledge when it comes to how microglial function is maintained in the healthy brain and is prone to dysregulation in Alzheimer's disease (AD). We have observed that one of the checkpoint molecules, TIM-3 (HAVCR2), that we discovered to suppress immune cells is also expressed specifically in microglia in the brain and inhibits their phagocytic behavior. TIM-3 has also been linked to susceptibility to AD in a recent genetic analysis, thus raising the question of how TIM-3 regulates microglial behavior and contributes to the development of AD. Our preliminary studies show that in an AD mouse model, genetic deletion of TIM-3 in microglia results in activation of microglia and an increase in their phagocytic behavior and clearance of amyloid beta plaques. These data support the genetic linkage studies and show the importance of TIM-3 in regulating disease pathology in AD by modulating microglial function. We propose to study how TIM-3 is induced in the central nervous system in microglia, and how loss of TIM-3 in microglia can promote clearance of amyloid beta plaques in animal models of AD. Since there are antibodies against TIM-3 (Sabatolimab) already in the clinical trials for cancer and up for approval by the U.S. Food and Drug Administration, one can envision that our data may provide a ready drug candidate that can be repurposed for the treatment of AD.

Neuroinflammation Contributions to Alzheimer's Disease: Role of the Choroid Plexus

MARIA K. LEHTINEN, PH.D., Boston Children's Hospital
LIISA MYLLYKANGAS, M.D., PH.D., Helsinki University Hospital, Finland

This project seeks to understand the role of the choroid plexus (ChP) in Alzheimer's disease (AD), especially as it relates to neuroinflammation. The ChP is a highly vascularized structure located within the cerebrospinal fluid-filled compartments deep inside the brain. It forms the principal barrier between the blood and brain fluid. Substances inside this fluid have free access to the brain. A contribution of neuroinflammation to AD pathology is well known but difficult to discern, because aspects of this complex process may be helpful or hurtful depending upon when, where and how they take place. Important current efforts are focused mainly on microglia, brain inflammatory immune cells. However, during brain inflammation, many types of peripheral immune cells, including monocytes, neutrophils and lymphocytes, may migrate from the blood into the brain through the ChP, and a fraction of microglia may have originated from the blood. Tissue samples from both AD patients and animals with AD-like symptoms show signs of ChP inflammation and disrupted barrier integrity, and yet the functional state of the ChP and associated immune activities have not been studied extensively in the context of AD. We will use our groundbreaking real-time *in vivo* imaging system to study disease progression in mice in the absence and presence of currently used therapeutics, and perform parallel studies on human ChP samples from AD patients.

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 Alzheimer's disease (AD) brain, microglia become reactive and release factors we identified 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.

The Role of Interferon-Induced Transmembrane Protein 3 (IFITM3) and Gamma-Secretase in Microglia

YUEMING LI, PH.D., Memorial Sloan Kettering Cancer Center

Alzheimer's disease (AD) leads to amyloid beta accumulation in the brain in the form of plaques, along with tau tangles. Gamma-secretase is an enzyme that is involved in amyloid beta production in neurons. Microglial cells, the resident macrophages of the brain, undergo the most prominent changes in response to AD pathology, and respond by removing and clearing plaques. Our lab has identified IFITM3 as a gamma-secretase modulatory protein that regulates amyloid beta cleavage in neurons. We propose to conduct *in vitro* and *in vivo* studies to delineate the role of IFITM3 in microglial proliferation and maturation, as well as in functions such as TREM2 signaling and phagocytosis. This study will develop a molecular mechanism of IFITM3 in AD and offer novel targets for drug development.

The Role of Astrocyte-Derived Toxic Lipids Mediating Degeneration in Alzheimer's Disease

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

Astrocytes, star-shaped support cells of the central nervous system (CNS), have essential roles in brain development and normal functioning. They also have well-described responses to disease termed "astrocyte reactivity," characterized by profound changes in the genes these cells express and how well they perform important normal functions. Gene expression analysis of reactive astrocytes highlights multiple different types, with novel markers for each. Recent genetic association studies have implicated many disease-associated genes that almost exclusively are associated with support cells, like astrocytes, in patients with a range of neurodegenerative diseases, including Alzheimer's disease (AD). Beyond pathogenic proteins like amyloid and tau, astrocytes are implicated in the onset and progression of AD. In addition, immune cells, which provoke inflammation in the CNS, also are major contributors. Inflammation itself represents a balance between beneficial (e.g., removing dead cells) and detrimental (e.g., increased cell death) effects. Immune cells, and the inflammation they induce, inform reactive astrocytes at the site of disease—leading to devastating expansion of the pathology.

During AD, one reactive astrocyte substrate switches from a support role to a pathological one: slowing neuron communication, decreasing connections between neurons and becoming less efficient at removing waste products—detrimental to all of these processes that are important for a healthy and normally functioning brain. In extreme cases, these astrocytes secrete a toxin that kills neurons. We have localized these toxic reactive astrocytes to regions of dead and dying neurons in both animal models of AD and in human patients. Importantly, we find this neurotoxic function does not depend on the underlying genetics of individual patients. This makes targeting neurotoxic reactive astrocytes an exciting novel avenue for the development of new therapies.

Our methods to maintain positive components of inflammation and target only the production and release of a specific astrocyte neurotoxin provide unrivaled control over this complex system. We will investigate the role astrocyte-derived neurotoxins have in the initiation and progression of AD. Results from these studies will give us a better understanding of basic astrocyte biology, and will provide new targets for development of future therapies.

Targeting a Master Innate Immune Adaptor Molecule in Alzheimer's Disease

JOHN R. LUKENS, PH.D., University of Virginia

Mounting evidence indicates key roles for the immune system in Alzheimer's disease (AD). While recent advancements have been made in identifying cell surface immune receptors that influence AD progression, we still lack knowledge of the intracellular messengers used by these receptors to instruct immune responses in Alzheimer's disease. Identifying these intracellular signaling molecules is important, as targeting of shared signaling messengers may prove more effective than modulating individual receptors in isolation. Our preliminary studies have identified a novel intracellular signaling pathway that is centrally involved in the disposal of neurotoxic agents from the brain; we have shown that genetic deletion of this messenger results in worsened neurodegenerative disease. These findings suggest that therapeutics that activate this immune signaling pathway may offer novel strategies to treat Alzheimer's disease. In the proposed studies, we will further reveal how this intracellular immune messenger functions to limit the spread of damaging amyloid beta aggregates in the brain, and also explore a novel role for it in tauopathy. In addition, we will assess the therapeutic efficacy of activating this immune pathway to limit AD pathogenesis.

Extracellular ATP Is a Key Factor in Promoting Alzheimer's Disease Neuroinflammation

PAOLA PIZZO, BC.S., PH.D., University of Padova, Italy
FRANCESCO DI VIRGILIO, M.D., University of Ferrara, Italy

Alzheimer's disease (AD) is a neurodegenerative disease caused by poorly known pathogenetic mechanisms and aggravated by delayed therapeutic intervention; it still lacks an effective cure. However, it is clear that some important neurophysiological processes are altered years before the onset of clinical symptoms, offering the possibility of identifying biological markers useful for early diagnosis and implementation of effective therapies. It has become clear over recent years that nonneuronal cells, mainly microglia, are dysfunctional in the AD brain, and that inflammation of the brain (neuroinflammation) has a very important pathogenic role.

A key molecule involved in the activation and propagation of inflammation is ATP. ATP is well known for being the fundamental intracellular energy currency; however, we now know that this molecule also is released into the extracellular space when cells are stressed or injured. In the tissue *interstitium*, extracellular ATP (eATP), is a signal of danger to nearby cells, thus acting as a "damage-associated molecular pattern" (DAMP). At sites of inflammation, eATP accumulates at high concentrations and stimulates specific receptors named P2 purinergic receptors, P2X7 being the subtype most frequently involved, thus promoting secretion of other DAMPs and pro-inflammatory cytokines.

We aim at investigating the role played by the eATP/P2X7 receptor pathway in the promotion of microglia dysfunction and in AD-associated neuroinflammation. Our final goal will be to validate eATP/P2X7 as novel potential therapeutic targets and/or early diagnostic markers in AD.

Elucidating the Role of Soluble Epoxide Hydrolase and Arachidonic Acid Metabolism in Neuroinflammation and Alzheimer's Disease

HUI ZHENG, PH.D., Baylor College of Medicine

The development of amyloid beta plaque and neurofibrillary tangle pathologies in Alzheimer's disease (AD) is accompanied by prominent neuroinflammation. Prolonged activation of microglia and astrocytes in the brain and the release of pro-inflammatory cytokines and reactive oxygen species create a toxic environment to neurons, leading to memory impairment and neurodegeneration. In support of this idea, epidemiological studies indicated protective effects of nonsteroidal anti-inflammatory drugs (NSAIDs) against AD. However, randomized clinical trials failed to demonstrate efficacy, underscoring the need to identify a more effective therapy targeting neuroinflammation.

The most common NSAIDs are cyclooxygenase (COX) inhibitors that act on the arachidonic acid (ARA) metabolism to block the release of pro-inflammatory lipids, the prostaglandins. Contrary to prostaglandins, ARA metabolism also produces epoxy lipids, and these specialized lipids have been shown to display anti-inflammatory and vascular-protecting activities. However, their effects are limited because they are rapidly broken down by the soluble epoxide hydrolase (sEH). We found that sEH levels are elevated and, correspondingly, the epoxy lipids are diminished, in the brain of AD patients and mouse models. We thus reasoned that blocking sEH may restore the epoxy lipids and promote brain health in AD conditions. We tested this hypothesis by removing sEH in AD mice and by treating the AD mice with a small molecule sEH inhibitor with blood-brain barrier (BBB) penetration. We found that both the sEH removal and the inhibitor treatment restored the epoxy lipids, reduced neuroinflammation, attenuated amyloid pathology and improved cognition. These findings support sEH blockade as a potential therapy for AD treatment.

