2022

ANNUAL REPORT

Cure Alzheimer's FUND

OUR MISSION

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

Annual Report 2022

Dear Friends,

2022 was the strongest year in Cure Alzheimer's Fund history for our contribution to slowing, stopping or even preventing Alzheimer's disease.

Thanks to the generosity of nearly 24,000 donors who provided a record $27.4 million for research, CureAlz was able to fund 100 research grants, a remarkable increase of 30% from 2021. Since our founding, we have distributed $170 million to support more than 700 grants, leading to 1,000 published papers and a notable 78,000 citations in the world's preeminent scientific publications. More important than these numbers is the fact that the innovative foundational and translational research from the scientists supported by CureAlz donors is providing knowledge vital to the development of effective therapies.

CONSORTIA AND SCIENTIFIC COLLABORATION

Since our inception, CureAlz has insisted on collaboration among our funded scientists, and they have embraced this tenet with great enthusiasm. To better harness the shared expertise from the researchers and the advancements made in their specific areas of study, CureAlz has formalized six consortia. The consortia include leading investigators from many institutions and universities in the United States and elsewhere in the world. We now are allocating approximately 30% of our research funding each year to these key teams.

- Brain Entry and Exit Consortium: Jony Kipnis, Ph.D., Washington University School of Medicine in St. Louis, Chair
- Alzheimer's Disease Drug Discovery and Development (AD4) Consortium
- Collaboration to Infer Regulatory Circuits and Uncover Innovative Therapeutic Strategies (CIRCUITS) Consortium: Li-Huei Tsai, Ph.D., and Manolis Kellis, Ph.D., Massachusetts Institute of Technology and Broad Institute, Chairs
- Fleming APOE Consortium: David Holtzman, M.D., Washington University School of Medicine in St. Louis, Chair
- Neuroimmune Consortium: Beth Stevens, Ph.D., Boston Children's Hospital, Chair
- Tau Consortium: Karen E. Duff, Ph.D., University College London, Chair

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

The members of our newest consortium are investigating the role of tau in Alzheimer's disease. Tau pathology—neurofibrillary tau tangles—correlates very strongly with neurodegeneration and cognitive impairment in AD, but key questions remain unresolved, such as how amyloid pathology induces it, how and why it spreads in a classic pattern throughout the brain, and why neurons bearing it survive while other neurons die off in its presence. The consortium's work will enable deeper understanding for improved diagnostic and prognostic biomarkers, as well as the identification of new opportunities for effective therapeutic intervention.

HUMAN CLINICAL TRIALS OF A NEW DRUG

Amyloid plaques long have been the earliest recognized indicator and a distinguishing feature of Alzheimer's disease. Accumulating evidence only has reinforced the consensus view that the buildup of amyloid beta (Aβ) peptides in the brain, and in particular longer lengths of Aβ, is a causal factor leading to other aspects of Alzheimer's pathology and to clinical cognitive decline. The recent clinical trial success of the amyloid-targeting monoclonal antibody Leqembi (summary information included in this annual report) and its accelerated approval by the U.S. Food and Drug Administration (FDA) have reenergized efforts to target amyloid. For more than 20 years, Drs. Rudy Tanzi and the late Steven Wagner sought to reduce the production of toxic Aβ42 while interfering as little as possible with other, healthy aspects of brain functioning. CureAlz provided vital funding to Drs. Tanzi and Wagner to design and test an effective and safe small molecule gamma-secretase modulator (GSM), derisking

their academic lab project to ready it for for-profit investment and eventual human trials. CureAlz is pleased to share that the Investigational New Drug (IND) filing with the FDA for this GSM has been made and that the GSM's high potential has led the National Institutes of Health (NIH) to commit to funding the Phase 1 human safety trials. We will share updates from the company now developing the GSM as additional milestones are met.

CONTINUED GROWTH

While our strategic investments in planned, larger-scale research efforts are essential to our understanding of Alzheimer's disease, we continue to allocate the majority of our research distributions to proof-of-concept studies responsive to great ideas as they emerge in the $200,000+/- range as described in this annual report.

In 2022, we welcomed two distinguished members to our Research Strategy Council. Dr. John S. Lazo is acclaimed for his work in molecular pharmacology, cancer drug research and drug discovery, as well as in Alzheimer's disease, and has been a part of CureAlz scientific leadership since our founding. Dr. Patrick C. May is president of ADvantage Neuroscience Consulting, LLC. He previously spent 25 years at Eli Lilly and Co., where he retired as a Senior Research Fellow in the Neuroscience Discovery Research area.

Our culture of sharing work and scientific findings, providing our funded researchers with beneficial information advancing the work in each of their labs, has resulted in creating a global network of learning. The evidence of the effectiveness of this collaboration and of our research investments is the substantial financial leverage in the form of follow-on funding from NIH and the National Institute on Aging. For the three-year period 2018–2020, $47 million in grants distributed by CureAlz resulted in an extraordinary $350 million in follow-on funding—7.5 times our initial investment.

"Our culture of sharing work and scientific findings, providing our funded researchers with beneficial information advancing the work in each of their labs, has resulted in creating a global network of learning."

OUR GRATITUDE

In December 2022, Sherry Sharp resigned from her position on our Board of Directors to focus on her family. Sherry and her team have worked tirelessly to advance our understanding of Alzheimer's ever since her husband, Rick Sharp, battled the disease. Their contributions have made a difference to our foundation and to the entire Alzheimer's community. Their efforts are to be commended, and we are thankful for their leadership.

We also are grateful to our Board of Directors, our Trustees, the staff of Cure Alzheimer's Fund and to our CEO, Tim Armour, who all have worked to advance research funding for Alzheimer's disease. Their dedication has resulted in 18 consecutive years of growth for CureAlz, led to more than a decade of the highest rankings from the nonprofit watchdogs and allowed us to continue with our commitment to our donors of 100% of contributions going directly to our research.

It has been our honor to provide grants to nearly 300 of the world's leading researchers and the professionals working in their laboratories who are passionate about finding a cure. Their devotion to this cause leaves us in awe, and we are indebted to them.

A final note. Cure Alzheimer's Fund was founded in 2004, at a time when funding to understand Alzheimer's disease was marginal. We started this foundation because of the impact this disease has had on our friends, our families and our society. On Jan. 15, 2023, we lost one of our family members, Allison McCance, after her 22-year battle with Alzheimer's disease. Allison's energy and love for life was a true inspiration for all of us, and she will live on in our memories—and our hearts—and her spirit will live on through our efforts to find a cure for Alzheimer's disease.

Sincerely,

Jeff Morby	**Henry McCance**	**Rudy Tanzi, Ph.D.**
Co-Chair	Co-Chair	Chair, Research Leadership Group

Remembering Allison Jennings McCance

JUNE 1942–JANUARY 2023

The magnificent example that Allison gave us of living life completely and optimistically—even when that life confronts us with extraordinary challenges—deserves a permanent place in our memories.

For those fortunate to have known her, Allison was an inspiration. She embraced life with passion and intention, and resolve. She loved deeply and without condition. And she absolutely lived up to the nickname given her by her parents, "Sunny."

Born June 29, 1942, and raised in New Canaan, Connecticut, Allison was educated at Abbott Academy and Sweet Briar College. Allison worked as a grader and eventually became an Associate for Special Projects at Harvard Business School. On May 22, 1972, Allison married Henry F. McCance of Greylock Ventures and Co-Founder and Co-Chair of Cure Alzheimer's Fund.

Allison had an outstanding career as a tennis and paddle tennis player and was ranked No. 1 in women's tennis doubles in New England in 1972,1974 and 1975. She played on the professional paddle tennis circuit from 1976–1981 and was ranked each year nationally among the top 10 women's doubles teams while playing with three different partners. In 1977, Allison was a semifinalist in the Tribuno Professional Platform Tennis World Championship, played at the West Side Tennis Club in Forest Hills, New York. In 1978, Allison was a semifinalist in the Women's Platform Tennis National Championships and the National Platform Tennis Mixed Doubles Championship. After retiring from national tournaments, Allison won more than 40 tennis and paddle tennis titles at the Dedham Country and Polo Club in Dedham, Massachusetts, and The Country Club in Brookline, Massachusetts. She also played on The Country Club Division "A" team in the Dorothy Bruno Hills Indoor Tennis League from 1987 to 2006. The USTA/New England recognized her lifetime of contributions with the Gardner Chase Memorial Award, and the family's contributions with the Edwin Goodman Family of the Year Award. Throughout her sports career, Allison was known widely for her competitive spirit, unwavering sportsmanship and loyalty to her teammates.

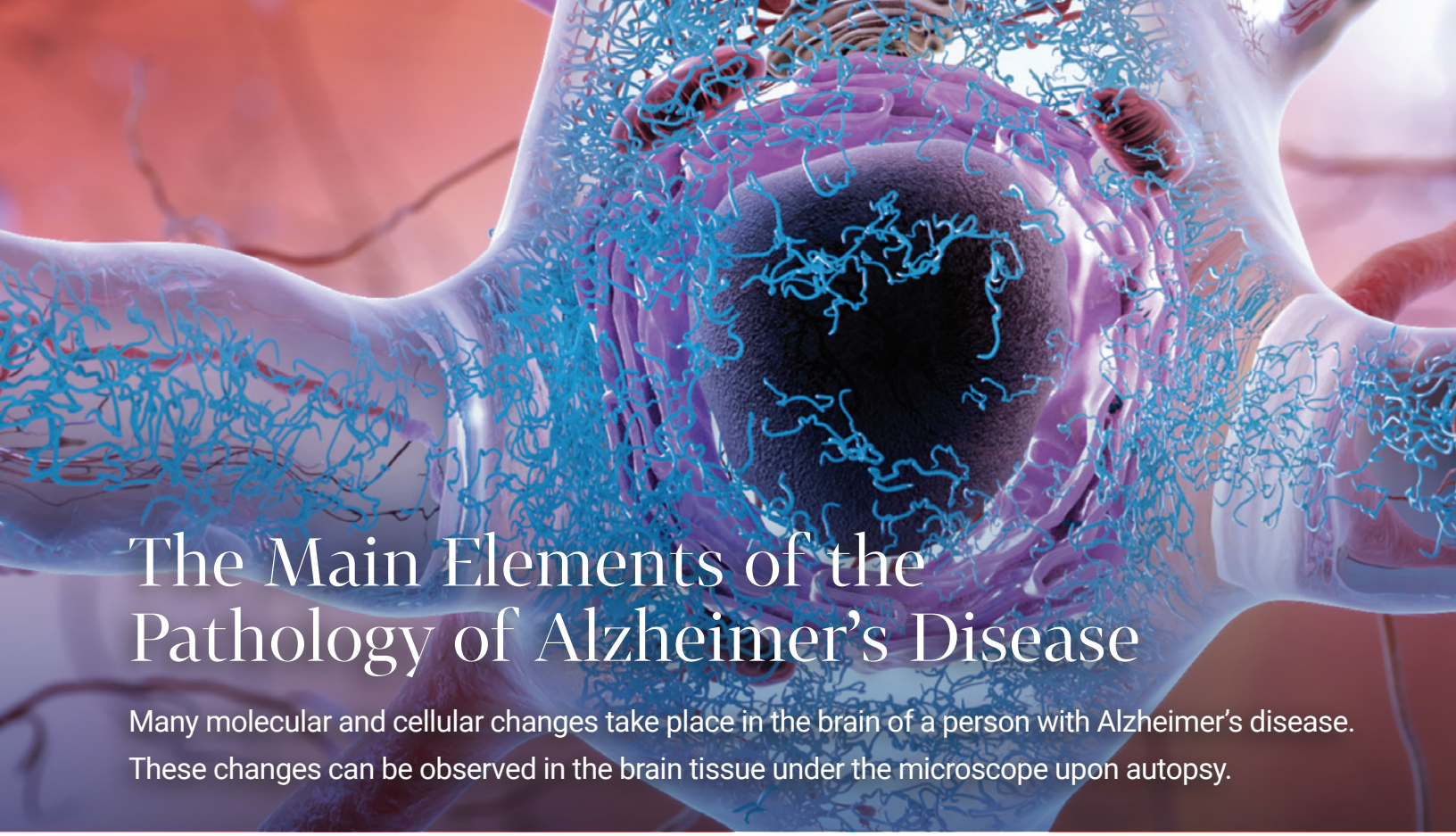
Allison also had an enduring interest in books—reading and writing them. She co-founded a book club in Boston that continues to this day. And she co-authored, along with Judy Duncan, "The Clock Watcher's Cookbook."

In the year 2000, at the age of 58, Allison was diagnosed with Alzheimer's disease. For nearly 23 years she faced each day with dignity, refusing to become defined by the disease. She continued playing for The Country Club well into her 60s and during the progression of the disease.

In 2004, Allison became the inspiration for Henry to join Jeff and Jacqui Morby and Phyllis Rappaport in founding Cure Alzheimer's Fund.

On Jan. 15, 2023, Allison passed away peacefully, surrounded by her family and caregivers. Allison will be remembered for her loyalty and devotion to her family and friends. She absolutely loved being a wife and a mother—and the joy and energy she received from this part of her life was contagious and will be a part of her everlasting legacy. Allison's many lifetime friends from Boston, Fishers Island, New York, and Mountain Lake, Florida, will fondly remember her laugh and smile, generosity of time and spirit, positive attitude and joy in living each day to the fullest.

She is survived by her husband and loving partner of 50 years, Henry; her daughter and son-in-law, Ellen McCance Pinschmidt and Patrick Pinschmidt of Dublin, Ireland; her stepdaughter, Elizabeth McCance of Fairfield, Connecticut; six grandchildren, Jack, Leah, Clara and Callan Pinschmidt, and Phoebe and Sadie McCance; as well as her brother and sister-in-law, Keith and Bev Jennings of Philadelphia and Hilton Head Island, South Carolina.



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*

FDA Awards Leqembi Accelerated Approval

On Jan. 6, 2023, the U.S. Food and Drug Administration (FDA) announced accelerated approval for Leqembi™, the brand name for lecanemab (BAN-2401).

Leqembi is a monoclonal antibody developed by pharmaceutical companies Eisai and Biogen designed to reduce the amount of amyloid beta in the brain for the treatment of mild cognitive impairment due to Alzheimer's disease (AD). The Amyloid Cascade Hypothesis of AD postulates that preventing amyloid from aggregating and accumulating in the brain, if done sufficiently early in the disease process, can prevent a series of downstream consequences that cause neuroinflammation, neurodegeneration and cognitive decline.

Accelerated approval requires that a drug show benefit against a biomarker that is expected to lead to eventual clinical benefit to patients; accelerated approval is supposed to be revoked and the drug removed from the market if a Phase 3 confirmation trial does not demonstrate such benefit. Leqembi demonstrated highly effective reduction of amyloid in the brains of treated patients in a Phase 2 clinical trial and thus was awarded accelerated approval.

Eisai and Biogen announced positive clinical results from a Phase 3 clinical trial a few weeks before accelerated approval was awarded, and immediately applied for regular approval. The Phase 3 clinical trial included 1,800 participants with mild cognitive impairment. The treatment was administered as an infusion two times every month. Twenty-five percent of participants were African American or nonwhite, making it one of the most diverse clinical trials for treating Alzheimer's disease. The trial met its primary endpoint of statistically significant slowing of cognitive decline compared with untreated/placebo trial participants when measured by the global cognitive and functional scale CDR-SB. After 18 months of treatment, the rate of cognitive decline of the patients receiving Leqembi was 27% slower than those in the control group. The difference between the treated and untreated participants was greatest at the 18-month mark, when the trial ended, suggesting that cognitive decline may have continued to slow with ongoing treatment, although it is not clear whether the slowing would continue as the disease progressed. Potentially dangerous brain swelling and lesions are recognized possible side effects of amyloid-reducing monoclonal antibodies. In this trial, 21% of treated participants experienced the side effects of brain swelling and/or lesions, compared with 9% in the placebo group. Only 3% of treated participants had symptomatic cases.

The FDA currently is reviewing additional data from the clinical trials provided by the pharmaceutical companies and a decision is expected in July 2023 on traditional approval. When the FDA announced approval of Leqembi through the accelerated process, the Centers for Medicare & Medicaid Services (CMS) released a statement declining funding for the treatment. CMS is expected to review its decision once the full FDA review is complete. However, the Veterans Administration has agreed to provide funding based on the FDA's accelerated approval.

This is only the second time that a treatment targeting amyloid has received accelerated approval from the FDA—the first being Aduhelm® in 2021. However, Aduhelm did not meet its preset primary clinical endpoints in its Phase 2/3 clinical trial; clinical benefit was achieved only for a small subset of treated patients identified after the study was over. CMS declined to cover Aduhelm for Medicare patients outside of clinical trials as a result, leading to tremendous controversy. The success of the Leqembi Phase 3 clinical trial marks a watershed moment for the Alzheimer's field: the first disease-modifying treatment to achieve clinical benefit offers real hope for patients and reinforces the Amyloid Cascade Hypothesis. As is common for the first drug for treatment of any disease, Leqembi is a starting point and not an end point. Cure Alzheimer's Fund celebrates this milestone achievement and the many, many scientists and clinical trial participants whose dedication led to this moment.

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 2022, a total of 160 high-impact science papers made possible by support from Cure Alzheimer's Fund were published in the world's leading science journals.

JANUARY 2022

Journal of Experimental Medicine

Gut Microbiota-Driven Brain Aβ Amyloidosis in Mice Requires Microglia

Rudolph E. Tanzi and Sangram S. Sisodia

Cell and Bioscience

Turning the Tide on Alzheimer's Disease: Modulation of Gamma-Secretase

Yueming Li

Molecular Psychiatry

Widespread Choroid Plexus Contamination in Sampling and Profiling of Brain Tissue

John D. Fryer

Genes

A Smoothed Version of the Lassosum Penalty for Fitting Integrated Risk Models Using Summary Statistics or Individual-Level Data

Rudolph E. Tanzi and Christoph Lange

Annual Review of Pharmacology and Toxicology

Prenatal and Postnatal Pharmacotherapy in Down Syndrome: The Search to Prevent or Ameliorate Neurodevelopmental and Neurodegenerative Disorders

William C. Mobley

Nature Protocols

Engineered Human Blood-Brain Barrier Microfluidic Model for Vascular Permeability Analyses

Roger D. Kamm

Journal of Extracellular Vesicles

Human Neural Cell Type-Specific Extracellular Vesicle Proteome Defines Disease-Related Molecules Associated with Activated Astrocytes in Alzheimer's Disease Brain

Mathew Blurton-Jones and Tsuneya Ikezu

The Journals of Gerontology: Series A

Relationship Between Five Epigenetic Clocks, Telomere Length and Functional Capacity Assessed in Older Adults: Cross-Sectional and Longitudinal Analyses

Lars Bertram

Frontiers in Genetics

Seven-CpG DNA Methylation Age Determined by Single Nucleotide Primer Extension and Illumina's Infinium MethylationEPIC Array Provide Highly Comparable Results

Lars Bertram

Glia

Sex-Specific Transcriptome of Spinal Microglia in Neuropathic Pain Due to Peripheral Nerve Injury

Oleg Butovsky

Alzheimer's Research & Therapy

A Novel D-amino Acid Peptide with Therapeutic Potential (ISAD1) Inhibits Aggregation of Neurotoxic Disease-Relevant Mutant Tau and Prevents Tau Toxicity in Vitro

Eckhard Mandelkow

Open Biology

Functional Insight into LOAD-Associated Microglial Response Genes

Yueming Li

Alzheimer's & Dementia

Endotype Reversal as a Novel Strategy for Screening Drugs Targeting Familial Alzheimer's Disease

Rudolph E. Tanzi and Steven L. Wagner

FEBRUARY 2022

Current Opinion in Neurobiology

Synaptic Proteostasis in Parkinson's Disease

Patrik Verstreken

Molecular Neurodegeneration

Selective Reduction of Astrocyte ApoE3 and ApoE4 Strongly Reduces Aβ Accumulation and Plaque-Related Pathology in a Mouse Model of Amyloidosis

Jason D. Ulrich and David M. Holtzman

Nature Cardiovascular Research

Blood–Brain Barrier Link to Human Cognitive Impairment and Alzheimer's Disease

Berislav V. Zlokovic

Alzheimer's & Dementia

Impact of Sex and APOE ε4 on the Association of Cognition and Hippocampal Volume in Clinically Normal, Amyloid Positive Adults

Richard B. Lipton and Ali Ezzati

Alzheimer's & Dementia

The P522R Protective Variant of PLCG2 Promotes the Expression of Antigen Presentation Genes by Human Microglia in an Alzheimer's Disease Mouse Model

Bruce T. Lamb and Mathew Blurton-Jones

Alzheimer's & Dementia

Protein Phosphatase 2A and Complement Component 4 are Linked to the Protective Effect of APOE ε2 for Alzheimer's Disease

Weiming Xia and Tsuneya Ikezu

Science

Caloric Restriction in Humans Reveals Immunometabolic Regulators of Health Span

Vishwa Deep Dixit

Nature

Single-Cell Dissection of the Human Brain Vasculature

Li-Huei Tsai and Manolis Kellis

Acta Neuropathologica Communications

Differential Protein Expression in the Hippocampi of Resilient Individuals Identified by Digital Spatial Profiling

Miranda E. Orr

Medical Review

Converging Multi-Modality Datasets to Build Efficient Drug Repositioning Pipelines Against Alzheimer's Disease and Related Dementias

Stephen T.C. Wong

Science Translational Medicine

Astrocytic α2-Na+/K+ ATPase Inhibition Suppresses Astrocyte Reactivity and Reduces Neurodegeneration in a Tauopathy Mouse Model

David M. Holtzman and Gilbert Gallardo

Journal of Biological Chemistry

Unbiased Proteomic Profiling Reveals the IP3R Modulator AHCYL1/IRBIT as a Novel Interactor of Microtubule-Associated Protein Tau

Eva-Maria Mandelkow and Eckhard Mandelkow

Seminars in Immunology

APOE Mediated Neuroinflammation and Neurodegeneration in Alzheimer's Disease

David M. Holtzman

Cells

Key Signalling Molecules in Aging and Neurodegeneration

Paola Pizzo

MARCH 2022

Scientific Reports

The Neuronal-Specific Isoform of BIN1 Regulates β-Secretase Cleavage of APP and Aβ Generation in a RIN3-Dependent Manner

Raja Bhattacharyya and Rudolph E. Tanzi

Journal of Biological Chemistry

Degradation and Inhibition of Epigenetic Regulatory Protein BRD4 Exacerbate Alzheimer's Disease-Related Neuropathology in Cell Models

Se Hoon Choi and Rudolph E. Tanzi

Molecular Psychiatry

Region-Based Analysis of Rare Genomic Variants in Whole-Genome Sequencing Datasets Reveal Two Novel Alzheimer's Disease-Associated Genes: DTNB and DLG2

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

Nature Neuroscience

Dissection of Artifactual and Confounding Glial Signatures by Single-Cell Sequencing of Mouse and Human Brain

Beth Stevens

Journal of Alzheimer's Disease

Transcriptome and Translatome Regulation of Pathogenesis in Alzheimer's Disease Model Mice

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

Frontiers in Aging Neuroscience

Endogenous and Exogenous Estrogen Exposures: How Women's Reproductive Health Can Drive Brain Aging and Inform Alzheimer's Prevention

Lisa Mosconi

Alzheimer's & Dementia

Application of Predictive Models in Boosting Power of Alzheimer's Disease Clinical Trials: A Post Hoc Analysis of Phase 3 Solanezumab Trials

Ali Ezzati and Richard B. Lipton

Neuron

ApoE Cascade Hypothesis in the Pathogenesis of Alzheimer's Disease and Related Dementias

Takahisa Kanekiyo, Alison M. Goate, David M. Holtzman and Guojun Bu

Nature Neuroscience

Cerebrospinal Fluid Regulates Skull Bone Marrow Niches Via Direct Access Through Dural Channels

Jonathan Kipnis

Annual Review of Biochemistry

Lipoproteins in the Central Nervous System: From Biology to Pathobiology

Guojun Bu

STAR Protocols

Microfluidic Separation of Axonal and Somal Compartments of Neural Progenitor Cells Differentiated in a 3D Matrix

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

Frontiers in Aging Neuroscience

Genome-Wide Association Study of Alzheimer's Disease Brain Imaging Biomarkers and Neuropsychological Phenotypes in the European Medical Information Framework for Alzheimer's Disease Multimodal Biomarker Discovery Dataset

Philip Scheltens, Christina M. Lill and Lars Bertram

Molecular Neurobiology

Assessment of the in Vivo Relationship Between Cerebral Hypometabolism, Tau Deposition, TSPO Expression, and Synaptic Density in a Tauopathy Mouse Model: A Multi-tracer PET Study

Eckhard Mandelkow and Eva-Maria Mandelkow

Neurobiology of Aging

ApoE4 Reduction: An Emerging and Promising Therapeutic Strategy for Alzheimer's Disease

Guojun Bu

Frontiers in Neuroscience

Neurotechnological Approaches to the Diagnosis and Treatment of Alzheimer's Disease

Mehdi Jorfi, Doo Yeon Kim and Rudolph E. Tanzi

ACS Nano

Rapid Biomarker Screening of Alzheimer's Disease by Interpretable Machine Learning and Graphene-Assisted Raman Spectroscopy

Se Hoon Choi and Rudolph E. Tanzi

Journal of Biological Chemistry

Mammalian Ddi2 is a Shuttling Factor Containing a Retroviral Protease Domain That Influences Binding of Ubiquitylated Proteins and Proteasomal Degradation

Alfred L. Goldberg

Molecular Neurodegeneration

Culture Shock: Microglial Heterogeneity, Activation, and Disrupted Single-Cell Microglial Networks in Vitro

John D. Fryer

Translational Psychiatry

Effects of APOE4 Allelic Dosage on Lipidomic Signatures in the Entorhinal Cortex of Aged Mice

Karen E. Duff and Tal Nuriel

Neurology

Associations of Stages of Objective Memory Impairment with Amyloid PET and Structural MRI: The A4 Study

Richard B. Lipton and Ali Ezzati

APRIL 2022

International Journal of Molecular Sciences

Sex Differences in Metabolic Indices and Chronic Neuroinflammation in Response to Prolonged High-Fat Diet in ApoE4 Knock-in Mice

Paula Grammas

Neuron

Astrocytes and Oligodendrocytes Undergo Subtype-Specific Transcriptional Changes in Alzheimer's Disease

Shane A. Liddelow

Alzheimer's & Dementia

The Small HDL Particle Hypothesis of Alzheimer's Disease

Berislav V. Zlokovic

Neurobiology of Disease

SOD1 Mediates Lysosome-to-Mitochondria Communication and Its Dysregulation by Amyloid-β Oligomers

George S. Bloom

Neurology

Effect of Race on Prediction of Brain Amyloidosis by Plasma Aβ42/Aβ40, Phosphorylated Tau, and Neurofilament Light

Krista L. Moulder, Randall J. Bateman and John C. Morris

Brain, Behavior, & Immunity — Health

Infection and Inflammation: New Perspectives on Alzheimer's Disease

David M. Gate, Alison M. Goate, Sangram S. Sisodia, Beth Stevens and Rudolph E. Tanzi

MAY 2022

Genetic Epidemiology

Selection Bias When Inferring the Effect Direction in Mendelian Randomization

Christoph Lange

Cancer Discovery

Melanoma-Secreted Amyloid Beta Suppresses Neuroinflammation and Promotes Brain Metastasis

Yueming Li and Shane A. Liddelow

Frontiers in Molecular Neuroscience

Proteomic Alterations and Novel Markers of Neurotoxic Reactive Astrocytes in Human Induced Pluripotent Stem Cell Models

Shane A. Liddelow

npj Science of Learning

Genetic Associations with Learning over 100 Days of Practice

Christina M. Lill and Lars Bertram

Journal of Biological Chemistry

The Dual Fates of Exogenous Tau Seeds: Lysosomal Clearance vs. Cytoplasmic Amplification

Marc I. Diamond

Acta Neuropathologica Communications

Changes in Glial Cell Phenotypes Precede Overt Neurofibrillary Tangle Formation, Correlate with Markers of Cortical Cell Damage, and Predict Cognitive Status of Individuals at Braak III–IV Stages

Teresa Gomez-Isla

Immunity

Concerted Type I Interferon Signaling in Microglia and Neural Cells Promotes Memory Impairment Associated With Amyloid β Plaques

Hui Zheng

Cell Reports

Functional Genome-Wide Short Hairpin RNA Library Screening Identifies Key Molecules for Extracellular Vesicle Secretion from Microglia

Seiko Ikezu and Tsuneya Ikezu

GeroScience

Vitamin D Supplementation is Associated with Slower Epigenetic Aging

Lars Bertram

Phytomedicine

Natural Medicine HLXL Targets Multiple Pathways of Amyloid-Mediated Neuroinflammation and Immune Response in Treating Alzheimer's Disease

Luisa Quinti, Ana Griciuc, Se Hoon Choi and Rudolph E. Tanzi

The Journal of Clinical Investigation

Biological Aging Processes Underlying Cognitive Decline and Neurodegenerative Disease

Miranda E. Orr

Neurology

Clinicopathologic Factors Associated with Reversion to Normal Cognition in Patients with Mild Cognitive Impairment

Takahisa Kanekiyo, Ronald C. Petersen and Guojun Bu

Blood Advances

Anti-HK Antibody Reveals Critical Roles of a 20-Residue HK Region for Aβ-Induced Plasma Contact System Activation

Sidney Strickland and Erin H. Norris

Acta Pharmaceutica Sinica B

Development of a Potential PET Probe for HDAC6 Imaging in Alzheimer's Disease

Se Hoon Choi and Rudolph E. Tanzi

Nature Reviews Neurology

Genome-Wide Analysis Furthers Decoding of Alzheimer Disease Genetics

Christina M. Lill and Lars Bertram

JUNE 2022

Cell Stem Cell

Recapitulation of Endogenous 4R Tau Expression and Formation of Insoluble Tau in Directly Reprogrammed Human Neurons

Randall J. Bateman, David M. Holtzman, Karen E. Duff and Andrew S. Yoo

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

Signatures of Glial Activity Can Be Detected in the CSF Proteome

Christian Haass, Mathias Jucker and Stephan A. Kaeser

Frontiers in Cellular Neuroscience

Editorial: Multifaceted Interactions Between Immunity and the Diseased Brain

Sandro Da Mesquita

Current Opinion in Neurobiology

How Neurons Die in Alzheimer's Disease: Implications for Neuroinflammation

John R. Lukens

Cell

Mild Respiratory COVID Can Cause Multi-Lineage Neural Cell and Myelin Dysregulation

Shane A. Liddelow

Cell Reports

Absence of Microglia Promotes Diverse Pathologies and Early Lethality in Alzheimer's Disease Mice

Mathew Blurton-Jones

Neurology

Predicting Amyloid Positivity in Cognitively Unimpaired Older Adults: A Machine Learning Approach Using A4 Data

Richard B. Lipton and Ali Ezzati

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

26S Proteasomes Become Stably Activated Upon Heat Shock When Ubiquitination and Protein Degradation Increase

Alfred L. Goldberg

STAR Protocols

Analysis of Brain Region-Specific mRNA Synthesis and Stability by Utilizing Adult Mouse Brain Slice Culture

Jaehong Suh

Science Advances

BACE-1 Inhibition Facilitates the Transition from Homeostatic Microglia to DAM-1

Manolis Kellis, Li-Huei Tsai and Riqiang Yan

Molecular Therapy — Methods & Clinical Development

Gene Replacement Therapy in a Schwannoma Mouse Model of Neurofibromatosis Type 2

Casey A. Maguire

Journal of Biological Chemistry

Seed-Competent Tau Monomer Initiates Pathology in a Tauopathy Mouse Model

Marc I. Diamond

Cell

Cholesterol and Matrisome Pathways Dysregulated in Astrocytes and Microglia

Edoardo Marcora, David M. Holtzman, Frederick R. Maxfield and Alison M. Goate

Frontiers in Aging Neuroscience

Most Pathways Can Be Related to the Pathogenesis of Alzheimer's Disease

Rudolph E. Tanzi, Lars Bertram and Winston Hide

Frontiers in Aging Neuroscience

Bacillus Calmette–Guérin in Immuno-Regulation of Alzheimer's Disease

Benjamin Y. Klein, Charles L. Greenblatt and Ofer N. Gofrit

Seminars in Immunology

Pathophysiology of Neurodegenerative Diseases: An Interplay Among Axonal Transport Failure, Oxidative Stress, and Inflammation?

Giuseppina Tesco

JULY 2022

Journal of Experimental Medicine

Charting the Meningeal Lymphatic Network

Sandro Da Mesquita

Molecular Biology and Evolution

Evolution of Human-Specific Alleles Protecting Cognitive Function of Grandmothers

Ajit Varki

Glia

Repurposing the Cardiac Glycoside Digoxin to Stimulate Myelin Regeneration in Chemically-Induced and Immune-Mediated Mouse Models of Multiple Sclerosis

Shane A. Liddelow

Current Opinion in Immunology

Spontaneous and Induced Adaptive Immune Responses in Alzheimer's Disease: New Insights into Old Observations

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Biomolecules

P2 Receptors: Novel Disease Markers and Metabolic Checkpoints in Immune Cells

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Aging Cell

Effects of Cerebral Amyloid Angiopathy on the Brain Vasculome

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Frontiers in Aging Neuroscience

Ovarian Steroid Hormones: A Long Overlooked but Critical Contributor to Brain Aging and Alzheimer's Disease

Lisa Mosconi

Frontiers in Aging Neuroscience

Selective Detection of Misfolded Tau from Postmortem Alzheimer's Disease Brains

George S. Bloom

Science Advances

Targeted BACE-1 Inhibition in Microglia Enhances Amyloid Clearance and Improved Cognitive Performance

Riqiang Yan

Physiology

Physiology of Glymphatic Solute Transport and Waste Clearance from the Brain

Allen R. Tannenbaum and Helene Benveniste

AUGUST 2022

Nature Neuroscience

Peripheral ApoE4 Enhances Alzheimer's Pathology and Impairs Cognition by Compromising Cerebrovascular Function

Takahisa Kanekiyo, John D. Fryer and Guojun Bu

Scientific Reports

PILRA Polymorphism Modifies the Effect of APOE4 and GM17 on Alzheimer's Disease Risk

Rudolph E. Tanzi

Cell Stem Cell

Lipid Accumulation Induced by APOE4 Impairs Microglial Surveillance of Neuronal-Network Activity

Li-Huei Tsai

Acta Neuropathologica Communications

Corpora Amylacea Are Associated with Tau Burden and Cognitive Status in Alzheimer's Disease

David M. Holtzman

Immunity

The Matricellular Protein SPARC Induces Inflammatory Interferon-Response in Macrophages During Aging

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Journal of Alzheimer's Disease

Association of Depressive Symptoms and Cognition in Older Adults Without Dementia Across Different Biomarker Profiles

Richard B. Lipton and Ali Ezzati

Journal of Alzheimer's Disease

Evoked Cortical Depolarizations Before and After the Amyloid Plaque Accumulation: Voltage Imaging Study

Riqiang Yan and Srdjan D. Antic

Immunity

Apolipoprotein E4 Impairs the Response of Neurodegenerative Retinal Microglia and Prevents Neuronal Loss in Glaucoma

Rudolph E. Tanzi, David M. Holtzman and Oleg Butovsky

Molecular Neurodegeneration

Microglial TYROBP/DAP12 in Alzheimer's Disease: Transduction of Physiological and Pathological Signals Across TREM2

Michelle E. Ehrlich and Samuel E. Gandy

Translational Psychiatry

Differential MicroRNA Expression Analyses Across Two Brain Regions in Alzheimer's Disease

Christina M. Lill and Lars Bertram

Journal of Experimental Medicine

A "Multi-Omics" Analysis of Blood–Brain Barrier and Synaptic Dysfunction in APOE4 Mice

Berislav V. Zlokovic

Immunological Reviews

An Introduction to Neuroimmunology

John R. Lukens

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Molecular Neurodegeneration

Trem2 Deletion Enhances Tau Dispersion and Pathology Through Microglia Exosomes

Huaxi Xu and Timothy Huang

EMBO Molecular Medicine

In Situ Mass Spectrometry Imaging Reveals Heterogeneous Glycogen Stores in Human Normal and Cancerous Tissues

Ramon Sun

Acta Neuropathologica Communications

Regulating Microglial miR-155 Transcriptional Phenotype Alleviates Alzheimer's-Induced Retinal Vasculopathy by Limiting Clec7a/Galectin-3+ Neurodegenerative Microglia

Seiko Ikezu, Tsuneya Ikezu and Oleg Butovsky

Journal of Experimental Medicine

Sleep Exerts Lasting Effects on Hematopoietic Stem Cell Function and Diversity

Cameron McAlpine, Matthias Nahrendorf and Filip K. Swirski

Seminars in Immunology

Redefining Microglia States: Lessons and Limits of Human and Mouse Models to Study Microglia States in Neurodegenerative Diseases

Beth Stevens

Journal of Biological Chemistry

The CX3CL1 Intracellular Domain Exhibits Neuroprotection Via Insulin Receptor/Insulin-Like Growth Factor Receptor Signaling

Riqiang Yan

GeroScience

Using Blood Test Parameters to Define Biological Age Among Older Adults: Association with Morbidity and Mortality Independent of Chronological Age Validated in Two Separate Birth Cohorts

Christina M. Lill and Lars Bertram

Translational Psychiatry

Epigenetic Aging and Perceived Psychological Stress in Old Age

Lars Bertram

Journal of Parkinson's Disease

New Perspectives on Immune Involvement in Parkinson's Disease Pathogenesis

David M. Gate

Science Advances

Neurons Burdened by DNA Double-Strand Breaks Incite Microglia Activation Through Antiviral-Like Signaling in Neurodegeneration

Andreas R. Pfenning, Manolis Kellis and Li-Huei Tsai

OCTOBER 2022

Fluids and Barriers of the CNS

VHHs as Tools for Therapeutic Protein Delivery to the Central Nervous System

Bart De Strooper and Maarten Dewilde

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

Early Death in a Mouse Model of Alzheimer's Disease Exacerbated by Microglial Loss of TAM Receptor Signaling

Greg Lemke

Molecular Neurodegeneration

Liver-ing in Your Head Rent Free: Peripheral ApoE4 Drives CNS Pathology

Lance A. Johnson

Journal of Alzheimer's Disease

Neurotoxicity of Diesel Exhaust Particles

Caleb E. Finch

Molecular Brain

Transcriptomic Profiling of Sporadic Alzheimer's Disease Patients

Steven L. Wagner

Cell

SYK Coordinates Neuroprotective Microglial Responses in Neurodegenerative Disease

John R. Lukens

Journal of Neuroendocrinology

Role of Estrogen in Women's Alzheimer's Disease Risk as Modified by APOE

Christian Pike

SLAS Discovery

High Content Screening Miniaturization and Single Cell Imaging of Mature Human Feeder Layer-Free iPSC-Derived Neurons

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

Nature Neuroscience

Age-Related Huntington's Disease Progression Modeled in Directly Reprogrammed Patient-Derived Striatal Neurons Highlights Impaired Autophagy

Andrew S. Yoo

Cell

TREM2 Drives Microglia Response to Amyloid-β Via SYK-Dependent and -Independent Pathways

David M. Holtzman and Marco Colonna

Brain Communications

Common Signatures of Differential MicroRNA Expression in Parkinson's and Alzheimer's Disease Brains

Lars Bertram and Christina M. Lill

BMC Bioinformatics

The Maximum Entropy Principle for Compositional Data

Allen R. Tannenbaum

Methods in Molecular Biology

Microfluidic Chamber Technology to Study Missorting and Spreading of Tau Protein in Alzheimer's Disease

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NOVEMBER 2022

Clinical Epigenetics

A Correlation Map of Genome-Wide DNA Methylation Patterns Between Paired Human Brain and Buccal Samples

Bradley T. Hyman, Christina M. Lill and Lars Bertram

Neuron

Microglia States and Nomenclature: A Field at Its Crossroads

Beth Stevens, Mathew Blurton-Jones, Oleg Butovsky, Marco Colonna, Bart De Strooper, Christopher K. Glass, Christian Haass, Jonathan Kipnis, Greg Lemke, Li-Huei Tsai and Tony Wyss-Coray

The Journal of Prevention of Alzheimer's Disease

Associations of Stages of Objective Memory Impairment with Cerebrospinal Fluid and Neuroimaging Biomarkers of Alzheimer's Disease

Ali Ezzati, Richard B. Lipton and John C. Morris

Biomedicines

Epigenome-Wide Association Study in Peripheral Tissues Highlights DNA Methylation Profiles Associated with Episodic Memory Performance in Humans

Christina M. Lill and Lars Bertram

Alzheimer's & Dementia

Sex-Specific Biomarkers in Alzheimer's Disease Progression: Framingham Heart Study

P. Murali Doraiswamy

Immunity

Emerging Roles of Innate and Adaptive Immunity in Alzheimer's Disease

David M. Holtzman

Molecular Neurodegeneration

ApoE in Alzheimer's Disease: Pathophysiology and Therapeutic Strategies

Guojun Bu

Nature

Parenchymal Border Macrophages Regulate the Flow Dynamics of the Cerebrospinal Fluid

Randall J. Bateman and Jonathan Kipnis

Neuron

TREM2-Independent Microgliosis Promotes Tau-Mediated Neurodegeneration in the Presence of ApoE4

Marco Colonna, Christopher K. Glass, Jason D. Ulrich and David M. Holtzman

Neuropharmacology

Extracellular ATP: A Powerful Inflammatory Mediator in the Central Nervous System

Francesco Di Virgilio

Nature

APOE4 Impairs Myelination Via Cholesterol Dysregulation in Oligodendrocytes

Joel W. Blanchard, Manolis Kellis and Li-Huei Tsai

Cells

Intranasal Peptide Therapeutics: A Promising Avenue for Overcoming the Challenges of Traditional CNS Drug Development

Michelle E. Ehrlich and Stephen R. Salton

Alzheimer's & Dementia

Baseline Characterization of the ARMADA (Assessing Reliable Measurement in Alzheimer's Disease) Study Cohorts

Bruno Giordani

Cell Reports

Plaque Contact and Unimpaired Trem2 Is Required for the Microglial Response to Amyloid Pathology

John Hardy and Frances A. Edwards

Nature Communications

Enhanced Activity of Alzheimer Disease-Associated Variant of Protein Kinase Cα Drives Cognitive Decline in a Mouse Model

Gentry N. Patrick, Rudolph E. Tanzi and Alexandra C. Newton

Molecular Neurodegeneration

Opposing Effects of ApoE2 and ApoE4 on Microglial Activation and Lipid Metabolism in Response to Demyelination

Guojun Bu

Biomedicines

Mitochondrial Ca2+ Signaling and Bioenergetics in Alzheimer's Disease

Paola Pizzo

Nature Communications

Experimental Evidence for Temporal Uncoupling of Brain Aβ Deposition and Neurodegenerative Sequelae

Stephan A. Kaeser and Mathias Jucker

Nature

PLD3 Affects Axonal Spheroids and Network Defects in Alzheimer's Disease

Jaime Grutzendler

Alzheimer's & Dementia

Microglial INPP5D Limits Plaque Formation and Glial Reactivity in the PSAPP Mouse Model of Alzheimer's Disease

Charles G. Glabe, Samuel E. Gandy, Shane A. Liddelow and Michelle E. Ehrlich

DECEMBER 2022

Journal of Neuroinflammation

APOE Genotype and Biological Sex Regulate Astroglial Interactions with Amyloid Plaques in Alzheimer's Disease Mice

Christian Pike

Cells

Dual-Specificity Protein Phosphatase 4 (DUSP4) Overexpression Improves Learning Behavior Selectively in Female 5xFAD Mice, and Reduces β-Amyloid Load in Males and Females

Samuel E. Gandy, Michelle E. Ehrlich and Stephen R. Salton

STAR Protocols

Adaptable Toolbox to Characterize Alzheimer's Disease Pathology in Mouse Models

Greg Lemke

ACS Chemical Neuroscience

Identification and Prioritization of PET Neuroimaging Targets for Microglial Phenotypes Associated with Microglial Activity in Alzheimer's Disease

Jacob M. Hooker

Alzheimer's & Dementia

Nutritional Metabolism and Cerebral Bioenergetics in Alzheimer's Disease and Related Dementias

Lance A. Johnson, Berislav V. Zlokovic and Rudolph E. Tanzi

The EMBO Journal

Cryo-EM Structures of Human ABCA7 Provide Insights into Its Phospholipid Translocation Mechanisms

Takahisa Kanekiyo

Cell

Cerebrospinal Fluid Immune Dysregulation During Healthy Brain Aging and Cognitive Impairment

Tony Wyss-Coray and David M. Gate

Alzheimer's & Dementia

Amyloid Futures in the Expanding Pathology of Brain Aging and Dementia

Caleb E. Finch

Scientific Reports

Sex and Menopause Impact 31P-Magnetic Resonance Spectroscopy Brain Mitochondrial Function in Association with 11C-PiB PET Amyloid-Beta Load

Lisa Mosconi

Scientific Reports

Aberrant Glial Activation and Synaptic Defects in CaMKIIα-iCre and Nestin-Cre Transgenic Mouse Models

Robert Vassar and Leah K. Cuddy

Alzheimer's Research and Therapy

The Performance of Plasma Amyloid Beta Measurements in Identifying Amyloid Plaques in Alzheimer's Disease: A Literature Review

Henrik Zetterberg, Oskar Hansson and Randall J. Bateman

Our Researchers

This gallery features researchers who received funding in 2022, as well as the members of our Research Leadership Group and Research Strategy Council.

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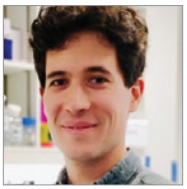

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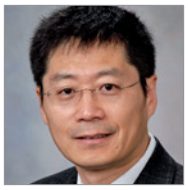

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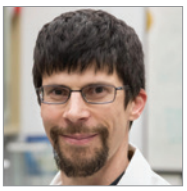

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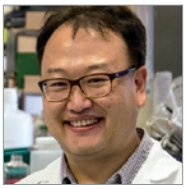

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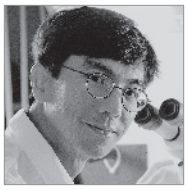

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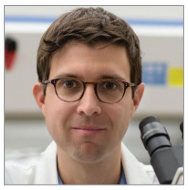

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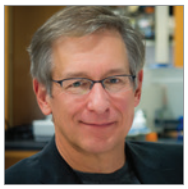

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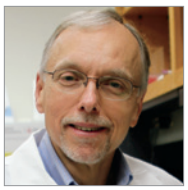
Amsterdam University Medical Centers,
The Netherlands

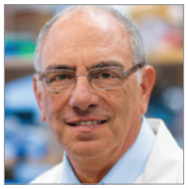


ROBERT J. VASSAR, PH.D.
Northwestern University Feinberg School
of Medicine
Research Leadership Group

PATRIK VERSTREKEN, PH.D.
VIB-KU Leuven, Belgium

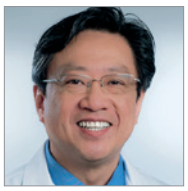
SAUL VILLEDA, B.S., PH.D.
University of California, San Francisco
New Funded Researcher, 2022

WILMA WASCO, PH.D.
Massachusetts General Hospital;
Harvard Medical School



HOWARD L. WEINER, M.D.
Brigham and Women's Hospital;
Harvard Medical School

CHERYL WELLINGTON, PH.D.
University of British Columbia, Canada
Research Leadership Group



STEPHEN T.C. WONG, PH.D.
Houston Methodist Research Institute;
Weill Cornell Medicine
Research Leadership Group

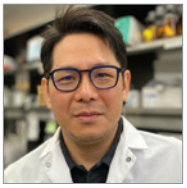
CHRISTIANE WRANN, D.V.M., PH.D.
Massachusetts General Hospital;
Harvard Medical School

TONY WYSS-CORAY, PH.D.
Stanford University
Research Leadership Group

WEIMING XIA, PH.D.
Boston University

RIQIANG YAN, PH.D.
University of Connecticut Health Center
Research Leadership Group

ANDREW YANG, PH.D.
University of California, San Francisco
New Funded Researcher, 2022



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

HENRIK ZETTERBERG, M.D., PH.D.
University of Gothenburg, Sweden
New Funded Researcher, 2022

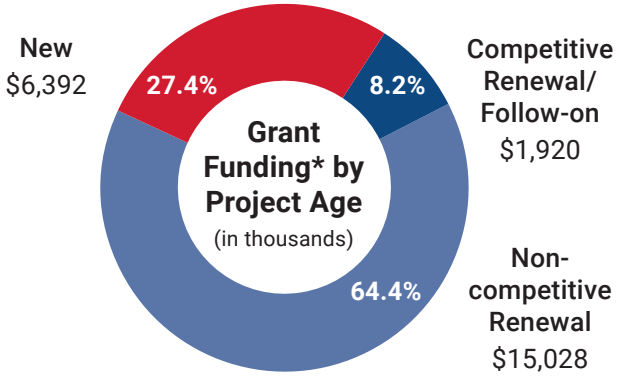
QISHENG ZHANG, PH.D.
University of North Carolina at Chapel Hill

HUI ZHENG, PH.D.
Baylor College of Medicine
Research Leadership Group

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

2022 Funded Research

Cure Alzheimer's Fund spent **$24.5 million to support 100 research projects** across our four research areas of focus. Visit **CureAlz.org/the-research** to read about all of our current research projects.