Neuroinflammation is a complex process that involves changes of multiple cell types and the cross-talk among them. Besides astrocytes and microglia, the vascular endothelial cells play an essential role in BBB integrity, and their impairment also has been implicated in AD. The ARA signaling pathway is active in all these cell types and produces both pro- and anti-inflammatory lipids. We suspect that the beneficial effect of sEH inhibition is conferred through a combination of the multiple cell types. However, how the sEH pathway and the ARA metabolism are regulated in these cells, and how they coordinate to impact AD progression, are not known. Building on our compelling work on sEH, we aim to gain a deeper and broader understanding of the sEH pathway and ARA metabolism in AD. We propose to isolate microglia, astrocytes and vascular endothelial cells from the brain of AD mouse models and perform gene expression and lipid profiling to decipher how the ARA pathway and their lipid metabolites are changed in response to amyloid beta and neurofibrillary tangle pathologies. In addition, we will determine whether sEH inhibition affords therapeutic benefit against both amyloid and neurofibrillary tangle pathologies, and what are the key cell types and lipid species that mediate these effects. Overall, these studies will achieve a new mechanistic and therapeutic understanding of sEH inhibition, and also identify new targets in the ARA pathway for AD therapy.

Role of Microglia in Degradation and Trimming of Alzheimer's Amyloid Beta

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

Microglia are the main type of immune cell in the central nervous system, and several genetic mutations associated with microglia are strongly linked with increased susceptibility to develop Alzheimer's disease. We have characterized a novel process by which immune cells related to microglia (i.e., macrophages) degrade large objects outside the brain. We now have preliminary evidence that microglia can use this process to degrade large objects such as amyloid plaques. We will carry out studies of wild type and mutant microglia interacting with amyloid plaques in cell culture to determine how this process works in detail. A longer-term goal is to extend this study to microglia in Alzheimer's disease model mice.

STUDIES OF ALTERNATIVE NEURODEGENERATIVE PATHWAYS

Glymphatic-Lymphatic Coupling in Alzheimer's Disease

HELENE BENVENISTE, M.D., PH.D., Yale School of Medicine
ALLEN TANNENBAUM, PH.D., State University of New York at Stony Brook

In Alzheimer's disease (AD), toxic waste such as amyloid beta (Aβ) and tau accumulate and damage the brain, leading to cognitive decline and dementia. In most body organs, the lymphatic vessels in the tissue help to remove waste and also control the amount of fluid that is present. However, there are no lymphatic vessels inside of the brain, only on the membranes covering the brain (so-called "meningeal lymphatics"). Instead, the brain has a "glymphatic" system constructed in a specialized way to allow cerebrospinal fluid (CSF) to circulate and exchange with the fluids surrounding brain cells to help flush waste such as Aβ and tau out of the brain. Notably, the glymphatic system must connect to the meningeal lymphatics to effectively drain waste out of the brain. The recent discovery of the glymphatic and the meningeal lymphatic systems has led to heightened interest in understanding how brain waste drainage might be accelerated over the lifespan to avoid Alzheimer's disease. Unfortunately, it has been technically challenging to study the waste removal processes and, most importantly, the important crosstalk between the glymphatic and lymphatic systems. Our laboratories have been developing and validating new imaging techniques and analysis tools based on computational fluid dynamics to visualize—in real time—how waste "solutes" and fluid pass through the two systems. The aim of this project is to implement these new technologies in a clinically relevant rat model of AD to characterize how the crosstalk between the glymphatic and lymphatic systems is affected by the disease. The results from this study will deliver novel tools and results to advance treatments for AD.

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

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

Alzheimer's disease (AD) is the most common form of dementia among older people. The blood-brain barrier (BBB) is a highly selective permeable barrier that separates the brain from circulating blood. It is formed by brain endothelial cells and prevents harmful materials from the blood from entering the brain. The BBB also plays critical roles in removing toxic molecules, such as amyloid beta that causes AD, from the brain. The meningeal lymphatic vessels (meningeal lymphatics) are a network of conventional lymphatic vessels located parallel to the dural venous sinuses and middle meningeal arteries of the mammalian brain. Recently, it has been shown that the meningeal lymphatics have an important role in homeostasis of the brain by draining it of macromolecules, including amyloid beta. Although disruptions of blood-brain barrier (BBB) and meningeal lymphatic vessels occurs in various neurological disorders including Alzheimer's disease (AD), their contributions to the onset and progression of AD have not been elucidated fully. This is due, in part, to the lack of an effective model to capture the complex interactions between the various fluid compartments in the brain. Drawing upon our considerable experience in models for the BBB and neurovascular units, in combination with our collaborators in AD neurobiology, we propose to create new and more realistic models to capture the key interactions between the vascular, neural and meningeal compartments, and to use these models to explore the process of disease and potentially identify new cures.

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 to be neuroprotective in AD animal models and human clinical studies. The mechanisms by which exercise protects the brain should be diverse and complex. We found that exercise increases a hormone called FNDC5 (fibronectin-domain III containing 5) and its secreted form, irisin. In our pilot studies, we found that irisin treatment decreased the level of amyloid beta (Aβ) peptide, a protein that causes AD, in our three-dimensional (3D) cell culture systems by increasing an Aβ-degrading enzyme called neprilysin. We also found that irisin is responsible for the beneficial effects of exercise on cognitive function, and that peripheral delivery of irisin was sufficient to improve cognitive deficits and neuropathology in AD transgenic mice. The goal of the proposed research is to explore the mechanism(s) by which irisin is neuroprotective in 3D cell culture and AD mouse models. Our study will provide a potentially promising way to generate novel therapeutic targets.

Disentangling the Role of Intracranial Arteriosclerosis in Alzheimer's Disease

DANIEL BOS, M.D., PH.D., Erasmus University Medical Center, The Netherlands
MEIKE VERNOOIJ, M.D., PH.D., Erasmus University Medical Center, The Netherlands
FRANK WOLTERS, M.D., PH.D., Erasmus University Medical Center, The Netherlands
GEERT JAN BIESSELS, M.D., PH.D., UMC Utrecht Brain Center, The Netherlands
JULIA NEITZEL, PH.D., Harvard T.H. Chan School of Public Health

Vascular disease is an important risk factor for dementia, often contributing in conjunction with Alzheimer's pathology (like amyloid beta and tau) to the clinical phenotype of Alzheimer's disease (AD). Yet, the exact role of vascular disease in brain health and the development of clinical AD, and its interaction with hallmark AD pathology, remains largely unknown. The current research project will provide insight into the role of arteriosclerosis—a hallmark of vascular disease—in AD, with a particular focus on the intracranial vasculature and the earliest form of disease, by using an innovative, population imaging-based approach. The Rotterdam Study is a large, population-based cohort study in which the development of many age-related diseases such as AD is studied prospectively. All participants in the study are ages 40 or older and regularly undergo a broad spectrum of examinations, such as physical examinations, blood sampling and interviews, to get a thorough impression of their health. The current study will wield data from two specific subsamples of the Rotterdam Study, in which computed tomography (CT) scans, positron emission tomography (PET) scans and magnetic resonance imaging (MRI) scans were made to 1) visualize arteriosclerosis in the brain, 2) visualize the presence and severity of amyloid beta depositions in the brain, and 3) measure pathology in and the function of the smallest blood vessels in the brain.

Together with the wealth of information from the Rotterdam Study on lifestyle, genetics, clinical risk factors and the occurrence of dementia, this will provide crucial novel insight into the role of arteriosclerosis in the development of AD. Ultimately, the results of the studies from this proposal may contribute to the development of therapeutic and preventive strategies for AD and dementia at large by targeting arteriosclerosis through novel therapies.

Harnessing Meningeal Lymphatics and Immunity to Alleviate APOE4-Induced Brain Dysfunction

SANDRO DA MESQUITA, PH.D., Mayo Clinic

Alzheimer's disease (AD) is an aging-related disorder characterized by the accumulation of toxic proteins (including aggregates of amyloid proteins) in the brain and ultimately neuronal death, leading to severe cognitive deficits. Aging and the altered expression of certain genes, including APOE4, represent major risk factors for AD. The central nervous system is wrapped by a protective tissue called the meninges that contain a functional lymphatic vascular network. The lymphatic vessels of the meninges are constantly draining brain fluids, excreting toxic molecular waste products and influencing immune responses in the brain. We previously have shown that an age-dependent reduction in brain drainage by the meningeal lymphatic vessels significantly impacts different aspects of AD pathogenesis, including brain amyloid deposition. However, little is known about the impact of the AD gene risk factor APOE4 on the meningeal immune response and lymphatic vasculature. Using preclinical mouse models, we will explore whether and how the therapeutic modulation of the immune response in the meninges and of brain drainage by the meningeal lymphatic vessels impacts brain function in the context of APOE4 expression and increased risk for AD.

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

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

Alzheimer's disease (AD) is a debilitating chronic neurodegenerative disease that is the leading cause of dementia and involves memory loss, disorientation, language issues, mood swings and many other behavioral abnormalities. Recently, it has been suggested that dysfunction of the blood-brain barrier (BBB) may be an important component of the pathogenesis of AD; however, very little is known about how the BBB may change in patients with AD. We were able to determine the molecular changes to the BBB in patients with AD, identifying many novel changes to the BBB that may affect the function of the BBB and the progression of AD. In addition, because patients with AD display neuronal hyperactivity as well as loss of circadian functions, we aimed to determine how both neuronal activity regulates the BBB, and whether there is a circadian oscillation of the BBB. We have identified that neuronal activity downregulates the key BBB efflux transporter P-glycoprotein (PGP), which is important for the removal of amyloid beta from the brain through modulation of the vascular circadian clock. Therefore, neuronal hyperactivity and loss of circadian function may act on the BBB to exacerbate the buildup of amyloid in the brain.

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

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

The brain is a remarkably fragile organ with limited self-renewal capacity following insults. Consequently, it has evolved a complex system of barriers to limit the access of unwanted matter, thus protecting itself from detrimental peripheral factors. As the brain is a highly metabolic organ, it also has developed a series of nonconventional clearance routes to drain tissue waste products. Correct functioning of these brain barriers and clearance routes is critical to appropriate entrance and exit of desired matter during homeostasis. However, dysfunction in these pathways has been observed in numerous neurological conditions, including Alzheimer's disease. Our analyses have shown that impairment of meningeal lymphatic drainage leads to alterations in vascular cells within the brain. We propose that brain barriers and clearance routes form an interconnected system, and that dysfunction of one will precipitate deterioration in additional routes, ultimately worsening disease progression. Thus, restoration of a single disrupted pathway may be sufficient to rescue detrimental aspects of numerous routes, offering an attractive therapeutic intervention to prevent widespread impairments.

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 are composed of 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. The Nobel laureate Elie Metchnikoff more than a century ago 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.

Investigating Bone Marrow Hematopoiesis as the Link Between Sleep Fragmentation and Vascular Inflammation in AD

CAMERON McALPINE, PH.D., Icahn School of Medicine at Mount Sinai
FILIP SWIRSKI, PH.D., Icahn School of Medicine at Mount Sinai

How sleep influences Alzheimer's disease (AD) is poorly understood. We know that many AD patients experience disturbed sleep, but the biological pathways that link sleep to AD are unclear. Our preliminary data support the hypothesis that poor sleep leads to inflammation of the blood vessels in the brain, which consequently worsens AD. We will test this hypothesis using advanced technologies and murine models of sleep fragmentation and AD. Firstly, we will study how sleep and AD alter the production of inflammatory immune cells. Secondly, we will interrogate how immune cells and their inflammatory products cause the breakdown of blood vessels in the brain. Our finding will begin to unravel the complex relationship between the immune system, sleep and AD. Studying previously unrecognized biological mechanisms and pathways will identify new anti-AD therapeutic opportunities.

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

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

Vascular problems are present in almost all patients with Alzheimer's disease (AD). However, the underlying mechanisms remain unclear. Importantly, none of the currently used animal models for testing AD therapies include vascular factors. Our project will, for the first time, (a) map for the "vasculome" in AD mouse models; (b) develop and characterize AD mouse models that include vascular insufficiency; and (c) test the effects of exercise as an intervention that can rescue the diseased Alzheimer's brain "vasculome."

Immunotherapies Targeting the Microbiota to Prevent Cognitive Decline in Alzheimer's Disease

GERALD B. PIER, PH.D., Brigham and Women's Hospital
COLETTE CYWES-BENTLEY, PH.D., Brigham and Women's Hospital
CYNTHIA A. LEMERE, PH.D., Brigham and Women's Hospital

The scope of our project is based on the potential role of infectious agents in the cognitive decline of Alzheimer's disease (AD). We hypothesize that microbial cells and fragments emanating from our normal microbiota gain access to neural tissues over time and promote inflammation, leading to loss of brain tissue integrity. Our approach will be to investigate whether vaccination against a highly conserved microbial surface polysaccharide, poly-*N*-acetyl glucosamine (PNAG), will impact the neurodegenerative decline in an aggressive mouse model of AD. We also will determine whether PNAG is associated with the brain pathology in this mouse model of AD. Success will support human trials of a vaccine or antibody to PNAG, in an appropriate clinical setting, to halt cognitive decline.

Lymphatics and Central Nervous System Fluid Homeostasis

LAURA SANTAMBROGIO, M.D., PH.D., Weill Cornell Medicine

In the central nervous system (CNS), the lymphatic system, together with the glymphatic system, controls fluid and waste disposal. As such, meningeal lymphatics are pivotal for maintaining fluid balance and, overall, a healthy brain. Our goal is to characterize the molecular mechanisms regulating the CNS lymphatic system by studying newly identified molecular players that regulate its function. Once completed, our studies will have characterized the proteins/molecules that regulate fluid and waste disposal in the brain. These studies will help uncover and potentially harness mechanisms that facilitate brain fluid clearance that is beneficial for preventing cognitive dysfunction.

Neural Synaptic Circuit Changes During Alzheimer's Disease Progression

HUIZHONG W. TAO, PH.D., University of Southern California

Functional disruptions in Alzheimer's disease (AD) have been well characterized. However, how AD affects the synaptic connectivity in neuronal networks leading to these functional disruptions has remained poorly understood. One major research direction in the principal investigator's laboratory has been to investigate the synaptic mechanisms, in particular excitatory and inhibitory synaptic circuit mechanisms, underlying visual information processing in the mouse primary visual cortex (V1), by applying challenging electrophysiological techniques such as *in vivo* whole-cell voltage clamp recording and two-photon imaging guided patch recording in normal healthy mice. This project proposes to apply similar techniques to disease models related to AD. Malfunctioning of the blood-brain barrier (BBB) has been strongly implicated in contributing to the onset and progression of AD. Since the BBB is important for maintaining normal functioning of neural circuits in the brain, pericyte diseases that cause BBB malfunction may result in abnormal neural circuit computation and information processing even before neuronal degeneration, which is a hallmark of AD. Using awake mouse visual cortex as a model system, this project will test a central hypothesis that pericyte degeneration initiates disruption of cortical information processing by selectively injuring some specific types of cortical inhibitory neurons, resulting in alterations of the balance between excitatory (E) and inhibitory (I) synaptic circuits and weakening of coordinated control of brain activity prior to neurodegenerative changes. In collaboration with Dr. Berislav Zlokovic, a renowned scientist in the fields of pericyte biology, BBB and AD, the principal investigator will test the hypothesis in two BBB deficiency mouse models: inducible pericyte-ablation model, and pericyte deficiency and rescue model. The group will examine functional spiking responses of excitatory and inhibitory neurons in V1 of these mouse models, as well as visually evoked excitatory and inhibitory synaptic inputs to individual cortical neurons, at different disease progression stages. Overall, the proposed studies will generate substantial understanding of how changes in the E/I balance contribute to the disruptions of neural circuit computation during AD disease progression.

Targeting the Microbiome and Innate Immunity in Alzheimer's Disease

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

Alzheimer's disease (AD) affects 5.5 million Americans and leads to progressive memory loss. Currently, there are few treatments to help prevent or slow this disease. Recently, the gut microbiota has emerged as a potential therapeutic target for AD, but little is known about which bacteria may be involved or how they can contribute to AD. We believe that slowing the aging process in the microbiome could be used to help prevent or treat AD. We have found that colonizing mice with bacteria associated with AD can increase amyloid plaques.

Our studies suggest that this is because AD-associated bacteria block beneficial immune response in the brain that helps clear up amyloid beta plaques. Furthermore, we have found beneficial bacteria that can secrete substances that reverse this and can increase the destruction of amyloid plaques. With additional studies, we are aiming to identify these bacterial substances, that then could be used to activate the immune system in AD and prevent disease.

DRUG SCREENING AND LEAD DRUG EVALUATION PROJECTS

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

There is an urgent need for a better understanding of how normal neurons in the brain are converted into Alzheimer's disease neurons, and there is an equally urgent need to identify drugs that can block or even reverse this conversion. We are developing and optimizing new human neuron testing systems that will more faithfully mimic human Alzheimer's disease and that can be used to rapidly screen for new Alzheimer's disease drugs. Our new assay systems use cultured adult human neurons (iNeurons), which are converted from human skin cells provided by healthy and Alzheimer's disease donors. To rapidly advance our iNeuron systems, we are leveraging our established cell culturing systems for embryonic-like human neurons that are also converted from skin cells. We have determined that extracellular cues (i.e., oxygen levels, extracellular proteins) influence how cultured human neurons grow and mature. We have also miniaturized our assay systems so they are compatible with drug screening and can test thousands of drugs simultaneously.

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

ANA GRICIUC, PH.D., Massachusetts General Hospital

The microglial regulator CD33 modulates brain amyloid beta clearance and neuroinflammation in Alzheimer's disease. Through an unbiased high-throughput screen of a natural product library, we identified natural products that reduced levels of pro-inflammatory mediators in microglia. We also independently identified several FDA-approved drugs that increased amyloid beta uptake and reduced inflammation in a microglial cell line stably expressing human CD33. Here, we will screen an FDA-approved drug library for modulation of amyloid beta uptake and clearance in microglial cells. We will investigate whether the hits from the primary screen increase amyloid beta uptake and reduce levels of pro-inflammatory mediators using dose-dependent assays in microglia. To identify CD33 inhibitors, we will screen novel CD33-specific antibodies for modulation in microglia of CD33 levels, amyloid beta uptake and inflammation. These studies should greatly facilitate novel therapeutic approaches for Alzheimer's disease based on targeting CD33 and neuroinflammation.