Number of New Investigators and Projects

	Number	% of Total
New Named Investigators	23	18%
New Projects	29	29%
New Institutions	9	15%

** Excludes Taconic and scientific meeting spending*

Project/Researcher	Distribution Amount
FOUNDATIONAL RESEARCH	
GENETIC RISK FACTORS	
The Alzheimer's Genome Project™ Rudolph E. Tanzi, Ph.D., Massachusetts General Hospital; Harvard Medical School	**$1,955,000**
BIOMARKERS, DIAGNOSTICS, AND STUDIES OF RISK AND RESILIENCE	
Characterization of Molecular Biomarker Profiles Throughout the Pathobiological Continuum Krista L. Moulder, Ph.D., Washington University School of Medicine in St. Louis	**$120,015**
Neurobiological Basis of Cognitive Impairment in African Americans: Deep Phenotyping of Older African Americans at Risk of Dementia—The Dementia (in) African American Population Phenotyping (for) Potential Elevated Risk (DAAPPER) Study Henry L. Paulson, M.D., Ph.D., University of Michigan Bruno Giordani, Ph.D., University of Michigan Benjamin M. Hampstead, Ph.D., ABPP/CN, University of Michigan	**$243,407**
Harnessing Big Data to Understand Alzheimer's Disease Risk Brad A. Racette, M.D., Barrow Neurological Institute Susan Searles Nielsen, Ph.D., Washington University School of Medicine in St. Louis Alejandra Camacho-Soto, M.D., M.P.H.S., Washington University School of Medicine in St. Louis	**$172,500**
Personalized Disease Prediction for Alzheimer's Disease Using Proteome Profiling: The EPIC4AD Study Christina M. Lill, M.D., M.Sc., University of Münster, Germany; Imperial College London, England Lars Bertram, M.D., University of Lübeck, Germany	**$541,897**
Cerebrospinal Fluid Neuroinflammatory Signature in Alzheimer's Disease and Related Proteopathies Mathias Jucker, Ph.D., University of Tübingen, Germany; German Center for Neurodegenerative Diseases (DZNE) Stephan A. Kaeser, Ph.D., University of Tübingen, Germany Stefan Lichtenthaler, Ph.D., German Center for Neurodegenerative Diseases (DZNE); Technische Universität München (TUM)	**$180,550**
Sex Differences in Alzheimer's Disease Progression: Framingham Heart Study P. Murali Doraiswamy, M.B.B.S., Duke University School of Medicine	**$199,162**
BIOLOGICAL RESEARCH MATERIALS: NEW ANIMAL AND CELLULAR MODELS, AND HUMAN SAMPLES	
Modeling Alzheimer's Disease by Direct Neuronal Reprogramming of Patient Fibroblasts into Neuronal Subtypes Andrew S. Yoo, Ph.D., Washington University School of Medicine in St. Louis	**$172,500**
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; Harvard Medical School Joseph Park, Ph.D., Massachusetts General Hospital; Harvard Medical School Rudolph E. Tanzi, Ph.D., Massachusetts General Hospital; Harvard Medical School	**$172,500**
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 T. Hyman, M.D., Ph.D., Massachusetts General Hospital; Harvard Medical School	**$250,000**
Genes to Therapies™ (G2T) Research Models and Materials Taconic Biosciences	**$528,064**

Project/Researcher	Distribution Amount
EPIGENETIC FACTORS	
CIRCUITS: A Unified Approach to Actionable Alzheimer's Disease Signatures Winston Hide, Ph.D., Beth Israel Deaconess Medical Center; Harvard Medical School	**$248,980**
CIRCUITS: Interpreting Alzheimer's Disease-Associated Genetic Variation at Enhancer Regions Andreas R. Pfenning, Ph.D., Carnegie Mellon University	**$200,000**
CIRCUITS: Characterizing Epigenetic Biomarkers of Human Cognitive Aging Lars Bertram, M.D., University of Lübeck, Germany	**$252,250**
CIRCUITS: Impact of Genetic, Epigenetic and Cellular Variants on Alzheimer's Disease Pathology Rudolf Jaenisch, M.D., Whitehead Institute; Massachusetts Institute of Technology Joseph R. Ecker, Ph.D., Salk Institute for Biological Studies	**$422,500**
TRANSLATIONAL RESEARCH	
STUDIES OF NOVEL ALZHEIMER'S DISEASE GENES	
Dissecting the Modulatory Roles of Interleukin-17 Receptor D in Alzheimer's Disease Jun Huh, Ph.D., Harvard Medical School	**$201,250**
Understanding and Mimicking the Biological Effects of the Phospholipase C-gamma-2 P522R Variant That Protects Against Alzheimer's Disease Rik van der Kant, Ph.D., Amsterdam University Medical Centers, The Netherlands	**$173,104**
ABCA7 Loss of Function in Aging and Alzheimer's Disease Takahisa Kanekiyo, M.D., Ph.D., Mayo Clinic, Jacksonville	**$201,250**
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**
Single Nucleus RNA Sequencing Analysis of ACE1 R1284Q Knock-in Mice Robert Vassar, Ph.D., Northwestern University Feinberg School of Medicine David M. Gate, Ph.D., Northwestern University Feinberg School of Medicine Leah K. Cuddy, Ph.D., Northwestern University Feinberg School of Medicine	**$246,804**
Functional Basis for Novel Protein Kinase C-eta K56R Mutation in Alzheimer's Disease Alexandra C. Newton, Ph.D., University of California, San Diego	**$172,500**
Exploring the Therapeutic Potential of Clusterin in a Preclinical Model of Alzheimer's Disease Alban Gaultier, Ph.D., University of Virginia	**$201,250**
STUDIES OF AMYLOID PRECURSOR PROTEIN (APP) AND AMYLOID BETA	
Structural Mimicry in Microbial and Antimicrobial Amyloids Connected to Neurodegenerative Diseases Meytal Landau, B. Pharm, M.S.C., Ph.D., Technion, Israel Institute of Technology; Deutsches Elektronen-Synchrotron (DESY)	**$200,760**
Effects of Depalmitoylation and ACAT Inhibition on Axonal Amyloid Beta Generation Via MAM-Associated palAPP Raja Bhattacharyya, Ph.D., Massachusetts General Hospital; Harvard Medical School Rudolph E. Tanzi, Ph.D., Massachusetts General Hospital; Harvard Medical School	**$172,500**
Secreted Frizzled Related Protein 1 (SFRP1) as a Therapeutic Target and Diagnostic/Prognostic Factor in Alzheimer's Disease Paola Bovolenta, Ph.D., Universidad Autónoma de Madrid, Spain	**$172,500**
Air Pollution and Alzheimer's Disease Risk Interact with Premature Aging of Neural Stem Cells and Apolipoprotein E Alleles Caleb E. Finch, Ph.D., University of Southern California Michael A. Bonaguidi, Ph.D., University of Southern California	**$219,535**
STUDIES OF TAU	
Alzheimer's Disease Tau Consortium: How Do Soluble Tau Species Replicate Bradley T. Hyman, M.D., Ph.D., Massachusetts General Hospital; Harvard Medical School	**$286,595**
Alzheimer's Disease Tau Consortium: The Role of Amyloid Beta-Induced Membrane Damage in Tau Pathology Katherine R. Sadleir, Ph.D., Northwestern University Feinberg School of Medicine Robert J. Vassar, Ph.D., Northwestern University Feinberg School of Medicine	**$286,357**
Alzheimer's Disease Tau Consortium: Impact of Tau Mutations and Amyloid Beta on Tau Post-Translational Modifications and Conformation Karen E. Duff, Ph.D., University College London, England	**$345,000**

Project/Researcher	Distribution Amount
Alzheimer's Disease Tau Consortium: Deep Mass Spectrometry Profiling of Tau Aggregates in Alzheimer's Disease and Other Tauopathies Henrik Zetterberg, M.D., Ph.D., University of Gothenburg, Sweden Gunnar Brinkmalm, Ph.D., University of Gothenburg, Sweden	**$287,500**
Alzheimer's Disease Tau Consortium: Role of VCP/p97 in Tau Prion Replication Marc I. Diamond, M.D., University of Texas Southwestern Medical Center	**$287,000**
Characterization of Tau Pathology Heterogeneity Across the Alzheimer's Disease Spectrum Oskar Hansson, M.D., Ph.D., Lund University, Sweden Rik Ossenkoppele, Ph.D., Amsterdam University Medical Centers, The Netherlands; Lund University, Sweden	**$201,250**
Properties of Tau in Posterior Cortical Atrophy Bradley T. Hyman, M.D., Ph.D., Massachusetts General Hospital; Harvard Medical School John R. Dickson, M.D., Ph.D., Massachusetts General Hospital; Harvard Medical School	**$172,500**
RNA as a Determinant of Tau Seeding Marc I. Diamond, M.D., University of Texas Southwestern Medical Center	**$230,000**
Targeting Tauopathies with Antisense Oligonucleotides to Synaptogyrin-3 Patrik Verstreken, Ph.D., VIB-KU Leuven, Belgium	**$215,625**
Using Long-Read Sequencing to Investigate the MAPT Locus and Transcripts in Neurodegeneration John Hardy, Ph.D., University College London, England	**$201,250**
Toxic Effects of Extracellular Tau Oligomers on Neurons George S. Bloom, Ph.D., University of Virginia	**$198,932**
Investigating the Role of Tau Protein in Neuronal Senescence Induction and Maintenance Miranda E. Orr, Ph.D., Wake Forest University School of Medicine	**$172,500**
STUDIES OF APOLIPOPROTEIN E (APOE)	
APOE Consortium: APOE4-Mediated Dysfunction of CD8 T-Cell-Microglia Crosstalk in Alzheimer's Disease Oleg Butovsky, Ph.D., Brigham and Women's Hospital; Harvard Medical School	**$287,500**
APOE Consortium: Modulation of Selective Neuronal Vulnerability in Alzheimer's Disease by Apolipoprotein E Jean-Pierre Roussarie, Ph.D., Boston University School of Medicine	**$167,707**
APOE Consortium: 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	**$252,077**
APOE Consortium: Effect of Cholesteryl Ester Transfer Protein Activity on Amyloid and Cerebrovascular Pathologies in Animal Models of Alzheimer's Disease Cheryl Wellington, Ph.D., University of British Columbia, Canada	**$287,500**
APOE Consortium: Role of APOE Isoforms in Immune Responses in a Model of Tauopathy David M. Holtzman, M.D., Washington University School of Medicine in St. Louis	**$345,000**
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**
Sex Matters: Understanding the Influence of Sex and Apolipoprotein E (APOE) Genotype on Hippocampal Plasticity and Cognition Liisa Galea, Ph.D., Centre for Addiction and Mental Health, Canada	**$170,200**
STUDIES OF THE IMMUNE RESPONSE IN ALZHEIMER'S DISEASE	
Neuroimmune Consortium: Biomarker Tool Development Jacob M. Hooker, Ph.D., Massachusetts General Hospital; Harvard Medical School	**$287,500**
Neuroimmune Consortium: Understanding the Consequences of Noncoding Alzheimer's Disease Risk Alleles on Microglia Function Beth Stevens, Ph.D., Boston Children's Hospital; Harvard Medical School; Broad Institute	**$300,000**
Neuroimmune Consortium: Assessing the Links Between the MS4A Risk Genes, Microglia and Alzheimer's Disease Sandeep Robert Datta, M.D., Ph.D., Harvard Medical School	**$250,000**
Neuroimmune Consortium: Investigation of Alzheimer's Disease Risk Alleles in Astrocytes—Focus on Cholesterol Transport and Microglia Interactions Shane A. Liddelow, Ph.D., New York University	**$115,000**

Project/Researcher	Distribution Amount
Neuroimmune Consortium: 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**
Neuroimmune Consortium: Leveraging Enhancer Landscapes to Decode Alzheimer's Disease Risk Alleles in Microglia Christopher K. Glass, M.D., Ph.D., University of California, San Diego	**$250,000**
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	**$167,637**
Systems Integration and Therapeutics Translation in Alzheimer's Disease Alison M. Goate, D.Phil., Icahn School of Medicine at Mount Sinai Edoardo Marcora, Ph.D., Icahn School of Medicine at Mount Sinai	**$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; Harvard Medical School	**$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; Harvard Medical School; Broad Institute Beth Stevens, Ph.D., Boston Children's Hospital; Harvard Medical School; Broad Institute	**$171,207**
Contributions of IL-34 Signaling to Microglial Function and Alzheimer's Pathology in Mice Staci D. Bilbo, Ph.D., Duke University	**$194,253**
Microglial-Specific INPP5D Knockdown Modulates Behavior, Amyloidosis and Tauopathy in Alzheimer's Mouse Models Samuel E. Gandy, M.D., Ph.D., Icahn School of Medicine at Mount Sinai Michelle E. Ehrlich, M.D., Icahn School of Medicine at Mount Sinai	**$217,327**
Human Brain CD33 Ligand, Receptor Protein Tyrosine Phosphatase Zeta (RPTPζ)S3L, Limits Microglial Phagocytosis and Contributes to Alzheimer's Disease Progression Ronald L. Schnaar, Ph.D., The Johns Hopkins University School of Medicine Tong Li, Ph.D., The Johns Hopkins University School of Medicine	**$201,250**
The Role of Astrocyte-Derived Toxic Lipids Mediating Degeneration in Alzheimer's Disease Shane A. Liddelow, Ph.D., New York University	**$174,883**
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**
Prenatal Inflammation Effects on Blood-Brain Barrier Function and Alzheimer's Disease-Related Pathologies Across the Lifespan Alexandre Bonnin, Ph.D., University of Southern California	**$201,250**
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	**$172,500**
Targeting a Master Innate Immune Adaptor Molecule in Alzheimer's Disease John R. Lukens, Ph.D., University of Virginia	**$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**
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 Microglia in Degradation and Trimming of Alzheimer's Amyloid Beta Frederick R. Maxfield, Ph.D., Weill Cornell Medical College	**$172,500**
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**
Neuroimmune Connectome Perturbations in Alzheimer's Disease Francisco J. Quintana, Ph.D., Brigham and Women's Hospital; Harvard Medical School	**$201,250**
STUDIES OF ALTERNATIVE NEURODEGENERATIVE PATHWAYS	
Brain Entry and Exit Consortium: Crosstalk of Central Nervous System Barriers and Clearance Routes in Homeostasis and Alzheimer's Disease Jonathan Kipnis, Ph.D., Washington University School of Medicine in St. Louis	**$345,000**
Brain Entry and Exit Consortium: Biochemical and Functional Analysis of Cerebrospinal Fluid and Lymph Following Changes in Brain Fluid Dynamics Laura Santambrogio, M.D., Ph.D., Weill Cornell Medical College	**$287,500**

Project/Researcher	Distribution Amount
Brain Entry and Exit Consortium: Identifying the Blood-Brain Barrier Changes During Alzheimer's Disease Richard Daneman, Ph.D., University of California, San Diego	**$287,500**
Brain Entry and Exit Consortium: Central Nervous System Fluid Homeostasis and Waste Clearance in Alzheimer's Disease Characterized by MRI Helene Benveniste, M.D., Ph.D., Yale School of Medicine Allen R. Tannenbaum, Ph.D., State University of New York at Stony Brook	**$286,404**
Neuroinflammation Contributions to Alzheimer's Disease: Role of the Choroid Plexus Maria K. Lehtinen, Ph.D., Boston Children's Hospital; Harvard Medical School Liisa Myllykangas, M.D., Ph.D., University of Helsinki, Finland	**$172,500**
Turning Up Mitophagy to Blunt Alzheimer's Tau Pathologies Evandro F. Fang, Ph.D., Akershus University Hospital, Norway	**$201,250**
Immunotherapies Targeting the Microbiota to Prevent Cognitive Decline in Alzheimer's Disease Gerald B. Pier, Ph.D., Brigham and Women's Hospital; Harvard Medical School Colette Cywes-Bentley, Ph.D., Brigham and Women's Hospital; Harvard Medical School Cynthia A. Lemere, Ph.D., Brigham and Women's Hospital; Harvard Medical School	**$183,562**
Targeting the Microbiome and Innate Immunity in Alzheimer's Disease Howard L. Weiner, M.D., Brigham and Women's Hospital; Harvard Medical School Laura M. Cox, Ph.D., Brigham and Women's Hospital; Harvard Medical School	**$201,250**
Stress and Neurovascular-Immune Networks in Alzheimer's Disease Scott J. Russo, Ph.D., Icahn School of Medicine at Mount Sinai Wolfram C. Poller, M.D., Icahn School of Medicine at Mount Sinai	**$172,500**
Neuroprotective Effects of the Exercise Hormone Irisin in Alzheimer's Disease Se Hoon Choi, Ph.D., Massachusetts General Hospital; Harvard Medical School Christiane Wrann, D.V.M., Ph.D., Massachusetts General Hospital; Harvard Medical School	**$345,000**
Circadian Perturbations of the Vasculome and Microgliome in Alzheimer's Disease Eng H. Lo, Ph.D., Massachusetts General Hospital; Harvard Medical School	**$200,417**
Harnessing Meningeal Lymphatics and Immunity to Alleviate APOE4-Induced Brain Dysfunction Sandro Da Mesquita, Ph.D., Mayo Clinic, Jacksonville	**$172,500**
Evaluating TMEM106B Accumulation in Alzheimer's Disease Leonard Petrucelli, Ph.D., Mayo Clinic, Jacksonville Casey N. Cook, Ph.D., Mayo Clinic, Jacksonville	**$201,250**
Alzheimer's Disease Pathophysiology Alters the Level of Electrical and Chemical Synapse Coupling in the Network of GABAergic PV+ Interneurons Early in Disease Course Srdjan D. Antic, M.D., University of Connecticut Health Center Riqiang Yan, Ph.D., University of Connecticut Health Center	**$230,000**
Cellular Vulnerability to Aging in Alzheimer's Disease Mathieu Bourdenx, Ph.D., University College London, England Karen E. Duff, Ph.D., University College London, England	**$230,000**
Gut Microbiota, Endothelial Dysfunction and Tau-Mediated Cognitive Impairment Giuseppe Faraco, M.D., Ph.D., Weill Cornell Medical College Costantino Iadecola, M.D., Weill Cornell Medical College	**$172,500**
Temporal Relationships Between Gut Dysbiosis and Microglia Cell Activation Following Antibiotic Treatment Sangram S. Sisodia, Ph.D., University of Chicago	**$229,033**
Role of the Circulating Exerkine GPLD1 in Ameliorating Alzheimer's Disease Pathology Saul Villeda, B.S., Ph.D., University of California, San Francisco	**$201,250**
Understanding How Human Brain Vascular Cells Mediate Genetic Risk for Alzheimer's Disease Andrew Yang, Ph.D., University of California, San Francisco	**$201,250**
Identifying the Sex-Specific Roles of the Gut Microbiome-Brain Axis in a Mouse Model of Amyloid Beta Amyloidosis Sangram S. Sisodia, Ph.D., University of Chicago	**$210,871**

Project/Researcher	Distribution Amount
DRUG DISCOVERY	
DRUG SCREENING AND LEAD DRUG EVALUATION PROJECTS	
Alzheimer's Disease Drug Discovery and Development Consortium: Blocking Synaptotoxicity in Alzheimer's Three-Dimensional Models Weiming Xia, Ph.D., Boston University	**$197,500**
Alzheimer's Disease Drug Discovery and Development Consortium: Modulating CD33 Function and Neuroinflammation as a Therapeutic Approach for Alzheimer's Disease Ana Griciuc, Ph.D., Massachusetts General Hospital; Harvard Medical School	**$197,500**
Alzheimer's Disease Drug Discovery and Development Consortium: 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; Weill Cornell Medicine	**$225,000**
Alzheimer's Disease Drug Discovery and Development Consortium: High-Throughput Drug Screening for Alzheimer's Disease Using Three-Dimensional Human Neural Culture Systems Doo Yeon Kim, Ph.D., Massachusetts General Hospital; Harvard Medical School Luisa Quinti, Ph.D., Massachusetts General Hospital; Harvard Medical School	**$230,590**
Stimulating Synaptic Proteasome Activity for the Treatment of Alzheimer's Disease Hermann Steller, Ph.D., The Rockefeller University	**$172,500**
A Transcriptional Rejuvenation Signature for Alzheimer's Disease Tony Wyss-Coray, Ph.D., Stanford University	**$172,500**
Identification of CD33 Antagonists Subhash Sinha, Ph.D., Weill Cornell Medicine	**$172,500**
Development of Human cGAS Inhibitors to Treat Alzheimer's Disease Li Gan, Ph.D., Weill Cornell Medicine Subhash Sinha, Ph.D., Weill Cornell Medicine	**$250,000**
Small Molecule Activators of PLC-gamma-2 as Novel Therapeutics for Alzheimer's Disease Qisheng Zhang, Ph.D., University of North Carolina at Chapel Hill John Sondek, Ph.D., University of North Carolina at Chapel Hill Kenneth Pearce, Ph.D., University of North Carolina at Chapel Hill	**$172,500**
DRUG DELIVERY AND ENABLING TECHNOLOGIES	
Novel Entry Routes for Therapeutic Biologicals to the Brain Maarten Dewilde, Ph.D., KU Leuven, Belgium Bart De Strooper, M.D., Ph.D., KU Leuven, Belgium; University College London, England	**$172,500**
PRECLINICAL AND CLINICAL DRUG DEVELOPMENT	
PRECLINICAL DRUG DEVELOPMENT	
Combined Hormone Therapy as a Novel Treatment for Alzheimer's Disease in the Face of a Metabolic Challenge: Influence of Sex and Genotype Liisa Galea, Ph.D., Centre for Addiction and Mental Health, Canada Annie Ciernia, Ph.D., University of British Columbia, Canada	**$201,250**
CLINICAL TRIAL DESIGN	
Application of Machine Learning Methods in Alzheimer's Disease Clinical Trials Ali Ezzati, M.D., Albert Einstein College of Medicine Richard B. Lipton, M.D., Albert Einstein College of Medicine	**$100,000**
OTHER	
SCIENTIFIC MEETINGS AND SUPPORT	
Genes to Therapies™ (G2T), Alzheimer's Disease Drug Discovery and Development (AD4) and General Scientific Support Wilma Wasco, Ph.D., Massachusetts General Hospital; Harvard Medical School	**$177,675**
Scientific Meeting Support	**$93,489**

Foundational Research

GENETIC RISK FACTORS

The Alzheimer's Genome Project™

Rudolph E. Tanzi, Ph.D., *Massachusetts General Hospital; Harvard Medical School*

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, making it one of the largest datasets of AD WGS/WES data in the world. We will analyze AD-associated genomic variants predicted to have functional consequences in our various three-dimensional cell culture models (Alzheimer's in a Dish™). The most promising AD-associated functional variants also are shared with Cure Alzheimer's Fund investigators and the greater AD research community. Our overarching goal not only is to elucidate the genetic basis of AD to better understand and treat this disease, but also to better predict AD risk, age at onset, resilience to AD, and the sex- and ethnicity-specific effects on AD risk, onset age and resilience.

BIOMARKERS, DIAGNOSTICS, AND STUDIES OF RISK AND RESILIENCE

Characterization of Molecular Biomarker Profiles Throughout the Pathobiological Continuum

Krista L. Moulder, Ph.D., *Washington University School of Medicine in St. Louis*

Recent evidence suggests that molecular markers of Alzheimer's disease may differ by race, but existing studies have been limited by small sample sizes. The Alzheimer's Disease Research Centers at Washington University School of Medicine in St. Louis and Emory University have embarked on a collaboration to share spinal fluid and plasma samples from well-characterized African American and non-Hispanic white research participants between their two centers. Such sharing will allow for combined larger sample sizes and, hence, the ability to ask more detailed scientific questions. Washington University will focus on the ability of spinal fluid and plasma markers to predict the transition from normal memory and thinking to symptomatic disease. Emory University will focus on characterizing the pattern of protein expression in spinal fluid and plasma samples from individuals across a range of disease severity. These complementary approaches will help to provide insight into whether racial factors could impact treatment and prevention strategies for Alzheimer's disease.

Neurobiological Basis of Cognitive Impairment in African Americans: Deep Phenotyping of Older African Americans at Risk of Dementia—The Dementia (in) African American Population Phenotyping (for) Potential Elevated Risk (DAAPPER) Study

Henry L. Paulson, M.D., Ph.D., *University of Michigan*
Bruno Giordani, Ph.D., *University of Michigan*
Benjamin M. Hampstead, Ph.D., ABPP/CN, *University of Michigan*

This proposal will leverage activities of the Michigan Alzheimer's Disease Center to explore the neurobiological basis of dementia in African Americans, an understudied population about which we still lack fundamental knowledge regarding biomarkers of cognitive impairment. Through these studies, we hope to determine whether vascular compromise and increased amyloid and/or tau deposition have unique or synergistic effects on cognition. This information may be crucial in designing new pharmacological and nonpharmacological interventions, and in providing important information about targeted enrollment for such interventions.