Development of Human cGAS Inhibitors to Treat Alzheimer's Disease

LI GAN, PH.D., Weill Cornell Medicine
SUBHASH SINHA, PH.D., Weill Cornell Medicine

Alzheimer's disease (AD), the most common form of late-onset dementia in the elderly, poses an existential threat to our health care system in modern society. It is characterized by the accumulation of pathological amyloid beta (Aβ) plaques and neurofibrillary tangles. There is compelling evidence from postmortem studies of both aging and AD showing that tau pathology rather than Aβ pathology more closely relates to memory decline. Most therapeutic strategies have focused on anti-Aβ approaches that largely have failed. More recent tau imaging studies provide further evidence that tau imaging, not Aβ imaging, shows a strong regional association with clinical and anatomical heterogeneity in AD. Understanding pathogenic mechanisms that cause dysfunction in tauopathies is urgently needed to

identify novel therapeutic targets to treat AD. Moreover, effective lead inhibitors and chemical tools are required to validate whether such targets are appropriate for pharmacological intervention. This proposal focuses on identification and development of potent inhibitors of a DNA-sensing enzyme, cGAS, which sits at the top of the inflammatory pathway that is also observed in AD and is recapitulated in the tauopathy mouse model of AD. Here, we will perform virtual high-throughput screening (vHTS) to identify hit cGAS inhibitors and evaluate the identified hit compounds to obtain highly potent inhibitors of human cGAS as tool compounds. The latter subsequently can be developed as lead inhibitors for treatment of AD.

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

HERMANN STELLER, PH.D., The Rockefeller University

Alzheimer's disease (AD) poses a major unmet health need since neither cures nor treatments that address its root cause currently exist. AD is caused by the accumulation of toxic proteins that impair cell function and eventually lead to the death of nerve cells. All our cells have potent clearance mechanisms to degrade unwanted and potentially dangerous proteins. Unfortunately, this "trash removal" process becomes less efficient with age.

We recently discovered a novel mechanism that transports "proteasomes," the nano-machines responsible for the removal of unwanted proteins, to nerve endings,

and showed that this mechanism is essential for neuronal health and brain function. Moreover, this process becomes less efficient with age; mutations in this pathway are found in human patients suffering from age-related neurological diseases, including AD. Importantly, stimulating the activity of this protein clearance pathway can prevent neuronal degeneration and extend lifespan in animal models. Finally, we identified an inhibitor of this pathway that represents a promising drug target for the treatment of AD. This work has the potential to radically transform the field and yield a novel class of drugs that promotes clearance of toxic proteins and stimulates brain function in AD.

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

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

We built an iterative scheme of "modeling->screening ->validation" through the collaboration within the AD4 consortium. More than 3,000 compounds were physically screened through automated imaging of the 3D Alzheimer's in a Dish™ assay developed by AD4 consortium collaborators, and nearly 30 compounds have shown an ability to significantly reduce the level of phosphorylated tau, also known as p-tau, in the 3D Alzheimer's disease (AD) model. Biochemical and toxicity validations not only confirmed some of these compounds' ability to clear p-tau, but also helped exclude those compounds with significant neurotoxicity and cell death. Interestingly, the validation process revealed the somehow counterintuitive but intriguing fact that more than half of the confirmed hits reduce p-tau induced by amyloid beta without significantly impacting amyloid beta levels in any way, and even more hits do not impact insoluble amyloid beta 42, long considered the main culprit for initiating p-tau accumulation. Such discoveries indicate potential novel mechanism of actions for AD drugs directly targeting tauopathy; this warrants detailed modeling using multiple-omics profiles for drug effects.

Targeting Microglial TSG101 for Synaptic Protection and Cognitive Enhancement in Alzheimer's Disease

SEIKO IKEZU, M.D., Mayo Clinic
TSUNEYA IKEZU, M.D., PH.D., Mayo Clinic

Alzheimer's disease (AD) is the most common form of senile dementia without effective treatments after a countless number of clinical trials for many decades. Previous efforts to understand the mechanisms of the development of the pathology in AD revealed that innate immune cells called microglia play a critical role in spreading pathological protein in AD patients' brains. Since microglia also are known to clean up the debris in the brain, simply wiping out microglia in AD patients' brains may not work as therapeutics, and it is critically important to precisely modulate their functional phenotype so they can work properly even in neurodegenerative conditions. We have recently identified that a specific target molecule, TSG101, in microglia may accelerate the inflammatory condition and bring unwanted effects, such as removing synapses or spreading pathological protein, in a tauopathy mouse model. Our exciting preliminary data showed that molecular manipulation to ablate microglial TSG101 in tauopathy mice reduced neuroinflammation, and improved cognitive function and tau pathology. Moreover, a detailed investigation of mouse brain tissues using RNA sequencing analysis revealed that ablation of TSG101 in microglia in tauopathy mice changed microglial phenotype, shifting toward more homeostatic and less inflammatory, suggesting that microglia may restore normal functions even in neurodegenerative conditions. In this current proposal, we are aiming to develop therapeutics by delivering antisense-oligonucleotide (ASO) targeting TSG101 specifically to microglia. We will formulate ASO targeting TSG101 with liposomes so that microglia can phagocytose ASO through recognition of liposomes; therefore, TSG101 in microglia will be removed. We also will validate the data obtained from the ASO experiment using a virus to knock down TSG101 in microglia. If we achieve this goal, the results obtained from this study will be a basis of clinical application of ASO-targeting microglial molecules and significantly advance the AD therapeutic field.

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 the therapeutic options are limited. Recently, ADUHELM® (Biogen) was conditionally approved as a new AD drug targeting pathogenic amyloid beta in the patient's brain. However, there is still an urgent need for affordable and more effective AD drugs. Therefore, we aim to accelerate AD drug discovery using our three-dimensional Alzheimer's in a Dish™ (ADiD) model as a drug screening platform. In this ongoing project, we will identify and validate novel AD drug candidates from libraries of natural products and FDA-approved drugs that reduce pathogenic amyloid beta accumulation and/or amyloid-induced synaptic/neuronal deficits. In addition, we will test and validate AD resilience-enhancing drug candidates that are predicted from bioinformatic analysis. Our study's overarching goal is to find novel drug candidates that can reduce pathogenic amyloid beta oligomers/aggregates and their toxicity, and that are clinically applicable and affordable for most AD patients.

Targeting Tauopathies With Antisense Oligonucleotides to Synaptogyrin-3

PATRIK VERSTREKEN, PH.D., VIB-KU Leuven Center for Brain & Disease Research, Belgium

"Tau pathology" is a major hallmark of the brains of patients with Alzheimer's disease (AD), and one that most closely correlates with the decline of cognition in the course of disease. During Alzheimer's disease, the protein tau changes its location inside brain cells, and we found that ectopic tau mislocalizes to the contacts between nerve cells: the synapses. We also show that tau binds to a synaptic protein called synaptogyrin-3 and that this causes important defects, including memory loss. We now found a way to undo these effects: We have developed tools to lower the expression levels of synaptogyrin-3. In this project, we propose to test these in relevant disease models by injecting human neuronal precursor cells in mice that produce lesions seen in AD. Under those conditions, these human cells die, mimicking the neurodegeneration seen in Alzheimer's patients' brains. We will test whether our tools that lower synaptogyrin-3 expression levels protect these cells. This will define whether we are able to stop synaptic and neuronal loss. Next, we will use a mouse that expresses disease-relevant tau protein. These mice suffer from cognitive decline. We will again test whether our tools are able to prevent this decline from happening. This will define whether our tools also can counteract memory loss. If we are successful, we will have created a new class of drugs that interferes with the synaptic defects that tau is inducing, paving the way for tests in human subjects.

Blocking Synaptotoxicity in Alzheimer's Three-Dimensional Models

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

Rescuing cognitive processes—that is, one's ability to remember things—is the ultimate goal of current and future therapeutics aiming to treat Alzheimer's disease (AD). Here, we will investigate multiple factors that kill nerve cells leading to cognitive decline, and screen for preventive drugs previously approved by the U.S. Food and Drug Administration for the treatment of other diseases. This will allow us to fast-track an effective drug to clinical trials that will test whether the drug can protect cognition in people suffering from AD. We will study the effects of AD pathological proteins in human nerve cells in a cultured model and establish new methods to measure the efficacy of drugs to reduce the toxicity of pathological proteins. The significance of this project is demonstrated by screening downstream blockers of neurotoxicity after our success in identifying FDA-approved drugs and natural products for reducing AD pathological proteins.

DRUG DELIVERY AND ENABLING TECHNOLOGIES

Development of a Multicellular Brain Model to Study Brain-Vascular-Peripheral Immune Cells Crosstalk in Alzheimer's Disease

MEHDI JORFI, PH.D., Massachusetts General Hospital
JOSEPH PARK, PH.D., Massachusetts General Hospital
RUDOLPH TANZI, PH.D., Massachusetts General Hospital

Increasing evidence suggests that Alzheimer's disease (AD) is not restricted to the aggregated proteins (amyloid and tau), but strongly proposes that immunological mechanisms have a key role in the pathogenesis. The study of the neuroinflammation surrounding this hypothesis is leading to novel findings that genes for brain resident immune cell receptors—microglia—including TREM2 and CD33, are associated with AD. Neuroinflammation not only relies on the innate immune cells that permanently reside in the brain, but also on the peripheral immune cells. Under specific circumstances, peripheral immune cells can enter the brain and have disease-modulating functions. However, little is known about the potential contribution of the immune system outside the brain to AD pathophysiology. Targeting leukocyte trafficking to the brain could, thereby, represent novel therapeutics and diagnostic approaches in AD. Here we propose to use microphysiological systems (also called organs-on-chips) to investigate the relevance of circulating peripheral immune cells trafficking in AD, and investigate the crosstalk between the brain, vascular and peripheral immune system.

PRECLINICAL DRUG DEVELOPMENT

_____

Continuing Studies of the Effects of GSM 776890 Administration on Amyloid Species and Microgliosis in Older Alzheimer's Model Mice

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

Amyloid plaques are pathological hallmarks of Alzheimer's disease (AD)—clumps of misfolded proteins that accumulate in the brain, disrupting and killing neurons and resulting in the progressive memory loss that is characteristic of the widespread neurological disorder. Researchers at the University of California, San Diego School of Medicine, Massachusetts General Hospital and elsewhere have identified a new drug that could prevent AD by modulating, rather than inhibiting, a key enzyme involved in forming amyloid plaques. In studies using rodents and monkeys, the researchers report the drug was found to be safe and effective, paving the way for possible clinical trials in humans. Amyloid plaques are composed of small protein fragments called amyloid beta (Aβ) peptides. These peptides are generated by enzymes called beta-secretase and gamma-secretase, which sequentially cleave a protein called amyloid precursor protein on the surfaces of neurons to release Aβ fragments of varying lengths. Some of these fragments, such as Aβ42, are particularly prone to forming plaques, and their production is elevated in patients with mutations predisposing them to early-onset AD. Several attempts have been made to treat or prevent AD using drugs that inhibit either beta-secretase or gamma-secretase, but many of these drugs have proved to be highly toxic or unsafe in humans, likely because beta-secretase and gamma-secretase are required to cleave additional proteins in the brain and other organs. Instead, Wagner and colleagues investigated the therapeutic potential of drugs known as gamma-secretase modulators or GSMs, which, instead of inhibiting the gamma-secretase enzyme, slightly alter its activity so that it produces fewer Aβ peptides that are prone to form plaques, while continuing to cleave other protein targets. The novel GSM then was tested in a mouse model of early-onset AD, treating the animals either before or shortly after they began to form amyloid plaques. In both cases, the novel GSM decreased plaque formation and reduced plaque-associated inflammation, which is thought to contribute to the development of disease. The findings suggest that the novel GSM could be used prophylactically to prevent AD, either in patients with genetic mutations that increase susceptibility to AD, or in cases where amyloid plaques have been detected by brain scans.

CLINICAL TRIALS

_____

PEGASUS Clinical Study of AMX0035 in Alzheimer's Disease

AMYLYX

The Amylyx PEGASUS Alzheimer's disease Phase 2 clinical trial will enroll 100 patients in sites across the country in a double-blind protocol to test a combination therapy. AMX0035 is composed of two known compounds that together address endoplasmic reticulum and mitochondrial stress, both of which have been implicated in neuronal death and degradation. The trial is enrolling patients who already are experiencing mild cognitive impairment or early dementia. Readout is anticipated in 2021.

Ongoing Research Projects

The research projects listed here were ongoing and active in 2021, having received funding from Cure Alzheimer's Fund in a previous year.

Project/Researcher	Distribution Amount
FOUNDATIONAL RESEARCH	
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
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, Germany	$459,977
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	$125,000
Neurobiological Basis of Cognitive Impairment in African Americans: Deep Phenotyping of Older African Americans at Risk of Dementia Henry Paulson, M.D., Ph.D., Bruno Giordani, Ph.D., and Benjamin M. Hampstead, Ph.D., University of Michigan	$241,738
Harnessing Big Data to Understand Alzheimer's Disease Risk Brad A. Racette, M.D., Susan Searles Nielsen, Ph.D., and Alejandra Camacho-Soto, M.D., M.P.H.S., Washington University School of Medicine in St. Louis	$172,500
A Transcriptional Rejuvenation Signature for Alzheimer's Disease Tony Wyss-Coray, Ph.D., Stanford University School of Medicine	$172,500
Physiological Method for Early Detection of Synaptic Vulnerability in Alzheimer's Disease Model Animals Riqiang Yan, Ph.D., and Srdjan D. Antic, M.D., University of Connecticut Health Center	$172,500
BIOLOGICAL RESEARCH MATERIALS: NEW ANIMAL AND CELLULAR MODELS, AND HUMAN SAMPLES	
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
EPIGENETIC FACTORS	
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
TRANSLATIONAL RESEARCH	
STUDIES OF NOVEL ALZHEIMER'S DISEASE GENES	
Role of Ataxin-1 in Regulating BACE1 Activity Jaehong Suh, Ph.D., Massachusetts General Hospital	$287,500
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, The Netherlands	$172,485
Molecular and Cellular Mechanisms of ACE1 Variant in Alzheimer's Disease Robert Vassar, Ph.D., Northwestern University	$250,000
STUDIES OF AMYLOID PRECURSOR PROTEIN (APP) AND AMYLOID BETA	
SFRP1 as a Therapeutic Target and Diagnostic/Prognostic Factor in Alzheimer's Disease Paola Bovolenta, Ph.D., CSIC-UAM, Spain	$172,500
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
STUDIES OF TAU	
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
STUDIES OF 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
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, Canada	$172,500

STUDIES OF THE IMMUNE RESPONSE IN ALZHEIMER'S 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	$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
Understanding the Consequences of Noncoding Alzheimer's Disease Risk Alleles on Microglia Function Beth Stevens, Ph.D., Boston Children's Hospital	$300,000
STUDIES OF 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
Direct Migration of Myeloid Cells from the Skull Marrow to the Brain Through Anatomical Channels: **Adding Fuel to the Fire in Alzheimer's Disease** Fanny Herisson, M.D., Ph.D., Massachusetts General Hospital	$172,443
Central Clock Influence on Alzheimer's Disease Pathogenesis Geraldine J. Kress, Ph.D., Washington University School of Medicine in St. Louis	$154,701
Patch-Seq Analysis of the Choroid Plexus Epithelial Cell Barrier in Homeostasis and in Alzheimer's Disease Fernanda Marques, Ph.D., University of Minho, Portugal	$115,000
Alzheimer's Risk is Higher in Women: Identification of Female-Specific Brain Bioenergetic Targets Lisa Mosconi, Ph.D., Weill Cornell Medical College/New York-Presbyterian Hospital	$173,486
The Circadian Clock Modulates Neurodegeneration in Alzheimer's Disease via REV-ERBα Erik S. Musiek, M.D., Ph.D., Washington University School of Medicine in St. Louis	$172,497
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
Interleukin-3 in Alzheimer's Disease Filip Swirski, Ph.D., Icahn School of Medicine at Mount Sinai	$171,914
DRUG DISCOVERY AND ENABLING TECHNOLOGIES	
DRUG SCREENING AND LEAD DRUG EVALUATION PROJECTS	
Novel APOE Mimetic Therapeutic Peptide CN-105 Attenuates Alzheimer's Disease Pathology and Improves Functional **Outcomes in a Murine Model of Alzheimer's Disease** Daniel Laskowitz, M.D., M.H.S., Duke University School of Medicine	$91,687
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
Treating with Gamma-Secretase Modulators to Prevent Neurodegeneration in Mouse Models of Down Syndrome and Alzheimer's Disease William C. Mobley, M.D., Ph.D., and Steven L. Wagner, Ph.D., University of California, San Diego	$150,000
Virtual High-Throughput Screening for CD33 Inhibitors Subhash Sinha, Ph.D., Weill Cornell Medicine	$172,500
The Effect of Chronic Gamma-Secretase Modulation on the Prevention of Traumatic Brain Injury-Provoked and Alzheimer's **Disease-Relevant Biochemical, Pathological and Behavioral Alterations** Steven L. Wagner, Ph.D., and Brian Head, Ph.D., University of California, San Diego	$230,000
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
DRUG DELIVERY AND ENABLING TECHNOLOGIES	
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	
CLINICAL TRIALS	
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

Dear Friends,

We are pleased to report that research distributions in 2021 totaled $17.7 million to fund 77 projects, the largest number of grants in a single year in our history. Since our inception in 2004 and through the end of 2021, Cure Alzheimer's Fund has provided more than $140 million for research.

With the introduction of COVID vaccines in 2021, the laboratories we fund were able to resume their on-site operations and continue much-needed research.

2021 was also the 17th consecutive record year for contributions raised by Cure Alzheimer's Fund. A total of $28.2 million for the year represented an increase of 9.1% from 2020; those dollars came from more than 24,000 donations.

We are honored to introduce a new group of donors as Trustees of Cure Alzheimer's Fund. The CureAlz Trustees are a volunteer group of individuals focused on advancing our mission; they serve as ambassadors to expand awareness of CureAlz while providing financial support for our capacity and to support research. Our Board of Directors assured continued progress with their generosity to support vital research by investing in our ability to contribute even more to the future.

We continue to keep our overhead costs low. Since inception through the end of 2021, our Board of Directors and Trustees have contributed $57.5 million to support operating expenses totaling $36.4 million. Our fiscal responsibility and commitment to transparency

have been contributing factors in Cure Alzheimer's Fund achieving the honorable distinction of a 4-star rating by Charity Navigator for the 11th consecutive time, the highest rating the charity watchdog offers.

Great advancements in understanding Alzheimer's disease are being achieved. The continued generosity of our Board, the Trustees and thousands of donors, along with the continued commitment and professionalism of the staff, and the extraordinary dedication of the hundreds of researchers focused on ending this disease, provide great hope for a future without Alzheimer's disease.