Harnessing Big Data to Understand Alzheimer's Disease Risk

Brad A. Racette, M.D., *Barrow Neurological Institute*
Susan Searles Nielsen, Ph.D., *Washington University School of Medicine in St. Louis*
Alejandra Camacho-Soto, M.D., M.P.H.S., *Washington University School of Medicine in St. Louis*

In our preliminary analyses, we have demonstrated that patients taking prescription medications with two specific mechanisms of action, xanthine dehydrogenase/oxidase blockers and tubulin alpha/beta chain blockers, important in treating both gout and hypertension, may be associated with a lower risk of Alzheimer's disease (AD) and other neurodegenerative diseases. This suggests that there may be common neurodegenerative pathways across AD, Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS). We also have preliminary evidence that meningitis may increase the risk of AD, although this may be due in part to those with meningitis accessing the health care system with greater frequency. The next steps in this project are to explore individual medication associations with AD risk and to obtain additional data from Medicare to determine whether the risk of AD in relation to meningitis is diminished as we consider meningitis occurring at longer intervals prior to AD diagnosis.

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

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Lars Bertram, M.D., *University of Lübeck, Germany*

At the time of a clinical diagnosis of Alzheimer's disease (AD), the underlying disease process already has evolved in the affected individuals for often more than a decade and led to irrecoverable brain damage. Without reliable predisease biomarkers, the development and successful application of effective treatment or preventive strategies thus is severely hampered. However, the identification of predictive biomarkers requires examining large groups of initially healthy individuals and following them over a long time to determine who eventually developed AD and who did not. Such cohort studies are very difficult and laborious to conduct, especially for a late-onset disease such as AD. In this Lill project, EPIC4AD, we will overcome this limitation by utilizing blood samples of participants of one of the largest cohort studies worldwide for systematic biomarker identification, i.e., the EPIC study (European Prospective Investigation into Cancer and Nutrition). For each of the more than 500,000 initially healthy participants, blood samples were collected and stored at baseline. During the more than 20 years of follow-up, several thousand EPIC participants eventually have been diagnosed with AD. To identify novel predisease biomarkers, we will utilize a recently developed high-throughput technology (SomaScan assay) to determine the concentrations of approximately 5,000 different proteins in blood samples from about 1,000 AD cases and about 5,000 healthy control individuals. The proteomic data will be combined with genetic as well as lifestyle and medical data, along with the measurement of existing established AD biomarkers, to develop disease prediction models using artificial intelligence. Given the enormous size of the EPIC cohort combined with the large number of proteins assayed simultaneously in one experiment, our study is in the unique position to advance the field of AD biomarker research beyond its current state, and will set the stage for finally being able to develop novel early detection/early prevention strategies against this devastating disease.

Cerebrospinal Fluid Neuroinflammatory Signature in Alzheimer's Disease and Related Proteopathies

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Stephan A. Kaeser, Ph.D., *University of Tübingen, Germany*
Stefan Lichtenthaler, Ph.D., *German Center for Neurodegenerative Diseases (DZNE); Technische Universität München (TUM)*

It is now well-accepted that neuroinflammation contributes significantly to the pathogenesis of Alzheimer´s disease (AD) and related cerebral proteopathies. However, little is known about how brain inflammatory states are reflected by molecular biomarker changes in bodily fluids. We have identified a panel of 25 proteins in cerebrospinal fluid (CSF) that may capture the neuroinflammatory states in AD patients. In this project, we aim to validate this protein panel and test the panel in well-characterized AD patient cohorts. The ultimate goal is to develop a multiplex immunoassay for these CSF proteins to assess human neuroinflammatory brain states in AD and related proteopathies.

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

P. Murali Doraiswamy, M.B.B.S., *Duke University School of Medicine*

The promise of personalized medicine includes understanding sex differences in health and disease. It has been well documented that women have a higher risk of developing Alzheimer's disease compared with men, but this is not simply because women on average live to older age than men. This proposal capitalizes on the 70 years of health-related data from the Framingham Heart Study, combined with traditional and machine learning analytic methods, to determine what combination of factors can explain sex differences in Alzheimer's disease risk and progression.

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

Modeling Alzheimer's Disease by Direct Neuronal Reprogramming of Patient Fibroblasts into Neuronal Subtypes

Andrew S. Yoo, Ph.D., *Washington University School of Medicine in St. Louis*

The risk of developing Alzheimer's disease (AD) increases with age, and identifying the cellular processes that occur in aged neurons will provide significant insights into the pathogenesis of AD. The ability to derive and grow human neurons that mimic neurons of elderly individuals will offer experimental tools to investigate cellular properties in aged human neurons that contribute to AD pathology. We previously have demonstrated the feasibility of generating human neurons by ectopically expressing small RNA molecules termed microRNAs in dermal fibroblasts and altering cells' "fate" directly to neurons. This conversion process occurs through microRNAs' function to erase fibroblasts' identity and orchestrate their identity transition to neurons. The overall goal of the Cure Alzheimer's Fund grant was to implement the microRNA-mediated direct conversion to model AD using patient-derived neurons by generating the types of human neurons affected in AD. From this project, we learned that human neurons generated through the direct neuronal conversion retained the age information stored in the starting fibroblasts, resulting in the generation of human neurons that reflect fibroblast donors' age. This age maintenance of converted neurons was an integral component of recapitulating cellular phenotypes associated with adult-onset neurodegenerative disorders, including Huntington's disease. The Cure Alzheimer's Fund grant offered opportunities to refine the cellular reprogramming approaches to generate different types of human neurons affected in AD. Our current research goal is to use reprogramming approaches to model AD from the patient samples and investigate AD-associated phenotypes in various types of human neurons.

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; Harvard Medical School*

Joseph Park, Ph.D., *Massachusetts General Hospital; Harvard Medical School*

Rudolph E. Tanzi, Ph.D., *Massachusetts General Hospital; Harvard Medical School*

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.

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 T. Hyman, M.D., Ph.D., *Massachusetts General Hospital; Harvard Medical School*

An astonishing discovery of how to convert skin cells into other kinds of cells—including brain cells—earned Dr. Shinya Yamanaka the Nobel Prize in 2012 and already has opened extraordinary new capabilities in science. Applied to Alzheimer's disease, it has the potential to revolutionize how we do experiments. Right now, we rely on examining brain tissue of patients who have died of the disease to understand the molecular changes that occur, but the promise of Dr. Yamanaka's discovery is that we could use a little piece of skin—from a living patient—instead. The major barrier to doing this is that we do not know whether the "brain" cells that can be made in a few weeks from a piece of skin actually act like the cells from a brain of a person who has been alive for 70 or 80 years. We propose to create a bank of skin cells taken from the same people who now donate brain tissue at autopsy to directly compare the two, and to make this resource available to the dozens (hundreds) of labs that have developed specialized assays in which comparison of the two different kinds of "brain" cells would be valuable. Our own studies will be directed to understanding whether there are different molecular characteristics in "brain" cells derived from the skin in patients whose course of disease was more aggressive—or more benign—to try to develop methods to understand this dichotomy.

Genes to Therapies™ (G2T) Research Models and Materials

Taconic Biosciences

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

CIRCUITS: A Unified Approach to Actionable Alzheimer's Disease Signatures

Winston Hide, Ph.D., *Beth Israel Deaconess Medical Center; Harvard Medical School*

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 Alzheimer's disease progression. 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 each 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.

CIRCUITS: 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 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 machine learning models that predict how mutations in the human genome influence

different cell types. These models identified a set of mutations that seem to selectively impact blood immune cell types. Second, we conducted a set of experiments in which we synthesized hundreds of fragments of the human genome that are associated with Alzheimer's disease, and then studied them in the context of the mouse brain and immune cells. These candidate genome fragments come from experiments conducted across the entire CIRCUITS consortium. Thus far, our results suggest that mutations that impact that function of the PU.1 gene influence Alzheimer's disease predisposition.

CIRCUITS: 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. 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 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 (DNAm) and microRNA (miRNA) measurements in blood at a second timepoint. This will effectively allow us not only to analyze the levels of these two types of molecular markers, but also to 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.

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

Rudolf Jaenisch, M.D., *Whitehead Institute; Massachusetts Institute of Technology*

Joseph R. Ecker, Ph.D., *Salk Institute for Biological Studies*

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 neuronal cells derived from induced pluripotent stem cells, and investigating the role of microglia, the immune cells of the brain, on AD initiation and progression.

Translational Research

STUDIES OF NOVEL ALZHEIMER'S DISEASE GENES

Dissecting the Modulatory Roles of Interleukin-17 Receptor D in Alzheimer's Disease

Jun Huh, Ph.D., *Harvard Medical School*

Alzheimer's disease (AD) is the most common type of dementia, affecting millions of people in the United States. Despite extensive efforts, we lack treatment or preventive options for AD. Recently, studies have suggested that the adaptive immune system may be an important component of this disease; however, very little is known about how immune cells contribute to the onset and progression of AD. Our proposal is aimed at examining the contributing roles of interleukin-17a (IL-17a), a peripherally driven cytokine affecting brain function and inducing neurological phenotypes, and its receptor IL-17 receptor D (IL-17RD) in the pathogenesis of AD. Importantly, polymorphic mutations in the IL-17RD associated with AD have been recently identified. Furthermore, our preliminary results suggest that IL-17a exacerbates AD-associated phenotypes in two different models that depend on amyloid beta. Thus, the successful completion of our proposed work will provide mechanistic insights into the roles of IL-17a and IL-17RD in AD, and may offer new solutions to suppress neurodegeneration and delay the irreversible cognitive decline of AD.

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

Rik van der Kant, Ph.D., *Amsterdam University Medical Centers, The Netherlands*

The cause of Alzheimer's disease remains unknown. However, thanks to the progress of genomic-wide association analysis, where genetic sequences are studied in big populations and related to the incidence of diseases, new genetic risk factors and genetic protective factors have been identified. Among those, it recently was shown that a variant in the gene coding for the protein called Phospholipase C-gamma-2 (PLCγ2) was associated with a diminished risk of developing late-onset Alzheimer's disease, the most common form of age-related neurodegenerative disorder. Interestingly, this variant of PLCγ2 also was associated with longevity. However, the mechanism of protection remains unknown, limiting our capacity to find drugs able to mimic this effect.

In this project, using the gene editing technology CRISPR/Cas9, we have generated a set of induced human pluripotent stem cell (iPSC) lines that possess identical genes but differ in the PLCγ2 gene, including the protective variant. From these cell lines, we will generate different human cell types, such as neurons and microglia, the immune cells from the brain, that are the ones that produce the PLCγ2 protein. We then will be able to study the response to different stimuli in cell cultures and identify a distinctive effect from this variant. We will use this knowledge to design an assay to search for drugs that reproduce this protective effect and therefore may be potential treatments for Alzheimer's disease.

ABCA7 Loss of Function in Aging and Alzheimer's Disease

Takahisa Kanekiyo, M.D., Ph.D., *Mayo Clinic, Jacksonville*

Alzheimer's disease (AD) is the most common cause of memory loss or dementia in the older 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 lipid metabolism and microglia-related inflammation play a critical role in the pathogenic mechanisms. Thus, a better understanding of lipid homeostasis in microglia 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 coded by one of the strongest AD risk genes, causes abnormal phenotypes in microglia as well as altered mitochondria properties. We also found that an AD risk ABCA7-A696S mutation suppresses microglial activation and exacerbates neuronal damage in amyloid model mice. Since ABCA7 is abundantly expressed in microglia in the brain, our overall goal is to explore the potential impacts of ABCA7 loss of function in microglia on lipid metabolism, mitochondrial functions and AD-related phenotypes using newly generated ABCA7 risk gene knock-in mice and microglia-specific ABCA7 knock-out mice

with or without the background of amyloid pathology. We also aim to identify novel cell-specific pathways through nontargeted approaches. Therefore, our study will give us unique opportunities to determine the roles of microglial ABCA7 in both physiological and pathological conditions, and to identify novel targets to develop effective therapeutic interventions for age-related cognitive decline and AD.

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

Giuseppina Tesco, M.D., Ph.D., *Tufts University School of Medicine*

We identified a novel genetic mutation in a gene called GGA3. This mutation increases the risk of developing Alzheimer's disease (AD). GGA3 is essential for the transport of BACE1, a key enzyme in AD, in neurons. We discovered that the absence of GGA3 is toxic for neurons. More importantly, this AD-linked GGA3 mutation produces a toxic effect similar to the one observed when GGA3 is completely absent in neurons. Our data indicate that this new genetic mutation makes neurons sick because GGA3 has lost its ability to transport BACE1. These findings are important for the development of personalized therapies for subjects carrying this specific mutation.

Single Nucleus RNA Sequencing Analysis of ACE1 R1284Q Knock-in Mice

Robert Vassar, Ph.D., *Northwestern University Feinberg School of Medicine*
David M. Gate, Ph.D., *Northwestern University Feinberg School of Medicine*
Leah K. Cuddy, Ph.D., *Northwestern University Feinberg School of Medicine*

The gene for angiotensin converting enzyme (ACE1) was recently shown to be a genetic risk factor for Alzheimer's disease (AD). Our collaborators, Dr. Rudolph Tanzi and his group, discovered mutations in the ACE1 gene that are associated with AD in families. One of these mutations was introduced into mice by genetic "knock-in" (KI) technology. We analyzed the effects of the ACE1 KI mutation on the brain and its functions, and the memory performance of mice. We discovered that the ACE1 KI mutation caused the hippocampus, a part of the brain that is important for memory, to degenerate in an age- and sex-associated manner, in that females were affected more severely than males, like in human AD. Moreover, the ACE1 KI showed impaired memory performance and electrical activity in the brain. Brain inflammation also was increased in the ACE1 KI mice. Drugs that block the ACE1 pathway were able to prevent the degeneration of the hippocampus in ACE1 KI mice. Finally, when crossed to mice that develop the AD hallmark amyloid plaque pathology, hippocampus degeneration was accelerated in ACE1 KI mice. Our results strongly suggest that the ACE1 pathway in the brain plays an important role in AD. However, very little is known about the ACE1 pathway in the central nervous system. In this project, we will use a technique called single nucleus RNA sequencing, an unbiased systems biology approach, to determine the genes that are turned on or turned off in different cell types of the hippocampus during early, middle and late stages of degeneration in ACE1 KI mice compared with wild-type mice. These data will allow us to define the ACE1 pathway in the brain that is important for the degeneration of the hippocampus caused by the ACE1 KI mutation—information we anticipate will be valuable for the design of therapies to block brain degeneration in AD.

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

Alexandra C. 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.

Exploring the Therapeutic Potential of Clusterin in a Preclinical Model of Alzheimer's Disease

Alban Gaultier, Ph.D., *University of Virginia*

This proposal is aimed at exploring a protein called Clusterin, a significant risk factor for Alzheimer's disease (AD) that is highly expressed in the brain of patients with this condition. Our data presented here suggest that Clusterin inhibits differentiation of cells that can repair damage of the protective neuronal sheet called myelin, leading to our hypothesis that Clusterin overexpression directly contributes to Alzheimer's disease. Our research proposed in this application could offer new solutions to promote neuroprotection and delay the irreversible cognitive decline in the AD brain.

STUDIES OF AMYLOID PRECURSOR PROTEIN (APP) AND AMYLOID BETA

Structural Mimicry in Microbial and Antimicrobial Amyloids Connected to Neurodegenerative Diseases

Meytal Landau, B. Pharm., M.S.C., Ph.D., *Technion, Israel Institute of Technology; Deutsches Elektronen-Synchrotron (DESY)*

Mounting evidence indicates the causal relationship between microbes and neurodegenerative diseases via several potential pathways; some involve amyloids, proteins that self-assemble into unique supramolecular fibers. A remarkable variety of microbial species of human pathogens and microbiome generates significant quantities of secreted amyloids utilized to facilitate multicellular and pathogenic behaviors. This project will explicitly evaluate the hypothesis that microbial amyloids could trigger human amyloids, in a pathological process reminiscent of diseases transmittable by prion-contaminated meat. In addition, we will clarify, at the protein structure level, the connection between amyloids and antimicrobial and immunomodulating activities, underlining a potential role of human amyloids reacting to microbial infections as part of neuroimmunity, which can, after many years, turn pathogenic to the brain. Owing to the revolution in resolution and advances in correlative cryogenic light and electron microscopy, we foresee high-resolution (nanometric to atomic) visualization of brain sections of neurodegeneration patients with a medical history of severe infections or abnormal microbiome. Such information would enable the development of prevention and therapeutic strategies for neurodegeneration.

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

Raja Bhattacharyya, Ph.D., *Massachusetts General Hospital; Harvard Medical School*
Rudolph E. Tanzi, Ph.D., *Massachusetts General Hospital; Harvard Medical School*

Only 10% of the amyloid precursor protein (APP) undergoes amyloidogenic processing to generate amyloid beta, 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 amyloid beta generation. We have 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 amyloid beta generation in a 3D cellular model of AD. MAMs are implicated in early- and late-onset AD, but their roles are largely unknown. The primary goal of this proposal is to demonstrate that small molecule depalmitoylating agents, such as hydroxylamine and its derivatives or inhibitors of MAM-resident ACAT1 enzymes, reduce amyloid beta 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.

Secreted Frizzled Related Protein 1 (SFRP1) as a Therapeutic Target and Diagnostic/Prognostic Factor in Alzheimer's Disease

Paola Bovolenta, Ph.D., *Universidad Autónoma de Madrid, Spain*

Patients with Alzheimer's disease (AD) present with a disease-dependent increase in the brain expression of a small glial-derived secreted protein named SFRP1, which interacts with harmful amyloid products (among the culprit of the pathology) and downregulates an enzyme that prevents their generation. Neutralization of SFRP1 activity in mice counteracts several of the pathological traits of the disease when administered at early stages of the disease. We have now begun to explore further the potential of immunoglobulin-based SFRP1 neutralization as a therapeutic strategy for AD. Our studies so far indicate that the treatment does not produce evident side effects even after three months of treatment. It also shows effectiveness when the animals with a consolidated pathology are treated. In contrast to this encouraging data, we have determined that plasma levels of SFRP1 cannot be used as a reliable diagnostic factor for AD, as we had initially postulated.

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

Caleb E. Finch, Ph.D., *University of Southern California*
Michael A. 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. We hypothesized that AirPoll impairs neuron replacement in adults, which we confirmed in experiments with mice exposed to AirPoll, which impaired proliferation of neural stem cells (NSC). Maintenance of NSC in older ages is hypothesized as critical for resistance to AD-related pathology and cognitive deficits.

This CureAlz project investigates the molecular pathways of NSC impairments by AirPoll and their relation to brain amyloid peptides believed to drive AD. In Year 1 of this project, we showed that AirPoll damage to NSC is attenuated by an anti-amyloid drug developed by CureAlz investigators and with CureAlz support, BPN-15606. Specifically, single cell studies of messenger RNA show that BPN-15606 attenuates AirPoll impairment of neurogenesis in adult brains. These pathways will be analyzed in Year 2 for targets that may protect against AD risk from AirPoll. These studies are the first to examine NSC aging at the single-cell level for modulation by AirPoll, and for environmental interactions with amyloid peptides. The findings could extend benefits of BPN-15606 and other anti-amyloid drugs to lowering environmental risks of AD.

Moreover, we showed that amyloid beta peptides, amyloid beta 40 and amyloid beta 42, increase sharply after brain maturation in normal mice. This finding parallels the exponential midlife increase of amyloid beta 40 and amyloid beta 42 in aging humans in a rigorous but neglected study by Fukumoto et al., published in the American Journal of Pathology in 2004. Normal brain aging in mice and humans thus increases amyloid beta peptides, which may predispose humans to AD.

STUDIES OF TAU

Alzheimer's Disease Tau Consortium: How Do Soluble Tau Species Replicate

Bradley T. Hyman, M.D., Ph.D., *Massachusetts General Hospital; Harvard Medical School*

The tau molecule is normally inside neurons and is attached to the cell's skeleton. Yet in Alzheimer's disease, tau becomes misfolded, detaches from the cell's skeleton, and aggregates or clumps together to form a large skein of twisted filaments within the cell called neurofibrillary tangles. When this happens in one neuron, it is probably a sign of stress. But in Alzheimer's disease, the surrounding neurons to the first one, and those connected to it even far away in the brain, tend to also develop misfolded tau and neurofibrillary tangles. We propose to use new microscopic techniques to image tau when it misfolds and begins the process of detaching from the cell skeleton and aggregating in the cell body, as well as examining what kinds of tau can travel from cell to cell. We hope that learning the details of this process will teach us how to keep tau from spreading across the brain.

Alzheimer's Disease Tau Consortium: The Role of Amyloid Beta-Induced Membrane Damage in Tau Pathology

Katherine R. Sadleir, Ph.D., *Northwestern University Feinberg School of Medicine*

Robert J. Vassar, Ph.D., *Northwestern University Feinberg School of Medicine*

Two protein pathologies occur in Alzheimer's disease brains—accumulation of amyloid beta in extracellular plaques and formation of tau neurofibrillary tangles inside neurons. After amyloid plaques build up for many years, tau pathology takes off and leads to neuron death and memory loss. The focus of our project is to understand how amyloid may cause tau tangles, with the goal of blocking this process for therapeutic purposes. Structures around amyloid plaques called dystrophic neurites (DNs) consist of swollen dysfunctional axons that are filled with vesicles and proteins that are not being properly transported. We think that contact with amyloid plaques, especially areas where the plaque is growing, damages the membrane of neurons and causes uncontrolled influx of calcium ions, which is very disruptive to neuronal function and causes the formation of DNs. Calcium changes the activity of enzymes called kinases and phosphatases, which add and remove phosphate groups, respectively, to other proteins, such as tau, potentially altering their shape, function and ability to interact with other proteins. When tau is excessively phosphorylated, it self-aggregates to form tau tangles. Therefore, we hypothesize that DNs that surround plaques contain high calcium levels and become sites where tau tangles may form, which then may spread to other parts of the neuron or other cells. To study this process, we will increase or decrease the amount of actively growing amyloid fibrils in the brains of mice that are genetically engineered to develop amyloid plaques. We will determine whether increased amyloid fibril growth causes greater DN formation, tau phosphorylation and tau spreading, while decreased fibril growth reduces these outcomes. We also will increase the expression of a protein called annexin A6 that repairs damaged cell membranes, which will block the injury caused by growing amyloid fibrils and decrease DN formation, tau phosphorylation and tau spreading. We anticipate that annexin A6 could be used to prevent amyloid plaques from causing membrane damage and creating the tau tangles that lead to neuron death in the brain. We also will block specific kinases in the brain that can phosphorylate tau to inhibit tau spreading.

Alzheimer's Disease Tau Consortium: Impact of Tau Mutations and Amyloid Beta on Tau Post-Translational Modifications and Conformation

Karen E. Duff, Ph.D., *University College London, England*

Alzheimer's disease (AD) is characterized by the buildup (accumulation) in the brain of two types of abnormal proteins—amyloid beta, in the form of amyloid plaques, and tau, in the form of neurofibrillary tangles. The accumulation of abnormal tau is thought to cause the death of brain cells directly, but the earliest events that lead to tau accumulation are not well understood. Amyloid beta accumulation is believed to occur before tau, but how the two proteins interact is also not well understood. Many cell and animal models have been created to examine these events, but the data coming from them does not truly represent what happens in the human brain as the models make too much protein too quickly, and it is often not of the type found in the human AD brain. These shortcomings could mislead us on what really happens in the earliest stages of the disease and prevent us from creating the right drugs to prevent the disease from taking off. We have recently developed two sets of tools that can be used to explore the earliest stages of tau and amyloid beta accumulation. The first set of tools are several types of mice that have had their DNA altered so they develop tau pathology (with and without amyloid plaques.) The second is a unique human brain cell model that develops very early tau pathology. Our aims and objectives are to use both models to identify the earliest events that lead to cell dysfunction associated with tau pathology, and examine how the amyloid and tau pathologies interact and drive the disease.

Alzheimer's Disease Tau Consortium: Deep Mass Spectrometry Profiling of Tau Aggregates in Alzheimer's Disease and Other Tauopathies

Henrik Zetterberg, M.D., Ph.D., *University of Gothenburg, Sweden*
Gunnar Brinkmalm, Ph.D., *University of Gothenburg, Sweden*

This proposal details in-depth work to find links between the two major brain changes in Alzheimer's disease: extracellular clumps of a protein called amyloid beta, and intraneuronal accumulations of another protein called tau. Specifically, we will investigate whether tau accumulations associated with amyloid beta clumps are different in regard to their molecular composition compared with tau accumulations that form independently of amyloid beta clumps. The question has been partly addressed with older and less sensitive and specific methodology, but never in the detail we are proposing here. We believe this work is essential to improve our understanding of why tau accumulations develop in neurodegenerative dementias, and the work should give clues on novel biomarkers and therapeutics.