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 2021

Chart legend:
- **CONTRIBUTIONS** (blue)
- **RESEARCH** (red)
- **OPERATING EXPENSES** (gray)

Y-axis: 0 MM, 5 MM, 10 MM, 15 MM, 20 MM, 25 MM, 30 MM

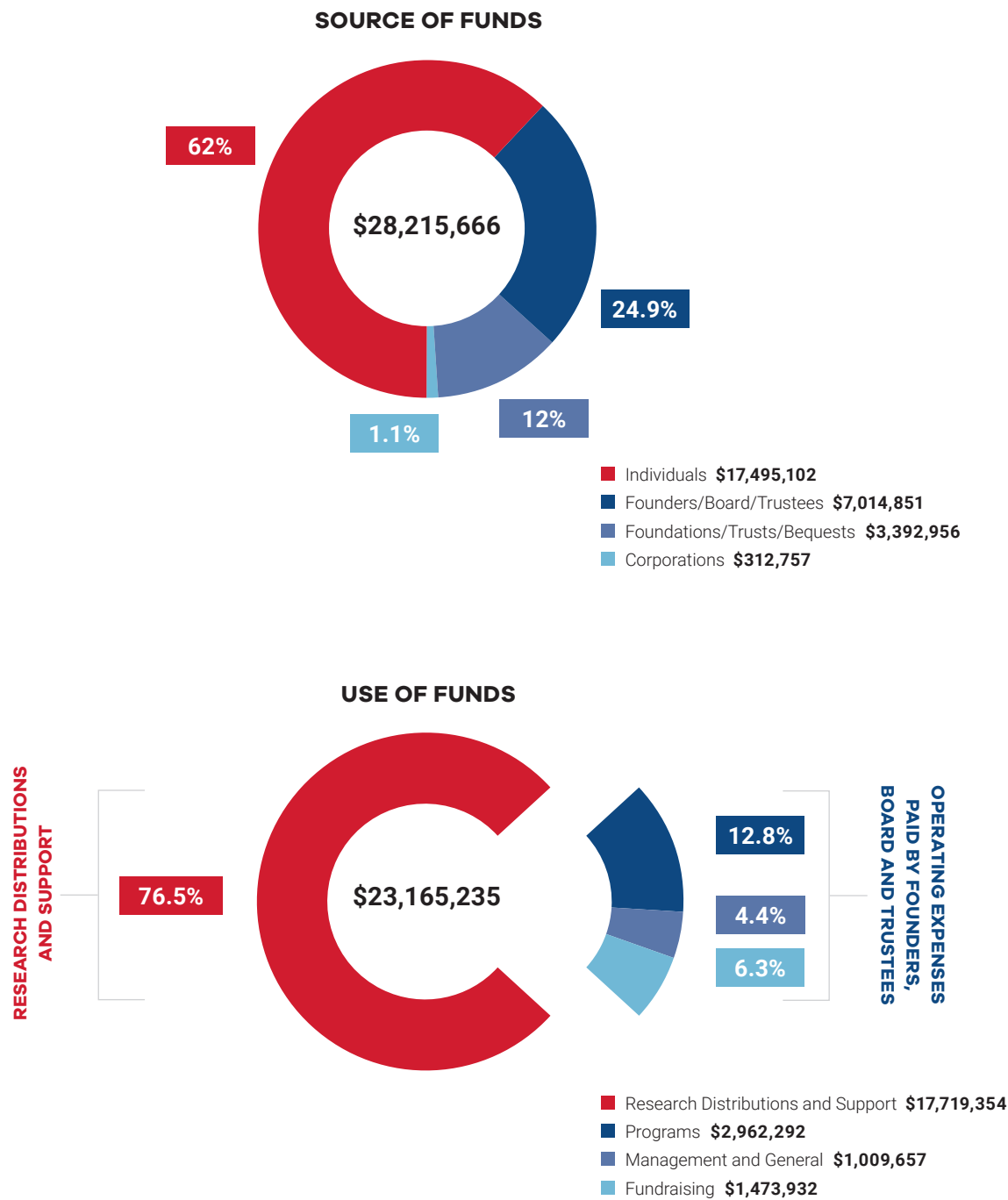X-axis: 2005, 2009, 2013, 2017, 2021
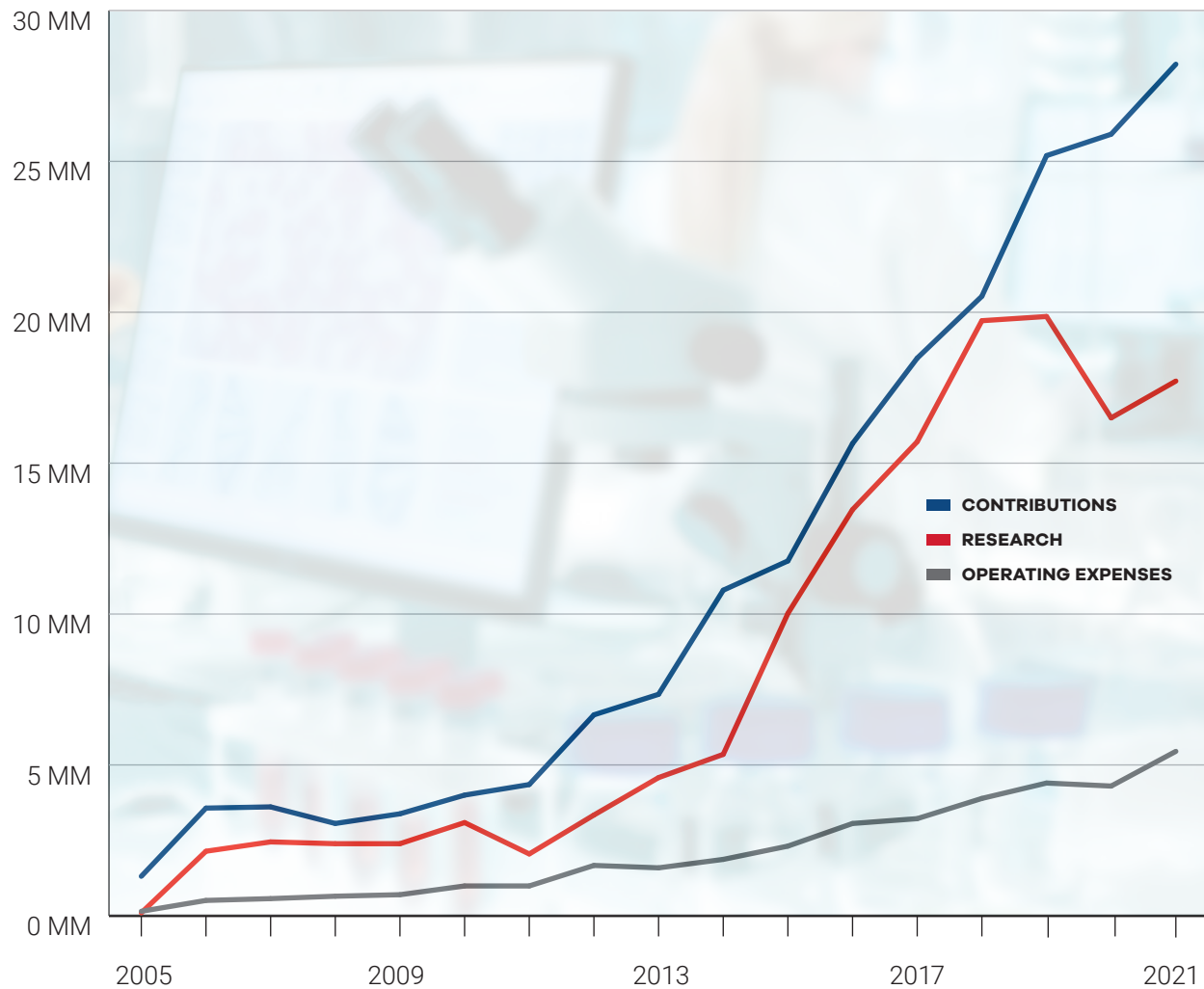
Seventeen Years of Growth:

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

2021 Fundraising

In 2021, Cure Alzheimer's Fund received 24,148 gifts—from individuals, the Board, Trustees, corporations and foundations—totaling $28,215,666. Cumulative contributions from inception given by our Founders, Board and Trustees total $57,457,789. Cumulative operating expenses from inception paid by the Founders, Board and Trustees total $36,393,684.

SOURCE OF FUNDS

62%

$28,215,666

24.9%

12%

1.1%

■ Individuals **$17,495,102**
■ Founders/Board/Trustees **$7,014,851**
■ Foundations/Trusts/Bequests **$3,392,956**
■ Corporations **$312,757**

USE OF FUNDS

RESEARCH DISTRIBUTIONS AND SUPPORT

76.5%

$23,165,235

12.8%

4.4%

6.3%

OPERATING EXPENSES PAID BY FOUNDERS, BOARD AND TRUSTEES

■ Research Distributions and Support **$17,719,354**
■ Programs **$2,962,292**
■ Management and General **$1,009,657**
■ Fundraising **$1,473,932**

Source and Use of Funds obtained from internal records.