Alzheimer's Disease Tau Consortium: Role of VCP/p97 in Tau Prion Replication

Marc I. Diamond, M.D., *University of Texas Southwestern Medical Center*

Neurodegenerative diseases such as Alzheimer's appear to progress along brain networks. This idea is supported by experiments in cell and mouse models. We have proposed that pathological forms of the tau protein, which accumulates in Alzheimer's brain as neurofibrillary tangles, move between brain cells to spread pathology. This involves formation and release of tau "seeds," which are small assemblies that can serve as templates for their own replication in cells. Once they enter cells, it is unknown how tau aggregates can replicate. We used a system termed "proximity labeling" to identify cellular factors that interact with tau as it begins the amplification process. We identified valosin-containing protein (VCP/p97) as the main interactor. The gene coding for VCP was coincidentally identified as having mutations in a family of patients with dominantly inherited tauopathy, indicating that the VCP gene plays a causal role in disease. We have studied the VCP protein in detail using genetics and chemical inhibitors and learned that it regulates the replication of tau seeds (both up and down) immediately after they gain access to the cytoplasm. This indicates that VCP could be an excellent target to treat tau pathology. This proposal will expand our understanding of the molecular mechanisms that govern tau replication by identifying and characterizing which of the myriad VCP-interacting proteins allow it to dynamically regulate this process.

Characterization of Tau Pathology Heterogeneity Across the Alzheimer's Disease Spectrum

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Alzheimer's disease (AD) is the leading cause of dementia worldwide; we still have no cure. Plaques of amyloid proteins and neurofibrillary tangles of tau proteins are the two hallmarks of AD. The last decades of research have mainly focused on amyloid, with limited success in clinical

trials to date. It is also increasingly clear that the causes and manifestations of the disease are multifactorial. There is thus a crucial need to develop new therapeutic avenues, along with identifying robust markers that can track disease progression. The proposed project will characterize the clinical, anatomical and molecular heterogeneity of tau pathology to help identify novel drug targets and better predict individual disease trajectories. It will build upon a large, longitudinal, well-characterized cohort, ranging from preclinical older adults to dementia patients, for which the latest technical research advances are available. Using the latest positron emission tomography ligand to image tau directly in the brain, we will group participants according to their pattern of tau deposition to form different subtypes. We then will study in great detail which brain and molecular mechanisms underlie the accumulation of pathology and cognitive decline in the different tau subtypes. Characterizing the multifactorial markers underlying tau pathology will clarify mechanisms of AD pathogenesis to improve future treatment development and disease prognosis.

Properties of Tau in Posterior Cortical Atrophy

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Alzheimer's disease (AD) typically manifests first with short-term memory problems. However, in less common circumstances, AD can start with cognitive symptoms other than memory deficits. Posterior cortical atrophy (PCA) is a less common form of AD that starts with changes in visual perception and/or spatial awareness rather than memory loss. Although typical AD and PCA AD have different symptoms, both conditions have the same pathological hallmarks of amyloid beta plaques and tau-containing tangles. However, the tau proteins tend to accumulate in different regions of the brain in PCA AD compared with typical AD, which are the regions that serve visual functions (posterior cortical areas) or memory functions (e.g., the hippocampus), respectively. Why does this happen? We postulate that tau in PCA AD differs from tau in typical AD at the molecular level, perhaps leading it to be predisposed to affect the posterior cortical regions rather than the hippocampus. We and others have developed methods to study the characteristics of pathological tau in typical AD, but these techniques have not been applied to asking about tau in PCA AD. This project aims to examine three characteristics of tau in key brain regions in PCA AD compared with typical AD: 1) the distribution of pathological tau in different brain regions, 2) the ability of pathological tau to provide a template for further tau aggregation, and 3) the patterns of protein modifications on the tau protein. Investigating these characteristics of pathological tau in PCA AD will enhance our understanding of the disease-related changes in the brain that occur in PCA AD. This study also will provide deeper insights into the differences in tau at the molecular level in PCA AD compared with typical AD. Overall, the knowledge gained through this project will expand our understanding of the disease process that occurs in PCA AD, and may suggest new avenues for treatment if we uncover unique molecular aspects of tau in PCA AD that can be targeted.

RNA as a Determinant of Tau Seeding

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Tau protein forms highly ordered aggregates that underlie diverse neurodegenerative diseases termed "tauopathies." Each tauopathy is associated with unique tau assembly structures, but it is unknown how these distinct structures initially form. Our work suggests that RNA is a trigger for these conformational changes in tau. RNA plays different roles in cells. One is to encode proteins, but many other forms of RNA regulate gene expression and contribute to the structures of intracellular molecular machines. We have found that a class of small RNAs (less than 200 nucleotides, and not likely to encode proteins) is particularly potent at inducing tau to form structures that could play a role in disease. We also have found that the pathological tau assemblies of Alzheimer's disease are stabilized by binding RNA. This leads us to speculate that RNA plays a critical role in the initiation of pathology in Alzheimer's disease. In this proposal, we will determine what specific forms of RNA bind and convert tau to a pathological state, using cell models and tau extracted from human brain. We will test the idea that unique conformations of tau are initiated and sustained by specific RNA molecules.

Targeting Tauopathies with Antisense Oligonucleotides to Synaptogyrin-3

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"Tau pathology" is a major hallmark of Alzheimer's disease (AD) patient brains, and one that most closely correlates with the decline of cognition in the course of disease. During AD, 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 have 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 patient's 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.

Using Long-Read Sequencing to Investigate the MAPT Locus and Transcripts in Neurodegeneration

John Hardy, Ph.D., *University College London, England*

Tau tangles are the most prevalent pathology in neurodegenerative diseases such as Alzheimer's disease (AD) and frontotemporal dementia (FTD), and the tau (MAPT) region is genetically associated with these diseases. Large gaps in our knowledge remain regarding how neurodegenerative disease-linked tau mutations and MAPT variation promote tau aggregation and neurodegeneration. In European populations, the MAPT gene variation exists as two types, H1 (~90%) and H2 (~10%). AD, progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) show associations with H1, whereas Pick's disease (PiD) has an H2 association. However, the effects of this MAPT association on tau expression and splicing are currently unknown.

In the past, we have been dependent on short-read DNA and RNA sequencing, but this has significant limitations. Short reads cannot fully assemble complex genomic rearrangements, especially repetitive sequences, nor can they accurately identify or quantify expressed RNA-differences (isoforms) as in the MAPT locus. To overcome these limitations, we have established a cutting-edge long-read sequencing facility with a range of genomic/transcriptomic techniques and analysis pipelines that we will use to investigate the MAPT locus in 12 brains from controls, AD, PSP, CBD, PiD and FTD (mutation and nonmutation cases) from four different brain regions. Additionally, we also will analyze neurons and organoids derived from induced pluripotent stem cells (iPSCs) with and without splicing mutations in MAPT, enabling us to understand the regulation of neuronal expression, validating an in vitro model to test novel therapies to modify tau expression. We will investigate splicing and allele-specific expression of MAPT in brains and iPSC lines compared with controls, and using these data, reassess genome sequencing in the dementia patients for previously hidden mutations. This will enable a complete understanding of the MAPT locus, expression and splicing across neurodegeneration and iPSC-derived lines, generating a sharable resource to drive the identification of novel therapeutic targets.

Toxic Effects of Extracellular Tau Oligomers on Neurons

George S. Bloom, Ph.D., *University of Virginia*

One of the many insults that neurons often suffer in Alzheimer's disease (AD) brain is that their nuclei, which normally have a relatively smooth surface marked by an occasional shallow invagination, develop multiple deeper invaginations that make the nuclei look "raisinlike." Because a neuron's genes reside in its nucleus, it is possible that this physical alteration of nuclear structure is accompanied by gene expression changes that contribute to the conversion of normal neurons into AD neurons. We now would like to test that possibility, as well as define molecular mechanisms responsible for forming misshapen neuronal nuclei. We already have an exciting clue about how neuronal nuclei invaginate: they form in cultured neurons within an hour of the cells' exposure to extracellular tau oligomers (xcTauOs). Tau is the protein that forms neurofibrillary tangles in AD and "non-Alzheimer's tauopathies," but it also exists as small aggregates, or oligomers, both inside neurons and in extracellular space. To determine whether any gene expression changes also are caused by xcTauOs, we will use tandem RNA-Seq and Ribo-Seq. RNA-Seq will provide a comprehensive picture of neuronal messenger RNA (mRNA), which is made from DNA in the genes, whereas Ribo-Seq catalogs which mRNAs actually direct synthesis of the proteins they encode. Our experimental systems will include cultured neurons with and without xcTauO exposure, and transgenic mice known to harbor tau oligomers. In this manner, we should be able to identify neuronal genes and proteins whose levels are altered by xcTauOs and, using big data tools, identify biochemical pathways that are associated with and may cause nuclear deformation and pathogenic gene expression. By extension, such genes and proteins represent potential targets for preventing or delaying AD symptom onset or slowing symptom progression.

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

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Advanced age is the greatest risk factor for developing Alzheimer's disease and related dementias. Evidence suggests that these diseases begin decades prior to noticeable symptoms. A better understanding of how the

brain changes with age may provide clues into how/why these diseases begin and progress. We discovered that the abnormal brain cells that closely track with memory loss and disease in Alzheimer's disease display characteristics of a stress response common to aging, called cellular senescence. Senescent cells accumulate in many tissues during aging and contribute to disease and dysfunction. In Alzheimer's disease brain tissue, we find that the senescent cells are neurons, the brain cells important for making, storing and retrieving memories. Many of the senescent neurons contain large deposits of tau protein. All neurons normally contain tau protein; however, abnormal forms of tau protein accumulate in many brain diseases. Tau aggregates called neurofibrillary tangles closely correlate with dementia and cell death. Similar to senescent cells, neurons with neurofibrillary tangles display signs of damage and stress, but they do not die. Also, like senescent cells, their survival comes with a tradeoff. They become toxic to surrounding healthy cells. Risk factors that increase cellular senescence in other tissues include advanced age and insulin resistance/diabetes; these risk factors also cause neurons to become senescent in the brain. We have found that regardless of the stressor, senescent neurons rely on tau to execute the stress response. Therefore, the objective of this project is to better understand how tau proteins guide neurons to become senescent in response to stress—a key piece of information because senescent cells contribute to disease and dysfunction. A better understanding of how, why and when neurons become senescent may lead to drug therapies that interrupt the toxic process. Moreover, some of these therapies may be most useful in midlife, when risk factors are evident but neurons are still healthy. This approach may reduce the risk for developing Alzheimer's disease in later life.

STUDIES OF APOLIPOPROTEIN E (APOE)

APOE Consortium: APOE4-Mediated Dysfunction of CD8 T-Cell-Microglia Crosstalk in Alzheimer's Disease

Oleg Butovsky, Ph.D., *Brigham and Women's Hospital; Harvard Medical School*

The human apolipoprotein E (APOE) gene has three variants: APOE2**,** APOE3 and APOE4**.** APOE4 is the major genetic risk factor for late-onset Alzheimer's disease (AD). APOE is abundantly expressed in brain immune cells (microglia) and in peripheral immune cells. We recently identified a critical role of APOE signaling in induction of microglial phenotype associated with neurodegeneration, including AD. A key question is whether APOE variants derived from peripheral innate immunity also control immune responses driven by microglia and contribute to disease progression. Inflammatory CD8 T-cells accumulate in the brain of AD patients and secrete cytotoxic molecules associated with cognitive decline. Our preliminary data show that human APOE variants mediate differential regulation of pro-inflammatory signature in CD8 T-cells. Importantly, recent studies identified induction of similar inflammatory signature in blood CD8 T-cells, which was associated with impaired cognition in AD patients. This proposal aims to investigate the role of APOE variants in the regulation of CD8-microglia interactions as a therapeutic target for AD. This follow-on proposal is to dissect the role of APOE variants in the regulation of CD8 T-cells in AD; we will use novel mouse models and techniques to specifically target APOE in order to restore microglia-mediated protein clearance and brain function in animal models of AD. We will validate our findings in human AD cohort with different APOE alleles, and study their interactions with human microglia.

APOE Consortium: Modulation of Selective Neuronal Vulnerability in Alzheimer's Disease by Apolipoprotein E

Jean-Pierre Roussarie, Ph.D., *Boston University School of Medicine*

Apolipoprotein E (APOE), the most important genetic predisposition factor for Alzheimer's disease (AD), long has been known for its effect on the formation of amyloid plaques and, more recently, for its importance in glial cell activation. There is evidence for another role of APOE on neuron function independent of amyloid plaques. Since some neurons are more vulnerable than others to neurodegeneration, we ask in this proposal whether APOE also could modulate their vulnerability. Our aim is to both better understand the role of APOE in AD, as well as the vulnerability of specific neurons. The most vulnerable neurons of the brain are the ones from 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—and found signals of cellular stress in the presence of the risk allele. We also obtained data showing a slightly decreased number of neurons within the entorhinal cortex when mice have the risk allele of APOE. Strikingly, this population corresponds to the absolute most vulnerable area of the entorhinal cortex during the natural course of AD. This is pretty remarkable, since this occurs in the absence of any detectable tau or amyloid pathology, demonstrating that APOE by itself potentiates the vulnerability of these cells. We will test whether the neurons

that regulate the activity of ECII neurons are functioning properly. We also will characterize the mechanisms by which APOE mediates pathology in vulnerable neurons by using a novel in vitro model: we will cultivate human ECII neurons from stem cells along with astrocytes that produce different alleles of APOE. We will test whether this model recapitulates the vulnerability observed in vivo. If it does, it will allow us to dissect which cellular processes are responsible for this vulnerability.

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

Randall J. Bateman, M.D., *Washington University School of Medicine in St. Louis*

An accurate blood-based test for preclinical Alzheimer's disease (AD) would revolutionize the clinical diagnosis of dementia and accelerate the development of effective AD treatments. Currently, amyloid PET scans and cerebrospinal fluid biomarkers are used in research, clinical trials and clinical practice to detect brain amyloidosis. Clinical utility of these biomarkers is ultimately limited by their cost, availability and perceived invasiveness. Apolipoprotein E (APOE) is the most significant genetic risk factor for AD and a molecular component of the amyloid plaques that are the hallmark of AD pathology. The current study will assess the diagnostic value of incorporating blood APOE protein measurements into an already high-performing blood-based biomarker assay.

APOE Consortium: Effect of Cholesteryl Ester Transfer Protein Activity on Amyloid and Cerebrovascular Pathologies in Animal Models of Alzheimer's Disease

Cheryl Wellington, Ph.D., *University of British Columbia, Canada*

The underlying cause of many human cardiovascular diseases, including atherosclerosis and coronary heart disease, is a high level of low-density lipoprotein (LDL), known as "bad cholesterol." Humans typically have about 70% to 80% of their circulating cholesterol in LDL, and only 20% to 30% in high-density lipoproteins (HDL), known as "good cholesterol." By contrast, mice and rats have about 80% of their circulating cholesterol in HDL rather than LDL and, as a result, are very resilient to atherosclerosis and, by extension, may also be resilient to the vascular contributions to cognitive impairment and dementia. The reason mice and rats don't have a human-like LDL:HDL ratio is that they are naturally deficient in an enzyme called cholesteryl ester transfer protein (CETP); i.e., they are essentially "CETP knockout" species. Importantly, low CETP activity in humans is associated with better cardiovascular health and reduced risk of AD. This project aims to improve the relevance of AD mouse model studies to the human condition by using commercially available CETP transgenic mice, which have a higher LDL:HDL ratio, to understand how LDL affects amyloid and APOE-mediated vascular pathologies in mice. Put simply, we plan to engineer mice to be more like humans in their lipid profiles, expecting that a higher LDL:HDL ratio will worsen both amyloid and vascular pathologies. If so, in the future we can test CETP inhibitors, currently in late-stage clinical trials for heart disease, to see whether these improve AD-relevant outcomes, and conduct additional studies to understand the mechanisms by which a high LDL:HDL ratio affects brain health.

APOE Consortium: Role of APOE Isoforms in Immune Responses in a Model of Tauopathy

David M. Holtzman, M.D., *Washington University School of Medicine in St. Louis*

The apolipoprotein E (APOE) gene is the strongest genetic risk factor for Alzheimer's disease (AD). APOE4 increases risk and APOE2 decreases risk. The Holtzman lab found that in addition to the effect of APOE on amyloid beta, APOE exacerbates tau pathology and tau-mediated brain damage. Tau-dependent neurodegeneration is accompanied by a strong inflammatory response in the brain. Further, buildup of post-translationally modified forms of tau, neurodegeneration and inflammation are exacerbated by the presence of APOE in the order E4>E3>E2, with the absence of APOE being very neuroprotective. The regional progression of brain injury in AD highly correlates with tau accumulation but not amyloid deposition, and the underlying mechanisms of tau-mediated neurodegeneration are not entirely clear. Certain cells in the brain called microglia are part of what is termed the brain's innate immune system, and we have found that these cells are required for tau-mediated neurodegeneration. However, there are other types of immune cells in the brain, and their role in APOE and tau-mediated neurodegeneration is not clear. We recently compared all of the immune cells in the brain in models of amyloid beta deposition (APP/PS1) without nerve cell loss, as well as in a mouse model

of tau accumulation in which there is marked neuronal loss (P301S). We found that P301S mice, but not APP/PS1 mice, develop a more severe inflammatory response in the brain, with both distinct and more activated microglia and infiltrated T-cells (part of the adaptive immune system). T-cells were markedly increased in areas with tau pathology in P301S mice and in the AD brain. Of note, T-cells consistently correlated with the extent of neuronal loss, and T-cells dynamically transformed their cellular characteristics in the P301S brain with greater changes in the presence of APOE4. We also found that T-cells are required for the brain injury in the P301S mice. Based on these data, we hypothesize that APOE plays an important role in facilitating the ability of specific types of T-cells to become activated, and contribute to tau-mediated neurodegeneration. This hypothesis will be tested in a series of experiments in animal models and in collaboration with other members of the APOE consortium.

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*

Apolipoprotein E4 (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. 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 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 chemotherapy-induced cognitive impairments 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 that further deciphering this relationship will uncover new therapeutic strategies for AD. 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 chemotherapy-induced cognitive impairments 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 potentially 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.

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

Liisa Galea, Ph.D., *Centre for Addiction and Mental Health, Canada*

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

The hippocampus is an important area for learning and memory, and shows a great deal of capacity to change (plasticity) in adulthood. One of the unique characteristics of this plasticity in the hippocampus is adult neurogenesis (the birth of new brain cells in the adult). Recent evidence indicates that neurogenesis in the hippocampus is decreased with AD. Furthermore, inflammation appears to contribute to AD, particularly signs of inflammation in the brain, called neuroinflammation. Females show reduced neurogenesis and increased neuroinflammation that may be related to the greater lifetime risk of females to develop AD. An understanding of how neurogenesis is regulated, and how inflammation in the brain is involved, may provide clues for devising new therapeutic treatments for AD. We have found that biological sex influences neurogenesis in the hippocampus, and now will examine how genetic differences that increase susceptibility to AD influences this plasticity. Further, we will determine whether we can manipulate this process to improve memory and reduce neuropathology associated with AD.

STUDIES OF THE IMMUNE RESPONSE IN ALZHEIMER'S DISEASE

Neuroimmune Consortium: Biomarker Tool Development

Jacob M. Hooker, Ph.D., *Massachusetts General Hospital; Harvard Medical School*

A well-recognized hallmark of Alzheimer's disease (AD) is the activation of the brain's immune system, sometimes called neuroinflammation. Despite having detailed information about neuroinflammation in AD from pathology samples after death, we have very limited tools for understanding neuroinflammation at the early stages of AD in living people. To address this need, we are developing imaging agents for use in positron emission tomography (PET) that will help characterize neuroinflammation.

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

Beth Stevens, Ph.D., *Boston Children's Hospital; Harvard Medical School; Broad Institute*

Alzheimer's disease (AD) is a significant public health challenge, as prevalence rises with an aging population and few, if any, treatments are effective at slowing disease progression. The vast majority of cases are late onset, and genetic sequencing reveals that these late-onset AD (LOAD) cases involve many weakly penetrant mutations that interact with environment and nondisease risk factors such as aging to induce disease onset. Current work implicates microglia, the brain's resident immune cells, in the pathogenesis of AD—more than half of all LOAD risk genes are solely expressed in microglia and/or peripheral myeloid cells. Despite this clear association, we know shockingly little about how these mutations contribute to microglial function, or how they may accelerate AD pathogenesis. By understanding how the normal surveillance and injury response functions microglia perform change in disease conditions, either beneficially, by removing toxic proteins and cellular debris, or detrimentally by inflammation, we can better understand the contribution of genetic risk to microglial function, and the role microglia play in AD pathogenesis.

Given the complexity and diversity of microglia in health and disease, there is a critical need for ways to distinguish beneficial from detrimental microglial states over the course of AD, and to determine how specific AD-relevant mutations may affect specific microglial states or functions. However, few studies can clearly link variants to specific functional changes. We have begun to systematically profile the ways in which microglia change their response to stimuli and normal functionality in the face of genetic mutation, and to map that response back onto disease models. This understanding of the relationship between genetic variation and function will be key for understanding how LOAD mutations result in AD, and identifying treatments that can slow or reverse disease progression.

Neuroimmune Consortium: Assessing the Links Between the MS4A Risk Genes, Microglia and Alzheimer's Disease

Sandeep Robert Datta, M.D., Ph.D., *Harvard Medical School*

Alzheimer's disease is caused by progressive changes in brain cells that culminate in memory loss, confusion, difficulty completing tasks, withdrawal, mood changes and, ultimately, death. The main cell type affected in the brain by Alzheimer's disease is the neuron, which is primarily responsible for processing information and generating action. Alzheimer's disease damages neurons and the connections between neurons required to pass information along; as the ability of the brain to process information declines, so does the ability to care for one's self and to interact with loved ones. Although the ultimate target of Alzheimer's disease is the neuron, recent advances in genetics have suggested that a different type of cell might be the cause. These cells are called glia, which for many years were thought to be merely the "glue" that holds the brain together. It is now thought that glia may act to protect or harm neurons, and in doing so may influence the odds of getting Alzheimer's disease and its progression. Here we focus on a set of genes, called the MS4As, that seem to have a surprising degree of influence on a given person's chances of getting Alzheimer's disease later in life. Interestingly, these genes seem to act in a subset of glial cells called microglia, rather than neurons, consistent with microglia playing an important role in disease initiation or progression. In order to make the link between the MS4As and Alzheimer's disease, we propose experiments to explore how the MS4A genes influence both the normal function of microglia and the function of microglia in the context of Alzheimer's disease. Further, we propose to build tools that will help us to build new drugs that target the MS4A genes. Results from these studies will teach us how a gene family that acts in microglia might influence the risk that a person will develop Alzheimer's disease. Our experiments also may identify a new set of promising targets that could be the substrate for future drug development.

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

Shane A. Liddelow, Ph.D., *New York University*

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.

Neuroimmune Consortium: 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*

Genetic and neuropathological studies have strongly implicated microglia in the development and progression of Alzheimer's disease (AD). Yet precisely how AD risk genes alter microglial function to impact amyloid beta pathology remains unclear. One popular hypothesis is that microglial risk genes reduce amyloid beta clearance from the brain by impairing phagocytosis. However, recent studies have surprisingly shown that pharmacological depletion of microglia reduces amyloid beta plaque load. In preliminary studies, we have similarly found that a genetic loss of microglia reduces parenchymal amyloid beta plaques, which in turn is accompanied by a dramatic increase in cerebral amyloid angiopathy (CAA). As CAA occurs in 80% to 90% of patients with AD, and is associated with a poorer prognosis, it is critical to understand how microglia impact the development of this often-overlooked AD pathology. In this CureAlz proposal, we will test the hypothesis that microglial TREM2 and apolipoprotein E (APOE) drive the compaction of parenchymal amyloid plaques, which inversely reduces the development of CAA. In Specific Aim 1, we will collaborate with each of the members of the CureAlz Neuroimmune Consortium to examine the impact of murine microglial deletion on amyloid beta pathology, neuronal and glial transcriptomes (Stevens, Glass, Liddelow Labs), synaptic and cognitive function (Stevens and Datta Labs) and inflammatory state (Hooker Lab). In Specific Aim 2, we will take advantage of isogenic APOE and TREM2 knockout induced pluripotent stem cells and a chimeric mouse model of AD to specifically determine whether human APOE or TREM2 impacts these same transcriptional, functional and neuropathological endpoints. Results from these studies will greatly improve our understanding of how microglia influence the development of AD, and provide important new insight into the potential impact of human microglia on the development and progression of CAA.

Neuroimmune Consortium: Leveraging Enhancer Landscapes to Decode Alzheimer's Disease Risk Alleles in Microglia

Christopher K. Glass, M.D., Ph.D., *University of California, San Diego*

Genetic studies have identified dozens of changes in DNA that are associated with risk of Alzheimer's disease (AD). Most of these changes do not occur in the regions of DNA that code for proteins. Instead, approximately 90% of these changes are in "noncoding" regions of DNA that used to be referred to as "junk DNA," which made them difficult to understand. Studies carried out over the past 10 years, including work from our laboratory, have shown that this so-called junk DNA actually provides the instructions that each cell in the body uses to determine which genes to turn on. In the proposed studies, we will extend our previous CureAlz-supported studies suggesting that changes in noncoding DNA that are associated with AD affect the amounts of specific proteins that are made within microglia and other cell types in the brain. We will specifically focus on the role of a region of the genome that selectively controls expression of the BIN1 gene in microglia and contains changes in noncoding DNA sequence that are highly associated with risk for AD. As a second aim, we will define regions in the genome that control microglia functions that are dependent proteins that are members of the MS4A gene family. These proteins are encoded by genes that reside in a region of the genome that also contains changes in noncoding DNA sequence that are highly associated with

risk of AD. These studies have the objective of determining how MS4A proteins regulate microglia functions that promote AD. Successful completion of this work will depend on extensive collaborations with members of the CureAlz Neuroimmune Consortium. These studies are expected to enable better understanding of how noncoding changes in DNA influence the risk of AD, and may lead to identification of new therapeutic targets.

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 the BBB integrity, and their impairment has also 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 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 key cell types and lipid species that mediate these effects. Overall, these studies will achieve new mechanistic and therapeutic understanding of sEH inhibition, and also identify new targets in the ARA pathway for AD therapy.

Systems Integration and Therapeutics Translation in Alzheimer's Disease

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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.

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; Harvard Medical School*

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 the microglia can develop a homeostatic

phenotype. But this behavior of microglia comes at a cost, in that the 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 about how microglial function is maintained in healthy brain and is prone to dysregulation in 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 also has been linked to susceptibility to AD in a recent genetic analysis, thus raising the question how TIM-3 regulates microglial behavior and contributes to the development of AD. Our preliminary studies show that in 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 plaque. 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 microglia in the central nervous system, and how loss of TIM-3 on microglia can promote clearance of amyloid beta plaques in animal models of AD. Since there are antibodies against TIM-3 (Sabatolimab) already in 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.

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

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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 are revealed only 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 goes 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.

Contributions of IL-34 Signaling to Microglial Function and Alzheimer's Pathology in Mice

Staci D. Bilbo, Ph.D., *Duke University*

Microglia, as the resident immune cells in the brain, serve many crucial functions related to long-term health. There are many molecular signals exchanged between neurons and microglia that establish and maintain homeostasis. In Alzheimer's disease (AD), these signals are disrupted, which results in changes in microglial function. Microglia in AD overeat synapses, the connections between neurons, as well as whole neurons, and this loss of neurons and their connections leads to loss of memory and cognitive ability. The signals leading to disruptions in normal microglial function in AD are largely unknown. One signal released specifically by neurons known to be important for regulating microglia is interleukin-34 (IL-34). This molecule is important for maintaining appropriate numbers of microglia within the brain and potentially other microglial functions as well. Interestingly, a mutation in the IL-34 gene was recently identified as a risk factor for developing AD. In line with this, decreased levels of IL-34 have been identified in human brains affected by AD, as well as in mouse models of AD. It is the primary goal of our experiments to identify the role of IL-34 signaling in AD, specifically in the context of microglia-neuron interactions. Furthermore, we hope to test whether overexpressing IL-34 in a mouse model of AD rescues molecular and behavioral deficits, which would establish IL-34 as a therapeutic target for treating AD.

Microglial-Specific INPP5D Knockdown Modulates Behavior, Amyloidosis and Tauopathy in Alzheimer's Mouse Models

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INPP5D is a human gene encoding an unusual enzyme associated with Alzheimer's disease. The enzyme is unusual partly because it appears to control access to a part of the cell known as the lysosome, a bubble-like structure that acts as a garbage disposal, among other actions. The enzyme also is unusual because it can decorate two disparate chemicals: proteins and inositide fats. In the brain, expression of the INPP5D gene is concentrated in inflammatory cells known as microglia; therefore, we propose to use genetic engineering of mouse models to assess how microglial-specific INPP5D knockdown modulates amyloidosis, tauopathy and behavior in Alzheimer's mouse models.

Human Brain CD33 Ligand, Receptor Protein Tyrosine Phosphatase Zeta (RPTPζ)S3L, Limits Microglial Phagocytosis and Contributes to Alzheimer's Disease Progression

Ronald L. Schnaar, Ph.D., *The Johns Hopkins University School of Medicine*
Tong Li, Ph.D., *The Johns Hopkins University School of Medicine*

Alzheimer's disease (AD) is characterized by accumulation of toxic proteins (amyloid beta and tau) in the brain. Human genetics reveals that dysfunction of microglia, the brain cells responsible for clearing debris, contributes to AD progression. Microglial activity is balanced by activating and inhibiting signals to ensure efficient debris removal while limiting collateral damage. When inhibiting signals dominate, debris removal is pathologically curtailed. We discovered a microglial-inhibiting signal in human brain that is overexpressed in AD. This project uses human cells and mouse models of Alzheimer's disease to explore ways to limit this inhibiting signal, restore microglial debris clearance and curb Alzheimer's disease progression.

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

Shane A. Liddelow, Ph.D., *New York University*

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. During Alzheimer's disease (AD), one type of astrocyte switches from a support role to a pathological one: slowing neuron communication, decreasing connections between neurons and becoming less efficient at removing waste products—all important for a healthy and normally functioning brain. In extreme cases, these astrocytes actively kill 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 exciting novel methods to maintain positive components of inflammation and target only the production and release of a specific astrocyte neurotoxin provides unrivaled control over this complex system. We continue to investigate the role of astrocyte-derived neurotoxins in 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.

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.

Prenatal Inflammation Effects on Blood-Brain Barrier Function and Alzheimer's Disease-Related Pathologies Across the Lifespan

Alexandre Bonnin, Ph.D., *University of Southern California*

It is well established that pathological blood-brain barrier (BBB) breakdown leads to neuronal injury and is associated with neurodegenerative disorders such as Alzheimer's disease (AD) and related dementias. However, the physiological events leading to BBB breakdown associated with AD are not well understood. We recently demonstrated that fetal inflammation alters BBB development, leading to long-lasting disruption of BBB integrity and chronic brain inflammation persisting into adulthood. Our preliminary data suggest that these effects depend on the sustained activation of microglia, the brain resident immune cells. Ultimately, this leads to endogenous amyloid beta peptide clustering, and cognitive and memory impairments in the aging offspring. These observations lead us to propose that incomplete BBB formation resulting from prenatal inflammation leads to a self-perpetuating cycle of chronic BBB leakage and brain inflammation lasting across the offspring lifespan, ultimately leading to accelerated brain senescence and the emergence of AD-like pathologies in aging. We will use pharmacological and genetic tools to uncover the molecular and cellular mechanisms of this self-perpetuating cycle of BBB disruption, microglial activation and brain inflammation promoting AD-like neuropathology. Our approaches explore vastly understudied mechanisms of the early etiology of vascular contributions to cognitive impairment and dementia, providing novel insights into the developmental origins, and potential prevention, of devastating diseases such as AD.

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

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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 is also 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.

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. Identification of the intracellular signaling molecules that coordinate immune responses in Alzheimer's disease is important, as targeting of shared signaling messengers may prove more effective than modulating individual receptors in isolation. In our preliminary studies, we have identified a novel intracellular signaling pathway that is centrally involved in the disposal of neurotoxic agents from the brain, and we have shown further 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.

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

Gilbert Gallardo, Ph.D., *Washington University School of Medicine in St. Louis*

Brain inflammation regulated by microglia and astrocytes is emerging as a contributor to Alzheimer's disease. While recent studies suggest that microglia certainly play a role in the development of the disease, the role of astrocytes has not been extensively evaluated despite being the most abundant glial cell type in the brain. Our studies show that the upregulation of an ion pump in astrocytes induces astrogliosis and progresses tauopathy, a pathological feature in Alzheimer's disease. These studies highlight that inflamed astrocytes potentially contribute to Alzheimer's disease progression. Perhaps suppressing their reactivity may be beneficial in reducing brain inflammation and delaying dementia in Alzheimer's disease.

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 they can respond to changes in the brain. We think these skull-derived cells are changed by Alzheimer's disease, and they may migrate into the brain to help or cause damage.

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.

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*

SPARC, secreted protein acidic and rich in cysteine, is a 32kDa calcium-binding matricellular protein. The matricellular proteins (thrombospondin-1, tenascin-C and SPARC) are extracellular matrix proteins that antagonize cell adhesions when presented to cells as soluble molecules. There is growing evidence that age-related inflammation mediated via the activation of NLRP3 inflammasome in microglia is an important mechanism in the loss of cognition and memory and the development of Alzheimer's disease. The inflammasome is a high molecular weight protein complex that assembles in the cytosol of microglia and myeloid-lineage cells upon encounter with "damage-associated molecular patterns," such as amyloids, lipotoxic fatty acids or extracellular ATP derived from necrotic cells. Given our data that SPARC is reduced in CR, and that increased SPARC levels can induce inflammasome activation and inflammation, we hypothesize that downregulation of SPARC in microglia will protect against inflammasome activation, age-related astrogliosis, and loss of memory and cognition.

The second year of funding will analyze the impact of SPARC knockdown in microglial cells on central nervous system inflammation and memory responses.

Neuroimmune Connectome Perturbations in Alzheimer's Disease

Francisco J. Quintana, Ph.D., *Brigham and Women's Hospital; Harvard Medical School*

Single-cell analyses have identified multiple cell subsets in the central nervous system (CNS). However, our understanding of the mechanisms that mediate CNS cell-cell communication in homeostasis and pathology is limited. A deep understanding of these cell-cell interactions and their perturbations is needed to define mechanisms associated with CNS aging and Alzheimer's disease (AD) pathogenesis. We propose to use novel and complementary technologies to comprehensively investigate, with unique spatial resolution, regulatory cell-cell interactions in the CNS, their dysregulation in AD and their potential as therapeutic targets.

STUDIES OF ALTERNATIVE NEURODEGENERATIVE PATHWAYS

Brain Entry and Exit Consortium: 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 has also developed a series of nonconventional clearance routes to drain tissue waste products. Correct functioning of these brain barriers and clearance routes is critical to the 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 (AD). Despite these initial observations, the consequences of individual barrier/clearance route dysfunction on one another are unclear, but will be critical for a holistic understanding of these devastating conditions. We propose that these barriers and clearance routes form an interconnected system, and that dysfunction of one will precipitate deterioration in additional routes, ultimately worsening disease progression. Thus, restoration of a single disrupted pathway may be sufficient to rescue detrimental aspects of numerous routes, offering an attractive therapeutic intervention to prevent widespread impairments. We propose to explore a largely understudied barrier between the brain and surrounding membranes termed the meninges, which is involved in the clearance of waste products of the brain, but whose detailed mechanisms and pathways are yet to be identified. Additionally, we will examine the functional consequences of brain barrier impairments on clearance pathways, and vice versa, in the healthy and AD brain.

Brain Entry and Exit Consortium: Biochemical and Functional Analysis of Cerebrospinal Fluid and Lymph Following Changes in Brain Fluid Dynamics

Laura Santambrogio, M.D., Ph.D., *Weill Cornell Medical College*

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.

Brain Entry and Exit Consortium: 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. In this proposal, we aim to determine the molecular changes to the BBB in patients with AD, and then, using mouse models, determine how these changes affect the function of the BBB and the progression of AD models. In particular, we have identified that there may be changes to the vascular lipid metabolism in patients with AD. Therefore, we aim to determine how altered vascular lipid metabolism affects BBB function, the buildup of amyloid,

the function of other brain entry and exit routes, and the progression of AD models. Overall, we aim to determine whether targeting vascular lipid metabolism may prove therapeutic for patients with AD.

Brain Entry and Exit Consortium: Central Nervous System Fluid Homeostasis and Waste Clearance in Alzheimer's Disease Characterized by MRI

Helene Benveniste, M.D., Ph.D., *Yale School of Medicine*
Allen R. Tannenbaum, Ph.D., *State University of New York at Stony Brook*

Alzheimer's disease (AD) is the most common neurodegenerative disorder of older adults and is characterized by slowly progressive and irreversible dementia. This fatal and currently incurable disease affects millions of people worldwide, including 1 in 10 adults older than 65. AD is associated with the progressive accumulation of two key waste proteins: misfolded amyloid beta (Aβ) and hyperphosphorylated tau. Recent studies have shown that therapeutically targeting early-onset amyloid beta deposition might be key in preventing progressive cognitive decline and dementia later in life. The glymphatic and lymphatic systems are capable of removing brain waste products, including amyloid beta and tau, and therefore hold strong promise of constituting alternative therapeutic targets for the prevention of AD. Over the last decade, much new knowledge has been gained on the functioning of the glymphatic and lymphatic systems in the live brain. However, some important parameters that are key to understanding glymphatic-lymphatic system function remain poorly understood; one is brain waste clearance rates (i.e., how a given "waste particle" moves inside the brain) in relation to local water mobility across the central nervous system (CNS). This information is critical in order to understand how fluid flow within the glymphatic-lymphatic systems might be therapeutically adjusted to sustain or accelerate brain waste disposal. Our project is focused on addressing the aforementioned critical gaps in knowledge: 1) determining waste clearance from the brain and its relation to water mobility as well as to lymphatic drainage in rats with and without AD, and 2) determining the relation between abnormal fluid flows observed in AD rats and cerebrospinal fluid secretion from the choroid plexus. Successful performance of our proposed experiments will advance therapeutic strategies for AD.

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

Maria K. Lehtinen, Ph.D., *Boston Children's Hospital; Harvard Medical School*
Liisa Myllykangas, M.D., Ph.D., *University of Helsinki, 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 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. Informed by ongoing analyses in bacterial and viral models of central nervous system inflammation, we will use our real-time in vivo imaging system to study inflammation at the ChP in the AD mouse model. Parallel histological analyses in ChP tissue from mouse and human AD patients will reveal the degree to which cellular changes are conserved. These analyses will reveal a time point for transcriptomic analysis of the mouse AD ChP, which will provide greater understanding of cell-cell interactions that are disrupted at the molecular level during disease progression.

Turning Up Mitophagy to Blunt Alzheimer's Tau Pathologies

Evandro F. Fang, Ph.D., *Akershus University Hospital, Norway*

Alzheimer's disease (AD) is on the rise, affecting approximately 45 million people worldwide. AD imposes a formidable socioeconomic burden on individuals, their families and society at large, to the annual tune of $1 trillion USD in 2018. Yet, despite more than a century of extensive research, there is still no cure. Many attempts to treat AD have been unsuccessful. As such, there is a need to expand the current range of research to elucidate additional causes of AD, allowing the identification of new culprits that will provide novel strategies and targets for anti-AD

drug development. Mitochondria are subcellular organelles and are the cell's "powerhouses." Our brain consumes startling amounts of energy, especially when compared with other organs. The provision of this level of energy is dependent on a healthy mitochondrial pool. Unfortunately, mitochondria are susceptible to endogenous (e.g., oxidative stress) and exogenous (e.g., unhealthy food) stressors. However, damaged mitochondria are specifically identified and removed by our body's "garbage disposal system"—a process known as "mitophagy." The efficiency of this "disposal system" deteriorates noticeably with age, leading to the accumulation of damaged mitochondria and other 'brain garbage.' Accordingly, the accumulation of massive "brain garbage" leads to neuronal death and impaired memory, as observed in neurodegenerative disease such as AD. The Evandro Fang group at the University of Oslo is among the first groups to propose and demonstrate a likely causative role for defective mitophagy as a key driver in AD initiation and progression. However, the exact mechanisms underlying the interplay of defective mitophagy in AD progression remain elusive. Thus, with this Cure Alzheimer's Fund grant, we aim to extend our research into understanding the mechanisms underlying the defective "garbage disposal system," both in tau pathology and in the broader development and progression of AD. This approach may revolutionize our understanding of AD and serve to direct clinical drug discovery in new and more fruitful directions. Ultimately, our work on AD could reduce the socioeconomic burden of the disease and help to improve the quality of life for millions of AD patients and their families across the globe.

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

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Cynthia A. Lemere, Ph.D., *Brigham and Women's Hospital; Harvard Medical School*

There have been numerous associations of the composition of the microbes in the gastrointestinal (GI) tract with the occurrence of Alzheimer's disease (AD), but how these microbes lead to changes in the brain and the associated signs and symptoms of AD are poorly understood. We have proposed that small fragments of the microbes continually break off from the cells residing on the GI tract and enter the blood or lymphatic circulation, and then can cross into the brain and lodge there. Throughout most human lives, this process is controlled in a manner that prevents any harm coming to the brain or other tissues where fragments might lodge, because they are prevented from reaching these distant tissues or cleared once lodged there. But when the factors leading to AD are present such as age, genes, diet, environment, smoking, etc., the fragments are not as easily prevented from reaching the brain or readily cleared from the brain, and therefore stay lodged there, where they become factors in the inflammatory process leading to the destruction of brain cells and tissues. We have found that many microbes have a conserved factor on their surface, a polysaccharide or sugar coating, chemically related to that of invertebrate shells such as shrimp or crab shells. This factor is called PNAG. We have developed PNAG into a vaccine that causes antibodies to be produced that we believe prevent these microbial fragments from getting to the brain, and also may promote clearance of microbial fragments if already in the brain. This should prevent destruction of brain cells and tissues. In our studies, we have used one of the mouse models of AD to test this by immunizing the mice and following the course of development of signs of AD. Our studies are still in the early stages, but we are very encouraged that AD mice that have received the PNAG vaccine are doing better in many measures compared with the AD mice that received a control vaccine. And in some of the measures, the PNAG-immune AD mice look like unaffected mice lacking any genes to cause an AD-type of disease. These studies will continue into the fall of 2022, and a second study testing passive therapy with a monoclonal antibody to PNAG will also commence in AD mice at that time.

Targeting the Microbiome and Innate Immunity in Alzheimer's Disease

Howard L. Weiner, M.D., *Brigham and Women's Hospital; Harvard Medical School*

Laura M. Cox, Ph.D., *Brigham and Women's Hospital; Harvard Medical School*

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 contribute to AD. We think 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 this is because AD-associated bacteria block beneficial immune responses in the brain that help 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.

Stress and Neurovascular-Immune Networks in Alzheimer's Disease

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Wolfram C. Poller, M.D., *Icahn School of Medicine at Mount Sinai*

Alzheimer's disease (AD) is the most common form of dementia; it has no available cure and a 100% fatality rate. The disease starts in the brain many years before the first symptoms occur. Two critical factors in the progression of AD are the vessels in the brain, termed neurovasculature, and the immune system. While the neurovasculature normally forms a tight barrier between the immune system and the brain, this barrier breaks in AD, enabling immune cells to enter the brain. Studies in mice and humans show that this barrier breakdown and AD progression are accelerated by psychosocial stress. In this project, we aim to understand how stress fuels AD, and to identify innovative therapeutic targets to stop this process. First, we will identify brain centers that are activated by stress using 3-dimensional activity mapping of the whole brain. Second, we will activate these brain centers under relaxed conditions and inhibit them under stressed conditions to understand their individual contributions to AD. We will apply cutting-edge technology, including chemical and light stimulation of specific neurons, to identify novel therapies to stop the detrimental effect of stress on AD and to potentially even slow down or reverse AD progression altogether. We envision that highly specific manipulation of distinct brain areas may offer new hope for AD patients and their families.

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

Se Hoon Choi, Ph.D., *Massachusetts General Hospital; Harvard Medical School*
Christiane Wrann, D.V.M., Ph.D., *Massachusetts General Hospital; Harvard Medical School*

Alzheimer's disease (AD) and associated dementia caused by neurological impairment have become an increasing health burden. Exercise has been shown in animal models and human clinical studies to be neuroprotective in AD. The mechanisms by which exercise protects the brain should be diverse and complex. Particularly, exercise increases a hormone called FNDC5 (fibronectin-domain III containing 5) and its secreted form, irisin. In our 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 injection of irisin was able to improve cognitive deficits and neuropathology in AD transgenic mice. Our findings suggest that irisin could be considered and developed as a therapeutic target for AD.

Circadian Perturbations of the Vasculome and Microgliome in Alzheimer's Disease

Eng H. Lo, Ph.D., *Massachusetts General Hospital; Harvard Medical School*

In 2017, Dr. Rudy Tanzi proposed the acronym "SHIELD" as a mnemonic for lifestyle strategies against Alzheimer's disease (AD). S denoted the importance of sleep. H represented the need to "handle the stress." I represented the importance of social interactions. E denoted the need for exercise. L represented the need to constantly learn in order to maintain brain plasticity. And D reminded us of the importance of a healthy diet.

Our first CureAlz project investigated the E. We discovered that genes in blood vessels from an AD brain were perturbed, and exercise may partly rescue these defects. This was important because the majority of AD patients also suffer from vascular problems. So, the importance of the E in SHIELD may be partly related to its ability to rescue blood vessels in the AD brain.

In this renewal project, we will focus on the interactions between the "E for exercise" and the very first and arguably most important yet underappreciated letter in the SHIELD acronym—S for sleep. Sleep-wake cycles are part of a fundamental biological mechanism called the circadian rhythm. It is now recognized that disruptions in circadian rhythms may be an important part of AD. In this new project, we will build on discoveries from our previous funding cycle. We will test the idea that gene expression in blood vessels and inflammatory cells within the brain also have their own circadian rhythms, but these rhythms are disrupted in AD. Using exercise as a probe, we hope to find ways to renormalize these circadian rhythms, thus rescuing function in the AD brain.

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

Sandro Da Mesquita, Ph.D., *Mayo Clinic, Jacksonville*

The goal of this project is to explore the functional alterations in the brain-draining meningeal lymphatic vasculature induced by aging, sex and APOE genotype. Our experimental results show that there are sex-dependent morphological changes in meningeal lymphatic vasculature

induced by APOE4 expression. Taking into consideration our data that points to macrophages as one of the main sources of APOE in the brain meninges, we will evaluate the effect of manipulating macrophage responses to decrease the levels of APOE4 in the meningeal dura of aged mice and normalize meningeal lymphatic function. We will further test whether vascular growth factor signaling can be therapeutically employed to restore meningeal lymphatic function in aged mice expressing human APOE4.

This proposal will provide mechanistic insights about the crosstalk between aging, APOE4 and meningeal lymphatic vessel dysfunction—three factors that were shown to affect Alzheimer's disease-related amyloid pathology and the appearance of cognitive deficits. The data generated in this project will provide the foundations for future basic and clinical studies exploring therapeutic strategies to improve brain lymphatic drainage in Alzheimer's disease.

Evaluating TMEM106B Accumulation in Alzheimer's Disease

Leonard Petrucelli, Ph.D., *Mayo Clinic, Jacksonville*
Casey N. Cook, Ph.D., *Mayo Clinic, Jacksonville*

Recent studies investigating a new type of filament found in patients with Alzheimer's disease and related disorders identified TMEM106B, a protein normally localized to the lysosome, as the protein constituent. The current project is focused on developing new tools to label TMEM106B, and to understand the significance of TMEM106B filament accumulation and its relationship to the disease course.

Alzheimer's Disease Pathophysiology Alters the Level of Electrical and Chemical Synapse Coupling in the Network of GABAergic PV+ Interneurons Early in Disease Course

Srdjan D. Antic, M.D., *University of Connecticut Health Center*
Riqiang Yan, Ph.D., *University of Connecticut Health Center*

Alzheimer's disease (AD) is an age-dependent chronic neurodegenerative disease, characterized by accumulation of aberrant proteins in the brain (amyloid beta and tau), loss of memory and cognitive capacity. At early stages of disease, prior to the detection of brain plaques and significant behavioral changes, a dysfunctional neuronal activity begins to emerge, and it appears that this neuronal electrical activity promotes faster degeneration of the brain tissue, leading to irreversible cognitive deterioration. A vicious downward cycle thus may exist: initially, the AD-mediated production of toxic materials (amyloid beta and tau) triggers stronger neuronal activity in some parts of the brain circuit, and then this aberrant neuronal activity accelerates the production of the same toxic materials (amyloid beta and tau). This project seeks to determine the components of the neural circuit that are sensitive to increased levels of amyloid beta and tau in animal models of AD. We are especially keen to investigate early stages of AD, before a significant accumulation of protein plaques inflicts irreparable damage to the brain structures. Once we identify the vulnerabilities in the brain circuit, we might then be able to develop therapeutic approaches to protect these neural circuits from the ongoing AD pathology.