2021 Financials   (Year ended December 31, 2021)

Statement of Financial Position

Assets

Current Assets:

Cash and cash equivalents	$9,308,773
Pledges receivable, current portion	1,350,000
Investments	12,993,868
Prepaid expenses and other current assets	160,657
Total current assets	23,813,298

Pledges receivable, less current portion, net	146,905
Equipment, net	6,949
Total Assets	$23,967,152

Liabilities and Net Assets

Current Liabilities:

Accounts payable	$430,625
Research grants payable	$5,103,487
Accrued expenses	232,539
Total current liabilities	5,766,651

Net Assets:

Without donor restrictions	16,316,372
With donor restrictions	1,884,129
Total net assets	18,200,501

Total Liabilities and Net Assets	$23,967,152

Statement of Activities

Revenue and Support:

Contributions	$26,293,856
Special events, net of direct expenses	246,821
Investment income, net	29,606
Total revenue and support	26,570,283

Expenses:

Program expenses:

Research distributions and support	17,719,354
Other program expenses	2,962,292
Total program expenses	20,681,646

Management and general	1,009,657
Fundraising	1,473,932
Total expenses	23,165,235

Change in net assets	3,405,048
Net Assets, beginning of year	14,795,453
Net Assets, end of year	$18,200,501

Statement of Cash Flows

Cash Flows from Operating Activities

Cash received from:

Contributions	$28,215,767
Investment income	4,457
Total receipts	28,220,224

Cash paid for:

Research distributions and support	(13,145,468)
Salaries and related expenses	(3,306,292)
Professional fees	(637,862)
Gift processing fees	(157,873)
Occupancy expenses	(182,873)
Other expenses	(1,274,602)
Total expenditures	(18,704,970)
Net cash provided by operating activities	9,515,254

Cash Flows from Investing Activities

Proceeds from sale of investments	2,093,774
Purchase of investments	(8,700,047)
Net cash provided (used) by investing activities	(6,606,273)

Net Increase in Cash and Cash Equivalents	2,908,981
Cash and Cash Equivalents, beginning of year	6,399,792
Cash and Cash Equivalents, end of year	$9,308,773

Source: Audited financial statements.

Our People

BOARD OF DIRECTORS
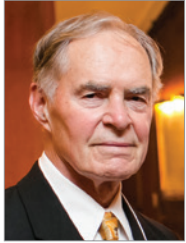
JEFFREY L. MORBY

Co-Chairman, Board of Directors

Founding Board Member

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

Co-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

JACQUELINE C. MORBY

Founding Board Member

Senior Advisor of TA Associates

Co-Chairman of the Morby Family Charitable Foundation

PHYLLIS RAPPAPORT

Treasurer

Founding Board Member

Chair of the Phyllis and Jerome Lyle Rappaport Charitable Foundation

Director of New Boston Fund Inc.
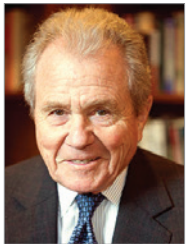
ROBERT F. GREENHILL

Chairman and Founder Greenhill & Company

SHERRY SHARP

Christian Writer

President and Director of the Rick Sharp Alzheimer's Foundation

TIM ARMOUR

President and Chief Executive Officer

TRUSTEES

KATHLEEN ARNOLD

Trustee, Fleming Foundation

SHARI CROTTY

Trustee, The Crotty Family Foundation

CHRISTINA KOHNEN

Trustee, Kohnen Family Foundation

JEANNE LESZCZYNSKI

Doctor of Public Health, Associate Professor of Pathology, UMass Medical School, retired

KUMAR MAHADEVA

Founder and Former CEO, Cognizant Technology Solutions

JEROME MAZURSKY

Founder, Mazursky Group

CHRISTINE VILLAS-BOAS

President, Michel and Claire Gudefin Family Foundation

CUREALZ ♥ 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 **2021 heroes**.

Alan, Nikki and Vasilios, aka The Floor Lords, Cure Alzheimer's Fund 24-Hour Charity Stream

Alfred Waterland and Natasha Raman Wedding

Ana Dias, Senior Project for Alzheimer's Research

Ben McKee, Imagine Dragons

Bethany Magley, Briteboom 12-Hour Charity Stream

Brian Alger and Jana Penfield Wedding

Casey LeFever, Next Day Koi

Clay Hardisty and Courtney Youngs Wedding

Corey Shagena, aka Shaggaliciouss, Shagg's Stream to End Alzheimer's

Courtney Vanderlinde Iverson, Morels & Memories—Mushroom Hunt & Alzheimer's Fundraiser

Dara, Taryn and Jantra, Stellaluna Raine

Darrylin Besnilian-Wasiuk and Tony Wasiuk, Medical Arts Hearing Instruments (DoNotShout.com)

David K. Johnson Foundation

David Karpay and Barrie Stern Wedding

David Lantz, M.J. Harrington Jewelers

Dick Thomalla, Kathy Thomalla Memorial Golf Tournament

DireHowl Gaming

Dylan Russell, Carma Cup

Elspeth Carnan

George Kalantzes Photography

HunterGhostal Coast to Coast Cure Alzheimer's Fund

HysideTV

International Association of Fire Fighters (IAFF) Local 792

Jason Kollat, aka Badgunpla

Jen Noonan, A Token Of

The Nagengast Family

Jim Jones and A. Ron Hubbard, aka Baldmove, 4th Annual 24-Hour Groundhog Day Movie Marathon

Jimmy Hamilton, Hammy Rel13f Fund Golf Tournament

Jog Your Memory

Joshua Crane, The Coffee Ride

Kaiwen (Kevin) Wang

Kelsey Livingston, aka Pandormancer, Champions Choice

Louie DeGeorge, Kitchen Table TCG, George Wendt, CompetESport, and Mitch Murray, Midtown Merchant

Matt Arthur, Taco Bell Fundraiser

MaximumChongish's Pink Hair for Alzheimer's

Meghan Daly and Family, Thanksgiving Walk to End Alzheimer's

Michael Bell, A Climate Ride to Remember

Missy and Pini Ben-Yehoshua

Nick Barkowski, aka HannibalDRU

Nick Gauldin, aka qneeks, The Fight to Cure Alzheimer's

Nicolas Martel, aka ShurieVR, Stream to Remember

Nikki Patrick, Strengthlets

Nikki Zazzali, Revive Jewelry

Nuckin's Alzheimer's Fundraiser

ONEHOPE Wine

Rev. John F. Michael, Journey Chess TV

Running 4 Answers

Ryan and Lisa Morin Wedding

Ryan Lally, Magic for Change

Shelly Mellott, Impact Charms

Stars Hollow Yarns

Stokeslahoma

Tessa Arias, Handle the Heat

Tommy Tai, Tyro Mature VR Community and TT's Bootcamp Charity Tournament

University of Wisconsin Undergraduate Neuroscience Society Spring Fundraiser

The Wanderer VR , Streamers Fighting Alzheimer's

The Whetton Family

Whit Collier, Wingfoil Upwind Challenge

Yvette Gonzalez-Nacer, Creative Minds Care

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.

The Cure Alzheimer's Fund Golf Tournament

On October 7, more than 100 golfers enjoyed playing in the first Cure Alzheimer's Fund Golf Tournament at the Fishers Island Club in New York. The golf course is among the most exclusive and scenic in the world. Ranked No. 9 in the 2021–2022 Golf Digest listing of America's 100 Greatest Golf Courses, Fishers Island Club offers picturesque views of Long Island Sound and the Atlantic Ocean from every hole.

Golf to Fund a Cure for Alzheimer's

THURSDAY, OCTOBER 7, 2021 | FISHERS ISLAND, NY

The full day began with golfers arriving by morning ferry followed by a hearty breakfast and 18 holes of golf. The tournament was a best ball format, with prizes awarded for the top three team scores, longest drive and closest to the pin. Dinner on the lawn and a live auction rounded out the day. More than $325,000 was raised for research.

First Republic Bank was a generous sponsor of the event, with several of their executives also in attendance.

"On behalf of Cure Alzheimer's Fund and the researchers who are working so hard to understand the causes of Alzheimer's disease, please accept our gratitude for your help in finding a cure," said Henry McCance, Cure Alzheimer's Fund Co-Founder and Co-Chairman, who hosted the event.

Cure Alzheimer's Fund is deeply grateful to Fishers Island Club for its generosity in providing this unique opportunity to enjoy one of the world's best golf courses while advancing our research for Alzheimer's disease.

Webinars

Throughout 2021, Cure Alzheimer's Fund continued to provide updates on research progress being made on Alzheimer's disease to audiences through presentations using online webinars.

OCEAN REEF MEDICAL CENTER FOUNDATION LECTURE SERIES

On January 12, at the invitation of Jeff Morby, Co-Founder and Co-Chair of Cure Alzheimer's Fund, Dr. Rudy Tanzi of Massachusetts General Hospital presented his research to guests of the Ocean Reef Medical Center Foundation in Key Largo, Florida, via ZOOM. Dr. Tanzi also provided his recommendations for brain health through S.H.I.E.L.D. (Sleep – Handle stress – Interact with friends – Exercise – Learn – Diet).