Cellular Vulnerability to Aging in Alzheimer's Disease

Mathieu Bourdenx, Ph.D., *University College London, England*
Karen E. Duff, Ph.D., *University College London, England*

The vast majority of people who develop Alzheimer's disease (AD) are age 65 or older. The aging of the baby boom generation will significantly increase the number of people in the world with AD, which has been described as an advancing "silver tsunami." However, AD is not a normal part of aging, and older age alone is not sufficient to cause this disease. Aging is, however, the major risk factor, and we believe that understanding how the brain ages will allow us to devise ways to better protect it against AD. We propose that certain brain cells are especially vulnerable to aging, and this makes them more likely to go awry in older age, leading to the cascade of events that results in AD. The aging process is poorly understood, and its impact very often is not taken into account in molecular and cellular studies of AD, making the effect of therapeutics administered to the elderly unpredictable. We propose to use novel, sophisticated, state-of-the-art methods to identify what changes occur in individual brain cells, which will lead us to understand how aging predisposes the brain to develop AD, and how to better protect it.

Gut Microbiota, Endothelial Dysfunction and Tau-Mediated Cognitive Impairment

Giuseppe Faraco, M.D., Ph.D., *Weill Cornell Medical College*
Costantino Iadecola, M.D., *Weill Cornell Medical College*

Bacteria colonizing the mucosal surfaces of our body have a profound effect on the cells of the immune system. In particular, due to the abundance of immune cells in the gut, gut bacteria can influence the immune system of the entire body. Therefore, alterations in gut bacteria can result in dysregulation of immune cells that can cause damage to other organs, including the brain. Indeed, alterations in the gut flora have been implicated in the brain pathology underlying Alzheimer's disease (AD), but how that happens

has not been elucidated. A certain class of gut immune cells (Th17 lymphocytes) are particularly sensitive to gut bacteria and play a major role in autoimmune diseases by producing the harmful cytokine IL17. IL17 also can result in the accumulation in the brain of the protein tau, a major culprit in AD. Therefore, this proposal will test the hypothesis that changes in gut bacteria that promote proliferation of Th17 cells in the gut lead to an increase in circulating IL17 that causes cognitive impairment by promoting accumulation of tau in the brain. To this end, we will colonize the gut of mice with bacteria that activate the proliferation of Th17 cells (segmented filamentous bacteria) to determine whether the increase in IL17 in the blood will lead to tau accumulation in the brain. The results of these studies will provide a direct link between gut bacteria and tau pathology, and may open new avenues for the treatments of AD and related tauopathies based on modulation of the gut flora.

Temporal Relationships Between Gut Dysbiosis and Microglia Cell Activation Following Antibiotic Treatment

Sangram S. Sisodia, Ph.D., *University of Chicago*

Alzheimer's disease (AD) remains the most common form of dementia, affecting 50 million people worldwide. Recent studies from our laboratory established a clear role for the gut microbiome in the pathology of AD. These studies also suggested rampant neuroinflammation in the AD brain, triggered by imbalances in gut microbiome diversity. However, the exact mechanism through which the gut microbiome exerts its effect on the AD brain remains unknown. The present study aims to identify temporal changes in microglial gene expression after antibiotic treatment and fecal microbiome transplantation (FMT) on the progression of AD. We anticipate that these studies will provide new insights into the molecular mechanisms of gut-brain communication, which may lead to development of new therapeutic approaches for AD treatment.

Role of the Circulating Exerkine GPLD1 in Ameliorating Alzheimer's Disease Pathology

Saul Villeda, B.S., Ph.D., *University of California, San Francisco*

The research described in this proposal will investigate the beneficial effect of the exercise-induced, liver-derived blood factor GPLD1 on the brain vasculature as a critical mediator in combating drivers of Alzheimer's disease. This study will delineate cellular and molecular mechanisms underlying the benefits of systemic GPLD1 in restoring cognitive function and ameliorating Alzheimer's disease pathology in the hippocampus. The results from this study will have significant translational potential, positing GPLD1 as a novel therapeutic target to reverse functional impairments in Alzheimer's disease.

Understanding How Human Brain Vascular Cells Mediate Genetic Risk for Alzheimer's Disease

Andrew Yang, Ph.D., *University of California, San Francisco*

The risk for late-onset Alzheimer's disease (AD) involves dozens of risk variants operating in diverse cell types. Elucidating the functions of these risk variants is critical to inform treatments but is challenging, in part because the vascular half of human brain cell types has eluded powerful single-cell assays. We will use our new vascular-capturing "VINE-seq" technique to comprehensively determine the cells and genes dysregulated by AD variants. We then will use chemical biology approaches to determine how identified AD variants dysregulate brain blood-brain barrier transport functions to compromise brain health and promote AD risk.

Identifying the Sex-Specific Roles of the Gut Microbiome-Brain Axis in a Mouse Model of Amyloid Beta Amyloidosis

Sangram S. Sisodia, Ph.D., *University of Chicago*

Alzheimer's disease (AD) remains the most common form of dementia, affecting 50 million people worldwide. Recent studies from our laboratory have established that perturbations of the gut microbiome with antibiotics lead to an attenuation of amyloid beta deposition and alterations in the physiology of microglia, cells that are critical for amyloid beta clearance. Importantly, these findings are unique to male but not female mice. Genetic and epidemiological studies have documented that women are at higher risk for AD than men. Is estrogen an important hormone that drives these differences? The current proposal seeks to delineate the mechanism(s) by which circulating levels of estrogen influence amyloid beta deposition and neuroinflammation. Our investigations will provide important information pertaining to the role of female sex hormones in modulating pathogenesis in our mouse models—findings that we anticipate will offer new therapeutic targets that will alter the onset and/or progression of AD in women.

Drug Discovery

DRUG SCREENING AND LEAD DRUG EVALUATION PROJECTS

Alzheimer's Disease Drug Discovery and Development Consortium: Blocking Synaptotoxicity in Alzheimer's Three-Dimensional Models

Weiming Xia, Ph.D., *Boston University*

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 the clinic to test its utility to 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.

Alzheimer's Disease Drug Discovery and Development Consortium: Modulating CD33 Function and Neuroinflammation as a Therapeutic Approach for Alzheimer's Disease

Ana Griciuc, Ph.D., *Massachusetts General Hospital; Harvard Medical School*

The innate immune receptor CD33 inhibits brain amyloid beta clearance and promotes neuroinflammation in Alzheimer's disease. CD33 is a very interesting target for developing therapeutics for the prevention and treatment of Alzheimer's disease. We identified two CD33-specific antibodies that downregulated CD33 protein levels in microglia. These antibodies will be evaluated for their ability to inhibit CD33 activity in microglial cells. Through an unbiased high-throughput screen of a natural product library, we identified natural products that reduced levels of pro-inflammatory mediators in microglia. Several combinations of natural products showed additive effects in reducing levels of pro-inflammatory mediators in microglia. Furthermore, we are currently screening an FDA-approved drug library for modulation of amyloid beta uptake in microglia. Hits from the primary screen will be validated in dose-dependent amyloid beta uptake assays in microglia. These studies are expected to facilitate Alzheimer's disease therapeutics based on modulation of neuroinflammation.

Alzheimer's Disease Drug Discovery and Development Consortium: 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; Weill Cornell Medicine*

We built an iterative drug repositioning scheme of "modeling–>screening–>validation" through the collaboration within the Alzheimer's Disease Drug Discovery and Development Consortium. Over the last eight years, 3,000 compounds were physically screened to reveal nearly 30 compounds with the ability of significantly reducing the level of p-tau in the 3D Alzheimer's in a Dish™ model. In addition to the imaging quantifications on p-tau, sophisticated biochemical and toxicity validations using specialized assays were applied to define the candidate hits' impacts on the 3D culture model.

Our pool of "hit compounds" is growing again this year, as another six in silico predictions were successfully validated as hit compounds for p-tau clearance. We also generated matched RNA-seq profiles and fluorescent imaging profiles for 11 compounds to model the key mechanisms underlying the ability of clearing p-tau.

Alzheimer's Disease Drug Discovery and Development Consortium: High-Throughput Drug Screening for Alzheimer's Disease Using Three-Dimensional Human Neural Culture Systems

Doo Yeon Kim, Ph.D., *Massachusetts General Hospital; Harvard Medical School*

Luisa Quinti, Ph.D., *Massachusetts General Hospital; Harvard Medical School*

Alzheimer's disease (AD) has become a significant public health problem, but the therapeutic options are limited. Recently, ADUHELM® (Biogen) has been 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. Using our 3D AD cellular models, we identified and validated novel AD drug candidates derived from unbiased natural products library screening and transcriptomic data analysis with AD patient brains. We also found that a group of anti-malarial drugs alters aggregation of the amyloid beta 42 isoforms, a major pathogenic molecule found in AD patient brains. Our findings are expected to accelerate AD drug discovery.

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.

A Transcriptional Rejuvenation Signature for Alzheimer's Disease

Tony Wyss-Coray, Ph.D., *Stanford University*

Aging is the leading risk factor for most noncommunicable diseases such as cancer, diabetes and neurodegenerative diseases, including Alzheimer's. Conversely, experimental interventions that can stave off the aging process—or even "reverse" it—protect against age-related maladies. We recently discovered that infusion of young plasma, which rejuvenates old brains, also may protect against Alzheimer's disease. We propose here to identify a gene activity signature of rejuvenation in Alzheimer's models. We show that such a signature enables the prediction of novel Alzheimer drugs in humans, and propose an experimental pipeline to test candidate compounds in neurons from reprogrammed skin cells of Alzheimer's patients. If successful, our study may provide a foundational pipeline to reverse-engineer the powerful capacities of rejuvenation into actionable targets for novel Alzheimer's therapeutics.

Identification of CD33 Antagonists

Subhash Sinha, Ph.D., *Weill Cornell Medicine*

Alzheimer's disease (AD) is an age-related disease of the central nervous system. Its prevalence has become a major concern in both developed and developing countries. There are 5.4 million AD patients in the United States; 96% of them are ages 65 and older, but no disease-modifying drug is available except for a few that treat the symptoms only. Accumulation of neurotoxic forms of amyloid beta and tau protein in the brain is the major hallmark of AD; together, they cause toxicity to neurons and their deaths. Microglia are the housekeeping cells in the brain, mediating the degradation of the accumulated amyloid beta, tau protein and other debris in the brain. Microglia express a cell surface protein, CD33, which has been implicated in late-onset AD. The CD33 protein reduces the ability of microglia to capture and degrade accumulated amyloid beta and tau protein when the former is expressed at a high level in microglia. It is argued that: 1) reducing the expression of CD33 protein in microglia, or 2) inhibiting binding of CD33 protein to agonists (molecules that will increase CD33 activity) expressed on the surface of the same cells or interacting cells will have a favorable response. We focused on the latter approach to identify small molecule CD33 inhibitors that can penetrate the blood-brain barrier.

We have performed virtual high-throughput screening to obtain 195 virtual hits, and preliminary testing to identify 50 potential hits. In the following year, we aim to further evaluate these compounds and identify two inhibitors for medicinal chemistry (MedChem) to improve their activity.

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 the modern society. It is characterized by accumulation of the 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 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.

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

Qisheng Zhang, Ph.D., *University of North Carolina at Chapel Hill*
John Sondek, Ph.D., *University of North Carolina at Chapel Hill*
Kenneth Pearce, Ph.D., *University of North Carolina at Chapel Hill*

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

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

DRUG DELIVERY AND ENABLING TECHNOLOGIES

Novel Entry Routes for Therapeutic Biologicals to the Brain

Maarten Dewilde, Ph.D., *KU Leuven, Belgium*
Bart De Strooper, M.D., Ph.D., *KU Leuven, Belgium; University College London, England*

The blood-brain barrier (BBB) is a vital barrier between the bloodstream and the brain. This barrier tightly controls which molecules can enter the brain. As a consequence of this barrier, the majority of currently available drugs cannot enter the brain. Importantly, to treat Alzheimer's disease, drugs need to reach the brain. Our laboratory has been validating an innovative methodology to discover and validate novel ways to deliver drugs over the BBB. The aim of this project is to implement this methodology in our drug discovery campaign and deliver novel tools to the community to advance treatments for neurological disorders like Alzheimer's disease.

Preclinical and Clinical Drug Development

PRECLINICAL DRUG DEVELOPMENT

Combined Hormone Therapy as a Novel Treatment for Alzheimer's Disease in the Face of a Metabolic Challenge: Influence of Sex and Genotype

Liisa Galea, Ph.D., *Centre for Addiction and Mental Health, Canada*
Annie Ciernia, Ph.D., *University of British Columbia, Canada*

Alzheimer's disease (AD) is a progressive brain disorder that causes memory loss and death of brain cells. Women are at a greater lifetime risk to develop AD, especially if they have a specific gene variant (APOE4 genotype). Women APOE4 carriers are at greater risk of developing AD than men, and we can use this information to understand the disease better. Although certain hormone therapies (HTs) containing estradiol can reduce memory deficits and may decrease the risk for AD, long-term use of certain HTs is associated with increased cancer risk, and thus other therapies targeting the hormone system are sought.

Modifiable risk factors for AD include obesity and type 2 diabetes (T2D). Another hormone called glucagon-like peptide-1 (GLP-1) reduces appetite and regulates blood sugar levels, and this hormone is used as a treatment for obesity and T2D. Indeed GLP-1 treatments are in trials for AD symptom relief. A compound was recently developed in which estradiol (the most potent of one of the estrogens) and GLP-1 are linked together (GLP-1+estradiol), making it possible to avoid side effects associated with estrogens alone. GLP-1+estradiol improves blood glucose levels and reduces body weight more effectively than GLP-1 alone. However, GLP-1+estradiol's effects on memory, and its protective characteristics on the brain, have not yet been examined. Thus, we will investigate potential effects of this compound to preserve memory decline and provide neuroprotection in an AD mouse model (which possesses the APOE4 genotype) under a metabolic challenge (diet of high fat and high sugar). We suspect that the linked hormones will be protective for both males and females—providing protection via different sex-specific pathways—and we will examine different pathways in our research. Our research has the potential to uncover new roles for GLP-1+estradiol as a novel treatment for AD in both men and women.

CLINICAL TRIAL DESIGN

Application of Machine Learning Methods in Alzheimer's Disease Clinical Trials

Ali Ezzati, M.D., *Albert Einstein College of Medicine*
Richard B. Lipton, M.D., *Albert Einstein College of Medicine*

Alzheimer's disease (AD) is the leading cause of dementia in older adults. However, the majority of clinical trials aiming to modify the disease process have failed over the last two decades. This is due, in part, to variation among people with AD in both their clinical features and biological underpinnings. The benefits of treatment may differ with the stage of illness. Some people with AD decline rapidly, while others decline more slowly. Some people have concomitant vascular disease, which may influence cognitive trajectories in the absence of treatment and response to treatment. The ideal participants for AD clinical trials would show cognitive decline in the absence of treatment (i.e., placebo arm) and also would respond to the therapeutic intervention. Identifying such participants for AD trials has proven to be challenging. Our recent studies indicate that by using data collected from patients at the screening visit and machine learning predictive models, we can effectively predict disease progression in the trial population. These models could be used to improve patient selection and enrich AD trials. We are planning to further validate and replicate these predictive models in other trials, and ultimately use them to improve the design of future trials. Future research should be conducted using multimodal data (i.e., clinical tests, MRIs, PET scans, blood-based biomarkers) from new clinical trials, which have collected comprehensive biomarker data, to explore the validity and generalizability of these models. In addition, predictors of treatment response from trials could be used to optimize patient selection in practice.

Other

SCIENTIFIC MEETINGS AND SUPPORT

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

Wilma Wasco, Ph.D., *Massachusetts General Hospital; Harvard Medical School*

Wilma Wasco, Ph.D., is responsible for the day-to-day organization of the G2T Centralized Research Core and the AD4 Consortium. Dr. Wasco routinely meets with Dr. Tanzi, Meg Smith and CureAlz staff to outline and discuss progress with timelines and investigations, model generation and budgets for both groups. In addition, Dr. Wasco is the point person for Taconic and all other commercial or academic contacts as well as for the investigators who have been and will be recruited to work on each gene. She also assists with the general CureAlz grant pipeline, and in that capacity attends and plans key scientific meetings. Dr. Wasco has longstanding expertise in Alzheimer's disease genetic studies; she played a significant role in the original discovery of the presenilin genes and is familiar with the techniques that will be used for gene investigations.

Scientific Meeting Support

Direct and sponsorship funding to enable scientists to share, discuss and collaborate across institutions using emerging data that will advance the entire Alzheimer's field.

Ongoing Research Projects

The research projects listed here were ongoing and active in 2022, having received funding from Cure Alzheimer's Fund in a previous year.

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**
BIOMARKERS, DIAGNOSTICS, AND STUDIES OF RISK AND RESILIENCE	
Understanding Human Brain Resilience to Alzheimer's Pathology Teresa Gomez-Isla, M.D., Harvard Medical School; Massachusetts General Hospital	**$300,000**
Stable Isotope Labeling and Quantitative Mass Spectrometry Imaging of Alzheimer's Disease Pathology in Human Brain Katherine Schwetye, M.D., Ph.D., Washington University School of Medicine in St. Louis	**$150,000**
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**
EPIGENETIC FACTORS	
CIRCUITS: 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; Broad Institute	**$550,000**
TRANSLATIONAL RESEARCH	
STUDIES OF NOVEL ALZHEIMER'S DISEASE GENES	
The Role of Clusterin in Tau Pathology John D. Fryer, Ph.D., Mayo Clinic, Arizona	**$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**
The Nedd4-1 and PKCα Connection in Alzheimer's Disease Gentry N. Patrick, Ph.D., University of California, San Diego	**$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., German Center for Neurodegenerative Diseases (DZNE)	**$287,500**
Patient-Based Structural and Functional Biology of Tauopathies Leonard Petrucelli, Ph.D., Mayo Clinic, Jacksonville	**$172,500**
Influence of Plaque Vicinity on Microglial and Astrocyte Gene Expression; Role of Human Tau and TREM2 Frances A. Edwards, Ph.D., and John Hardy, Ph.D., University College London, England	**$172,289**
Mechanisms of Tau Propagation Across the Plasma Membrane Marc I. Diamond, M.D., University of Texas Southwestern Medical Center	**$250,000**
STUDIES OF APOLIPOPROTEIN E (APOE)	
APOE Consortium: Counteracting Pathogenic Events in Alzheimer's Disease with Peripheral or Central Apolipoprotein E Takahisa Kanekiyo, M.D., Ph.D., Mayo Clinic, Jacksonville	**$250,000**
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**
Protection Against APOE4 with Longevity-Promoting Interventions Christian Pike, Ph.D., Caleb E. Finch, Ph.D., and Bérénice A. Benayoun, Ph.D., University of Southern California	**$191,008**
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**
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**

Project/Researcher	Distribution Amount
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., German Center for Neurodegenerative Diseases (DZNE)	**$172,500**
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., Haddassah Medical Organization, Israel, and Benjamin Y. Klein, M.D., Hebrew University of Jerusalem, Israel	**$229,425**
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**
Tau and Amyloid Beta are Innate Immune Antimicrobial Peptides in the Brain William Eimer, Ph.D. , Massachusetts General Hospital; Harvard Medical School	**$172,500**
T Cell Epigenetics in Alzheimer's Disease David M. Gate, Ph.D., Northwestern University Feinberg School of Medicine	**$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**
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**
The Neuroprotective Glial Barrier: A Multicellular Reaction with Therapeutic Potential in Azheimer's Disease Jaime Grutzendler, M.D., Yale School of Medicine	**$172,500**
STUDIES OF ALTERNATIVE NEURODEGENERATIVE PATHWAYS	
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 Ultrecht Brain Center, The Netherlands, and Julia Neitzel, Ph.D., Harvard T.H. Chan School of Public Health	**$172,052**
Investigating Bone Marrow Hematopoiesis as the Link Between Sleep Fragmentation and Vascular Inflammation in AD Cameron McAlpine, Ph.D., and Filip K. Swirski, Ph.D., Icahn School of Medicine at Mount Sinai	**$172,500**
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 E. Tanzi, Ph.D., Massachusetts General Hospital	**$250,000**
Microbes and Alzheimer's Disease: Metagenomics on Saliva, Cerebrospinal Fluid, Blood and Brain Nanda Kumar Navalpur Shanmugam, Ph.D., William Eimer, Ph.D., Deepak Kumar Vijaya Kumar, Ph.D., and Rudolph E. Tanzi, Ph.D., Massachusetts General Hospital	**$350,000**
Brain Entry and Exit Consortium: Human 3D Neurovascular Interaction and Meningeal Lymphatics Models with Application to Alzheimer's Disease Se Hoon Choi, Ph.D., Massachusetts General Hospital, and Roger Kamm, Ph.D., Massachusetts Institute of Technology	**$215,000**
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**
Neural Synaptic Circuit Changes During Alzheimer's Disease Progression Huizhong W. Tao, Ph.D., University of Southern California	**$172,500**
Central Clock Influence on Alzheimer's Disease Pathogenesis Geraldine J. Kress, Ph.D., Washington University School of Medicine in St. Louis	**$154,701**
DRUG DISCOVERY	
DRUG SCREENING AND LEAD DRUG EVALUATION PROJECTS	
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, Jacksonville	**$172,500**
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**
PRECLINICAL AND CLINICAL DRUG DEVELOPMENT	
PRECLINICAL DRUG DEVELOPMENT	
Continuing Studies of the Effects of GSM 776890 Administration on Amyloid Species and Microgliosis in Older Alzheimer's Model Mice Kevin Rynearson, B.S., M.S., Ph.D., University of California, San Diego	**$291,374**

Dear Friends,

We are pleased to report that research distributions in 2022 totaled $24.5 million, representing a 38% increase over our 2021 results. The funding represents 100 projects, the largest number of grants in a single year. Since our inception in 2004 and through the end of 2022, Cure Alzheimer's Fund has provided $165 million to scientists throughout the world.

2022 was also the 18th consecutive year for record contributions raised by Cure Alzheimer's Fund. A total of $32 million for the year represented an increase of 13.8% from 2021, and was the result of the generosity of nearly 24,000 donors, our Board of Directors and Trustees.

During 2022, Cure Alzheimer's Fund benefited from Amylyx Pharmaceuticals becoming publicly traded. Amylyx is a global company based in Cambridge, Massachusetts, which uses unconventional approaches to "discover and develop potential treatments for neurogenerative diseases," including ALS and Alzheimer's disease. CureAlz was a very early supporter of the company's research initiative, and in 2022 we realized $8.1 million from the sale of stock resulting from that early support.

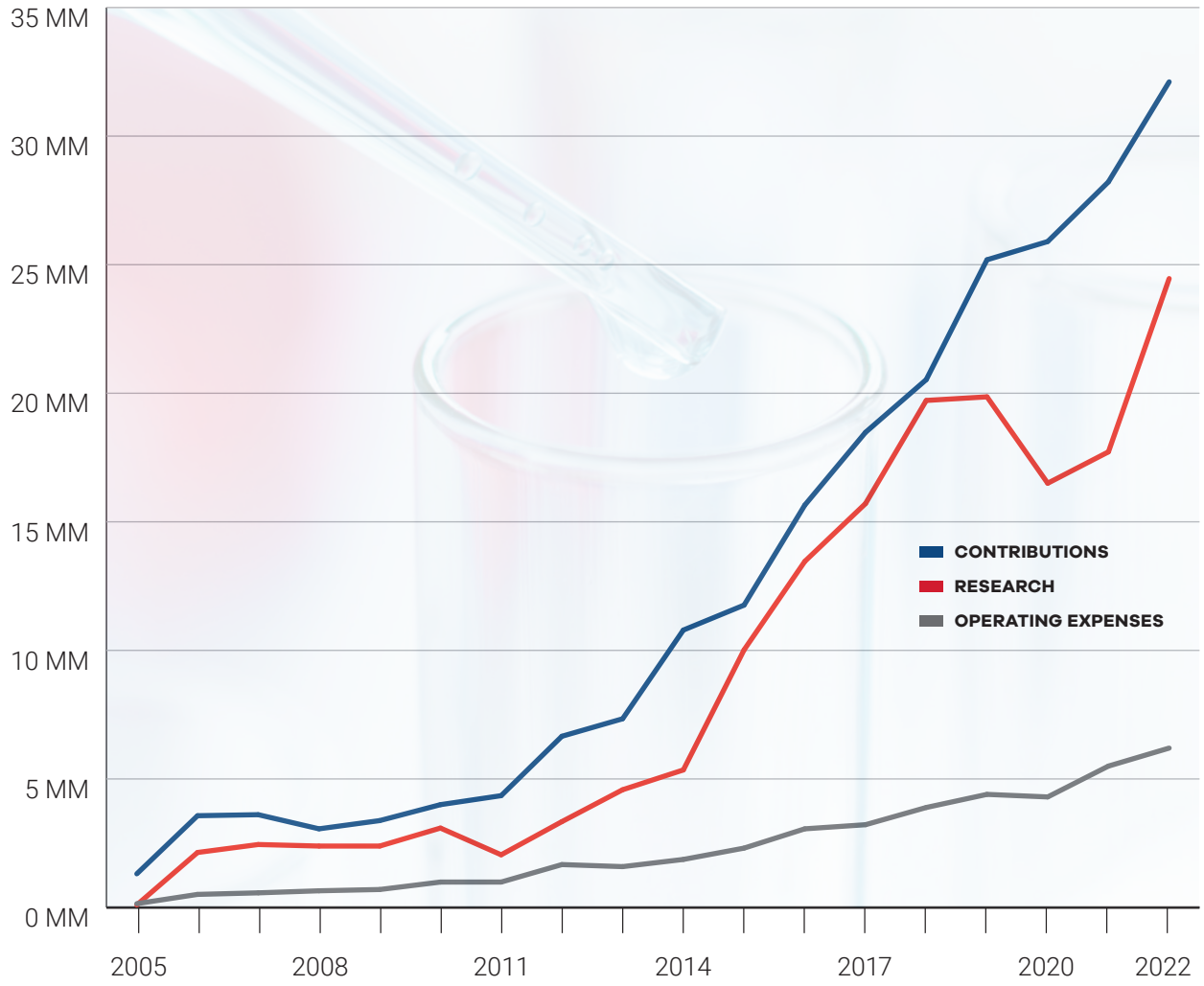
Our cost of operations continues to remain low. Since inception through the end of 2022, Founders, our Board of Directors and Trustees have contributed $62.2 million to support operating expenses totaling $42.5 million, allowing for the growth and sustainability of CureAlz.