AN EVENING OF DINING, DIALOGUE, & ENTERTAINMENT

To welcome spring, Sam and Alicia Brasch, along with Kate and Mark Shaw, hosted a ZOOM event on March 20 with 200 of their friends and family in attendance. In keeping with pandemic protocols, dinner was delivered to each guest to enjoy while Dr. Rudy Tanzi presented the latest research on Alzheimer's disease and brain health. Afterward, singer, songwriter and actor Chris Mann sang *Remember Me* to the online audience. The event was recorded and is available through the CureAlz website: **www.CureAlz.org/SpringBraschEvent/.**

A NEW BLOOD TEST TO ASSIST WITH DIAGNOSING ALZHEIMER'S DISEASE

On May 27, Dr. David Holtzman of the Washington University School of Medicine in St. Louis presented information about his groundbreaking new blood test to aid in the diagnosis of Alzheimer's disease, and the test's availability to the public. This presentation was open to the public and recorded for those who were not able to attend. You can view the webinar on the CureAlz website: **www.CureAlz.org/News-and-Events/Diagnostic-Tools-the-New-Blood-Test/.**

STOPPING ALZHEIMER'S DISEASE AND PRESERVING BRAIN HEALTH

On June 5, Co-Founder and Co-Chair Henry McCance was invited to make a presentation to the attendees of his class of 1966 reunion of Harvard Business School. Via ZOOM, Henry provided an overview of Cure Alzheimer's Fund and then introduced Dr. Rudy Tanzi, Chair of the CureAlz Research Leadership Group, who shared information about the disease and current research efforts. The presentation was recorded and is available through the CureAlz website: **www.CureAlz.org/News-and-Events/HBS1966Reunion/.**

**THE IMPORTANT ROLE OF BETA AMYLOID IN UNDERSTANDING—
AND SOLVING—ALZHEIMER'S DISEASE**

Dr. Robert Vassar of Northwestern University is a pioneer and expert in the study of beta amyloid. On September 20, Dr. Vassar presented the information and research that led scientists to conclude that beta amyloid is a key instigator in Alzheimer's disease pathogenesis. The presentation is available through the CureAlz website: **www.CureAlz.org/News-and-Events/Important-Role-of-Beta-Amyloid-to-Alzheimers-Disease/.**

AN UPDATE ON ALZHEIMER'S DISEASE

At the invitation of the management of Farm Neck on Martha's Vineyard, Jeff Morby, Co-Founder and Co-Chair of Cure Alzheimer's Fund, was invited to give an update on research to its members on September 22. Jeff introduced Dr. Rudy Tanzi, who provided an overview of the disease and the current research taking place, as well as the hope for therapeutics in the near future. The presentation was recorded and can be found on the CureAlz website: **www.CureAlz.org/News-and-Events/Update-on-Alzheimers-Disease-by-Dr-Rudy-Tanzi/.**

THE IMPORTANT ROLE OF SLEEP IN THE HEALTH OF YOUR BRAIN AND ALZHEIMER'S DISEASE

On November 30, Dr. Erik Musiek of the Washington University School of Medicine in St. Louis presented his research about the role sleep plays in the health of the human brain and the impact on Alzheimer's disease. Dr. Musiek also shared insights regarding the steps we all can take with our sleep for healthy brains. The presentation was open to the public and recorded for those who were not able to attend. You can view the webinar on the CureAlz website: **www.CureAlz.org/News-and-Events/Sleep-Its-Important-Role-in-Brain-Health-and-Alzheimers-Disease/.**

Sleep! And Help the Health of Your Brain

Erik S. Musiek, M.D., Ph.D.
Meg Smith, EVP, Research Management, Cure Alzheimer's Fund

Our Webinar Will Begin Shortly
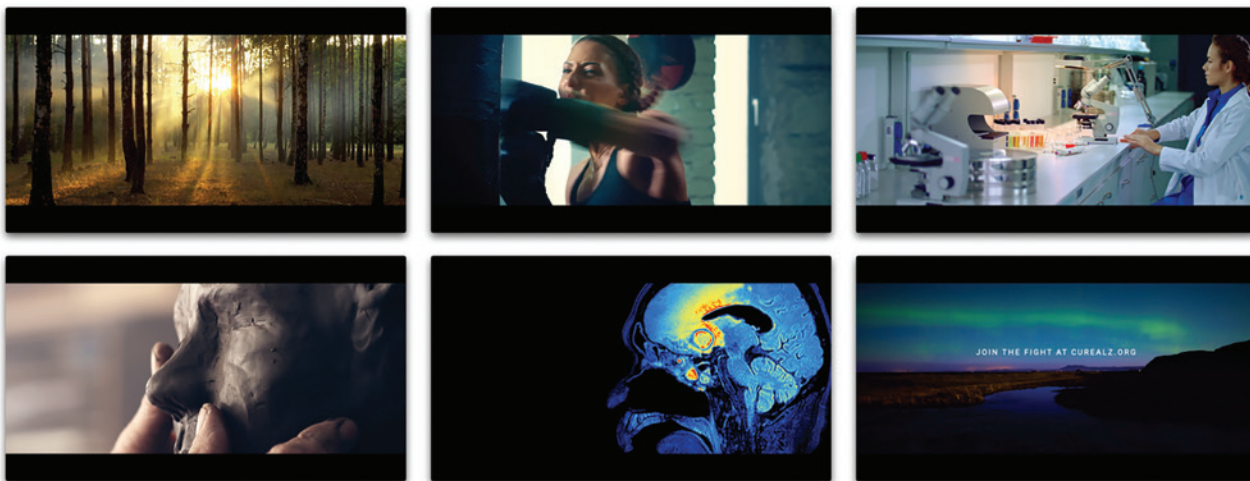
Cure Alzheimer's FUND
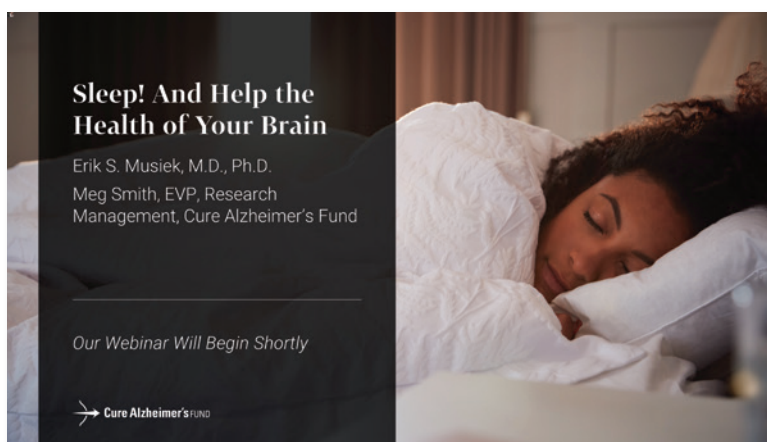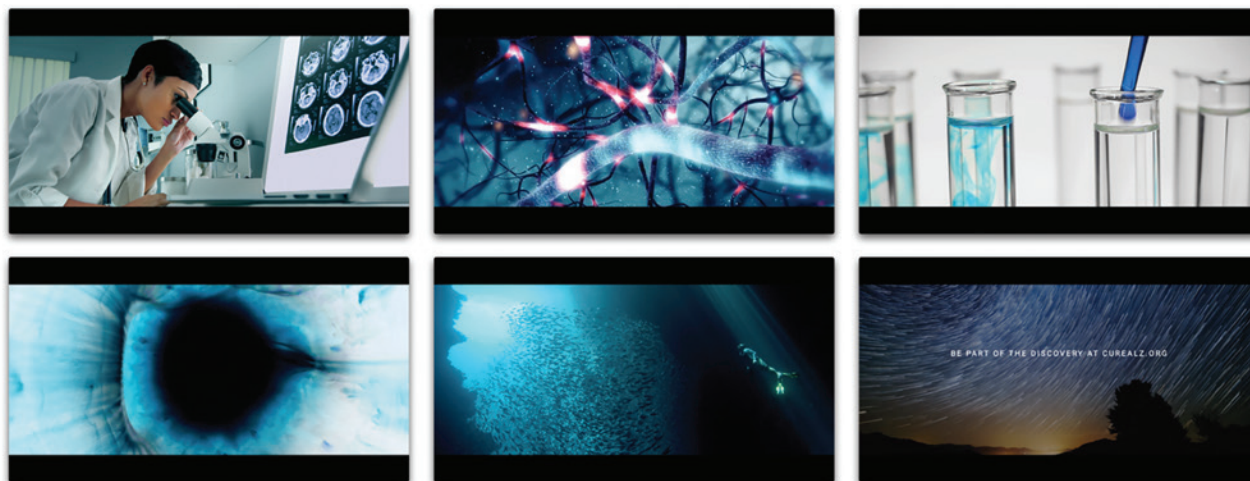
Award-Winning Public Service Announcements

In 2020, two new public service announcements (PSAs) were created for use on broadcast and digital media outlets. Each has as its key message the vital role of scientists and their discoveries in solving 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."

In 2021, *Night Sky* and *The Call* each received the prestigious Silver Graphis International Award. Graphis award competitions are juried by award-winning leading creative professionals from the design industry. The PSAs were created by the agency Proper Villains on behalf of Cure Alzheimer's Fund, and aired on Comcast and its digital properties.

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.
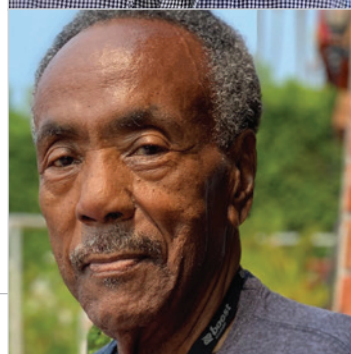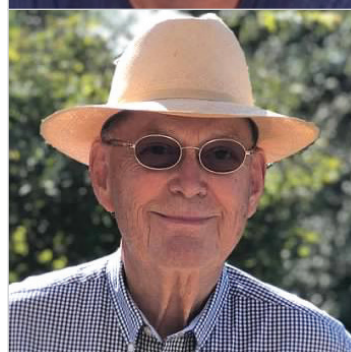
Support Our Research

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.

Online Gifts
Make a secure gift online by credit card, PayPal or Venmo by visiting **CureAlz.org/giving/donate/**.

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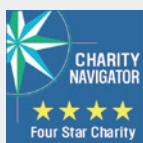
Cure Alzheimer's Fund has been awarded the highest rating of 4 stars for more than 10 consecutive years.

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