Our extraordinary funding of research combined with our fiscal responsibility and commitment to transparency have resulted in the 12th consecutive 4-star rating by the nonprofit watchdog Charity Navigator, the highest designation that can be achieved.

2022 was another exceptional year in understanding the causes and pathology of Alzheimer's disease. Behind all these very good numbers we are pleased to report stand hundreds of researchers, thousands of donors, our staff, Founders, our Board of Directors and Trustees. We are deeply grateful and humbled by the dedication of all these people and their commitment to find solutions that will slow, stop or reverse Alzheimer's disease. Thank you.

Sincerely,
Tim Armour
President and CEO

Growth: Inception Through 2022

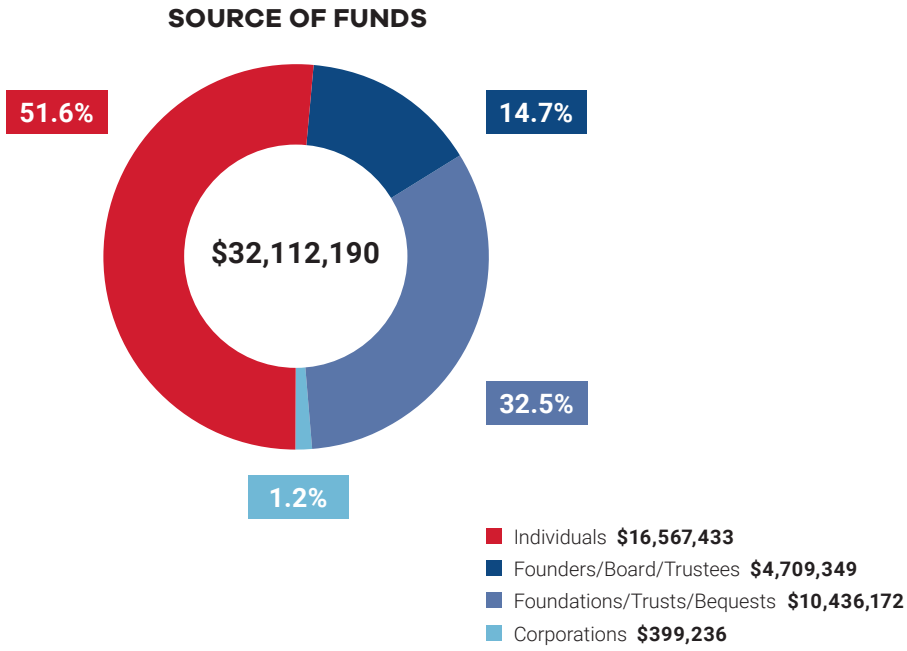


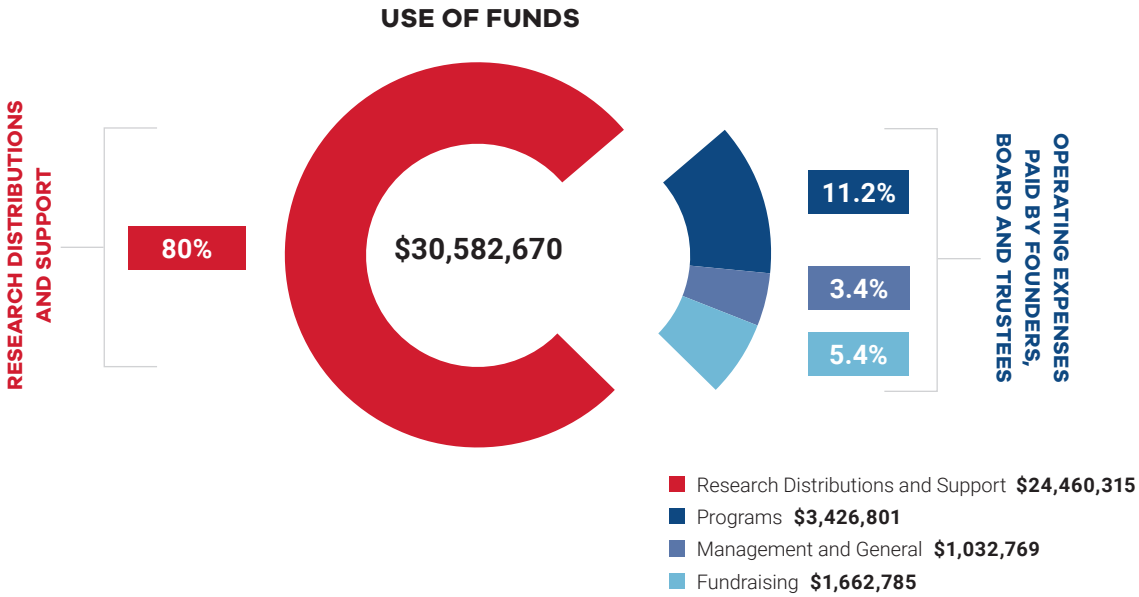
Eighteen Years of Growth:

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

2022 Fundraising

In 2022, Cure Alzheimer's Fund received 23,795 gifts—from individuals, the Board, Trustees, corporations and foundations—totaling $32,112,190. Cumulative contributions from inception given by our Founders, Board and Trustees total $62,167,138. Cumulative operating expenses from inception paid by the Founders, Board and Trustees total $42,516,039.





Source and Use of Funds obtained from internal records.

2022 Financials (Year ended December 31, 2022)

Statement of Financial Position

Assets	
Current Assets:	
Cash and cash equivalents	$10,033,492
Contributions receivable	66,406
Pledges receivable, current portion	1,100,000
Investments	17,733,326
Prepaid expenses and other current assets	218,532
Total current assets	29,151,756
Pledges receivable, less current portion, net	711,329
Equipment, net	3,042
Right-of-Use, Asset, net	326,657
Total Assets	$30,192,784
Liabilities and Net Assets	
Current Liabilities:	
Current portion of operating leases payable	$171,830
Accounts payable	129,949
Research grants payable	763,585
Accrued payroll and related	528,365
Total current liabilities	1,593,729
Long-Term Liabilities:	
Operating leases payable, less current portion	140,445
Total long-term liabilities	140,445
Total Liabilities	1,734,174
Net Assets:	
Without donor restrictions	26,297,281
With donor restrictions	2,161,329
Total net assets	28,458,610
Total Liabilities and Net Assets	$30,192,784

Statement of Activities

Revenue and Support:	
Contributions	$26,122,432
Donated stock	5,919,199
Special events, net of direct expenses	306,887
Investment income, net	8,492,261
Total revenue and support	40,840,779
Expenses:	
Program:	
Research distributions and support	24,460,315
Other program expenses	3,426,801
Total program expenses	27,887,116
Management and general	1,032,769
Fundraising	1,662,785
Total expenses	30,582,670
Change in net assets	10,258,109
Net Assets, beginning of year	18,200,501
Net Assets, end of year	$28,458,610

Statement of Cash Flows

Cash Flows from Operating Activities:	
Cash received from:	
Contributions	$26,126,586
Investment income	63,064
Total receipts	26,189,650
Cash paid for:	
Research distributions and support	(28,800,217)
Salaries and related expenses	(3,950,396)
Professional fees	(607,648)
Gift processing fees	(151,928)
Occupancy expenses	(211,088)
Other expenses	(1,352,592)
Total expenditures	(35,073,869)
Net cash provided (used) by operating activities	(8,884,219)
Cash Flows from Investing Activities:	
Proceeds from sale of investments	14,929,740
Purchase of investments	(5,808,011)
Net cash provided (used) by investing activities	9,121,729
Net Increase in Cash and Cash Equivalents	237,510
Cash and Cash Equivalents, beginning of year	9,795,982
Cash and Cash Equivalents, end of year	$10,033,492
Noncash Operating and Investing Activity:	
Donated stock	$5,919,199
Donated use of facility	$58,806

Source: Audited financial statements.

Our People

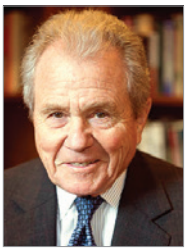
BOARD OF DIRECTORS

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

TIM ARMOUR
President and Chief Executive Officer

TRUSTEES

KATHLEEN ARNOLD
Trustee, Fleming Foundation

JONO BACON
Founder, Community Leadership Core

ANOOSHEH BOSTANI
Director of Alfred E. Mann Charities

SHARI CROTTY
Trustee, The Crotty Family Foundation

KAREN FRIEND, PH.D., ACPS
Senior Researcher and Evaluator, Pacific Institute for Research and Evaluation; Adjunct Professor, Brown University Department of Public Health

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

ADMINISTRATION

JO ANTONELLIS
Controller

TIM ARMOUR
President and Chief Executive Officer

TAMMY AWTRY, PH.D.
Science Communicator

LISA BIDA
Marketing Manager

BARBARA CHAMBERS
Executive Vice President, Marketing and Communications

KYRSTEN CONOVER
Development Associate, Operations

INGRID DANKERS
Gift Processing Assistant

LORI FEDERICO
Accounting Assistant

DANNY HARPER
Senior Philanthropic Advisor

MAHUA HEATH
Senior Philanthropic Advisor

MORGAN HERMAN
Executive Vice President, Development

LAUREL LYLE
Vice President, Board Relations and Development Operations

LORI MARCHETTI
Accounting Supervisor

LAINIE MORRIS
Development Associate

JESSICA MUTCH
Chief Financial Officer

CHRISTINA NOVAK
Senior Philanthropic Advisor, Institutional Relations

LISA RAND
Vice President, Marketing and Communications

EMANUELA ZAHARIEVA RAPPOPORT, PH.D.
Science Communicator

CAITLIN SAIA
Director, Grant Administration

CHARLES SEAKS, PH.D.
Director, Grant Management

NIKKI SENGSAVANH
Director, Development Operations

SHARON SEVRANSKY
Coordinator, Development Operations

JOHN SLATTERY
Senior Vice President, Major Gifts

MEG SMITH
Executive Vice President, Research Management

CONNOR SWAN
Senior Manager, Leadership Gifts and Heroes Program

JENNIFER TEGAN
Director, Marketing

DOROTHY VACARO
Gift Processing Coordinator

KELLY WESTERHOUSE
Vice President, Leadership Giving

ELIZA WHYTE
Office Manager

MONICA ZGOLA
Vice President, Human Resources

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 2022 heroes.

A. Ron Hubbard and Jim Jones, aka Bald Move, 4th Annual 24-Hour Groundhog Day Movie Marathon
Alan Arnette
Alexa Burton
Alexa Mach and Nolan Austin
Banger Pickleball™
Bethany Magley, Briteboom 12-Hour Charity Stream
Blue Awning's Charity Stream
Bowieowie's End Alzheimer's Fundraiser
Bry Bo's BetterMinds Stream
Bryan Severance, Chicken Wire Challenge
Carl Foote, Magical Memory Tour 2022
Carolyn Mastrangelo, Running 4 Answers
Casey LeFever, Next Day Koi
Council Rock North High School
Courtney Iverson, Morels & Memories—Mushroom Hunt & Alzheimer's Fundraiser
David K. Johnson Foundation
Diana Fiske, Essex Platform Tennis Club Alzheimer's Tournament
Dick Thomalla, Kathy Thomalla Memorial Golf Tournament
DireHowl Gaming
Don Lachapelle, Lucille Lachapelle Charitable Foundation Golf Tournament
Dylan Russell, Carma Cup
Ed Willett, 2022 Hoka Hey Motorcycle Challenge™
Ella O'Donnell
Fraternal Order of Eagles–Riverside Aerie 997
Grace Munaco
Hammy Rel13f Fund Golf Tournament
Heather McCarthy
Helensen's Charity Stream
International Association of Fire Fighters (IAFF) Local 792
Irene Young, Race to Remember 5K
Jacob Stein, Dollar Donations
Jake Wolfe, Tim Noll and Andrew Pfriem, Racing for a Cause
Jason Kollat, aka Badgunpla, Plastic Model Weekender
Jessica Lawshe, Runs for a Purpose
Joanna Nowak and Lauren Leonard, The Loneliness Project
Jog Your Memory 5K
John Fraraccio, Hudson/Essex Challenge to Cure Alzheimer's
Jonathan Cohen, 4x4x48 Challenge in Memory of Ziva Cohen
Joshua Crane, The Coffee Ride
Julia Gastrinakis
Kerri Tillquist
Kimberly O'Mahony
Ladies Shoot Straight Golf League Alzheimer's Day
Marilyn's Legacy
Matt Hofbauer, Sweating for Alzheimer's
Mike Dermont, Coterie
Montgomery Country Club Men's Golf Association, Mark McKenna Memorial Golf Tournament
Multicultural Association of Pre-Health Students
Nicolas Martell, aka ShurieVR, Stream to Remember 2
Nikki Patrick, Strengthlets
Nikki Zazzali, Revive Jewelry
Nuckin's Alzheimer's Fundraiser
ONEHOPE Wine
Patrick Toon, Feet for Brains
Rebecca and Megan Lovell, aka Larkin Poe, Larkin Poe Mind Over Matter Talisman Necklace
Renae Haddadin, Quilts on the Corner
Shelly Mellott, Impact Charms
SingStrong
sumBee's Charity Stream
Sunwink PBC
Sustainable Sports Foundation
That TCG Guy's Lest We Forget Stream
The Nagengast Family
The Neon Knights for Alzheimer's
The Stake Club
The Turner Family
The Walters Family
The Whetton Family
Vincent Purpura III, Purpura Family Foundation
Waking Up Foundation
Weeble Spleen
William Jepson
Yvette Gonzalez-Nacer, Creative Minds Care

Heroes at Work

PATRICK TOON

Feet for Brains
New York, New York

Patrick Toon has raced through deserts, up mountains and even the stairwells of the Empire State Building in New York City. In 2022, he set a personal challenge to celebrate the perseverance of his father, Dan, who was diagnosed with Alzheimer's disease in 2018: run 2,000 miles and raise $2,000 by April 17, 2023, when he would run the Boston Marathon. Sadly, Dan passed just days before the race. "This one's for Dan," he wrote. Patrick ran the 26.2 miles from Hopkinton to Copley Square and crossed the finish line at 3:15, completing a yearlong journey and raising more than $4,000 for CureAlz.

VINCENT PURPURA III

Purpura Family Foundation Golf Tournament
Hopkinton, Massachusetts

"The Purpura Family Foundation is a direct response to my mother Jane's Alzheimer's diagnosis," said Vin Purpura. The foundation runs one event—a golf outing—and 2022 was its inaugural year. "We hope to raise awareness of the fight against Alzheimer's and money for that fight. The Purpura Family Foundation's simple goal is that a child in the future will never have the Alzheimer's talk with a loved one; we hope that we can be part of this gift to future generations." The event raised $80,000 for CureAlz research.

Members of the Purpura Family; Vin is the fourth person on the right, in blue shirt and sunglasses.

A. RON HUBBARD AND JIM JONES

Bald Move
Cincinnati, Ohio

Podcasting out of a small studio in Cincinnati, A. Ron Hubbard (left) and Jim Jones (right) generate hundreds of hours of video, audio and gaming content each year. Their mission: to deliver passionate, fan-first, honest commentary on their favorite television shows and movies. Each Groundhog Day, they use their Twitch channel to conduct 24-hour movie marathons of franchises including "Star Trek," "James Bond" and "Fast & Furious." For the past three years they have asked their viewers and followers to contribute to Cure Alzheimer's Fund, raising an incredible $62,173 for Alzheimer's research.

The Turner Family. Kate is on the far left.

KATE TURNER

The Turner Family
Ridgefield, Connecticut

Kate's husband, John, was diagnosed with early-onset Alzheimer's more than six years ago. "He was 52 with no family history of the disease and [was] otherwise very healthy," Kate said. With help from her family, friends and community, Kate started a GoFundMe fundraiser that raised nearly $43,000 for CureAlz research. "John is a relentless fighter. He has fought like hell to slow the progression of the disease, following every recommendation from his doctors. It is not an easy road. But we are committed to not giving up hope."

IRENE YOUNG

Race to Remember 5K
Fishers, Indiana

The inaugural Race to Remember 5K Run/Walk, a family and community event to raise funds to combat Alzheimer's disease, was held on Sept. 17, 2022. The event, which honored those with Alzheimer's disease and their families, drew more than 130 people and raised more than $20,000 for research. "We look forward to making this an annual day to fight for the memory and cognition of those we love and future generations," said founder Irene Young.

Some of the130 volunteers and participants who helped make the first Race to Remember a success.

Participants gather for the paddle tennis tournament with a "festival" atmosphere organized each year by Bryan Severance.

BRYAN SEVERANCE

Chicken Wire Challenge
Atlantic Highlands, New Jersey

For the past two years, Bryan Severance has brought more than 250 friends together to hold a paddle tennis tournament to benefit CureAlz. "We based it around the chicken wire that covers all sides of the court. It started with just my college friends and has grown into a great paddle tennis tournament that everyone seems to look forward to each year," he said. "I always try to make it stranger and more fun each year. Hence the 20-foot blow-up chicken. Last year we had a marching band, this year stilt walkers, jugglers, face painters and a great band." Severance and company have raised more than $17,000 for research into Alzheimer's disease.

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 Story of Cure Alzheimer's Fund

"The human brain is magnificent. And mysterious."

As a nonprofit organization whose purpose is to end a massive and terrible human condition, we are steadfastly focused on our mission. Our operational model is complex, our ecosystem of researchers is wide-ranging and the problem we are obsessed with solving exists deep in the expanse of one of nature's most elaborate constructions: the human brain.

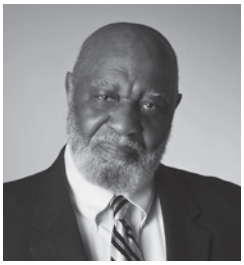
These factors do not make us any less committed to our intentions, but they do complicate the full telling of our story. This short film conveys the complete essence of our organization—from our founders to our researchers, from our quiet beginning to our current status as a leading fundraising organization in the field of Alzheimer's research.

The narration is delivered with wonderful nuance by talented actor Franklin Ojeda Smith. Born on the Sea Islands of South Carolina, his voice is rich with experience, humanity and compassion; it brings our story to life, and adds warmth and weight to our mission.

Underneath this, and almost in counterpart to Franklin's baritone, is the beautiful, captivating and emotional music of Jóhann Jóhannsson. A celebrated and award-winning composer, the beautiful and surreal landscapes of his native Iceland are indelibly etched in his work.

We are beyond proud that their talents are here, helping us to tell the story of our organization. We hope you enjoy watching, listening and learning.

CureAlz.org/about-us/our-story/



FRANKLIN OJEDA SMITH

"The Blacklist," "Boardwalk Empire," "The Black Hamptons," "Nurse Jackie," "Rescue Me"

JÓHANN JÓHANNSSON

"The Theory of Everything," "Arrival," "Prisoners," Academy Award nominee, Golden Globe winner

Selected Publications

During 2022, four publications were created to share information about the achievements being made as a result of the funded research, and also to share the stories of those who have dedicated themselves to a cure.

DISCOVERIES II

The researchers who have received grants from CureAlz have made significant advancements in our understanding of the disease. DISCOVERIES II, a companion piece to DISCOVERIES, provides summary descriptions of 16 of their projects, including updates on diagnostic tools, the Alzheimer's Genome Project™, apolipoprotein E4 and genetic risk to women. To read DISCOVERIES II, please visit **http://bit.ly/3iOC98p**

LEVERAGE

The best way to accelerate potential therapies for Alzheimer's disease is to support fundamental proof-of-concept research into its causes. Once validated through our grants, these ideas may receive follow-on funding from the National Institutes of Health/National Institute on Aging (NIH/NIA) far beyond what our resources alone can provide. LEVERAGE showcases the results of three years of CureAlz grants totaling $47 million that led to $350 million in follow-on funding from NIH. To read more, visit **http://bit.ly/3KkQ5Ba**

HONORING OUR HEROES

Dictionary.com defines a hero as a person noted for courageous acts or nobility of character; a person who…is regarded as a role model or ideal. A CureAlz Hero is someone who has felt the pain of loss caused by Alzheimer's disease. Someone who has chosen to be part of the solution and rallies others to join them. Someone who knows that funding research is the only path to a cure. **http://bit.ly/3mx1hmp**

HONORING OUR RESEARCHERS

At Cure Alzheimer's Fund, we are inspired every day by the dedicated researchers and the scientific progress being made in the fight against Alzheimer's disease. We proudly fund their theories, support their creative thinking and encourage them to collaborate, because that is what it will take to find a cure. We invite you to read their stories and get to know some of the remarkable people working in laboratories around the world. **http://bit.ly/3o5vNV6**

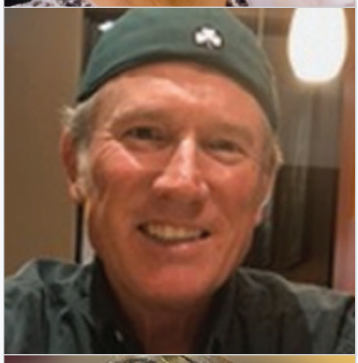
Special Event: The 2nd Annual Cure Alzheimer's Fund Golf Tournament

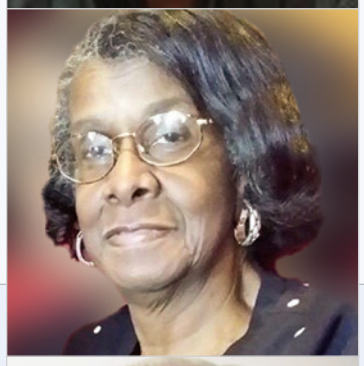
On Oct. 6, 104 golfers came together to enjoy a day of golf at Fishers Island Club in New York and to contribute to research being funded by Cure Alzheimer's Fund. Fishers Island Club is among the most exclusive and scenic golf courses in the world, and offers picturesque views of Long Island Sound and the Atlantic Ocean from every hole.

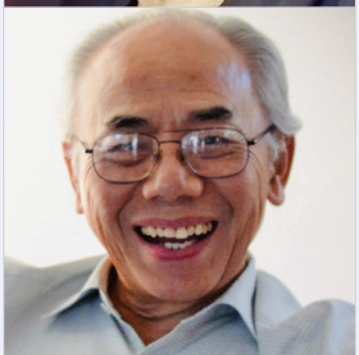
The full day began with golfers arriving by morning ferry, followed by a hearty breakfast and 18 holes of golf. The tournament was a best ball format, with prizes awarded for top three team scores, longest drive and closest to the pin. Dinner on the lawn and an auction rounded out the day. More than $326,000 was raised for research.

"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 raise funds for research.







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.

Cure Alzheimer's FUND

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.
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.
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.
Crypto	Cure Alzheimer's Fund is pleased to accept crypto for donations to support our research.

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

CHARITY NAVIGATOR ★★★★ Four Star Charity

Cure Alzheimer's Fund has been awarded the highest rating of 4 stars for 12 consecutive years.

GUIDESTAR PLATINUM PARTICIPANT

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

BBB ACCREDITED CHARITY

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

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