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


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
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

**FEBRUARY 2022**

*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

*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

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

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 Neuronal Cells Promotes Memory Impairment Associated With Amyloid β Plaques
Hui Zheng

**Cell Reports**
Absence of Microglia Promotes Diverse Pathologies and Early Lethality in Alzheimer's Disease Mice
Mathew Blurton-Jones

**Journal of Biological Chemistry**
The Dual Fates of Exogenous Tau Seeds: Lysosomal Clearance vs. Cytoplasmic Amplification
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**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

**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 Further Decoding of Alzheimer Disease Genetics
Christina M. Lill and Lars Bertram

**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

**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

**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
Rudolf 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

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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
Marco Colonna

Biomolecules
P2 Receptors: Novel Disease Markers and Metabolic Checkpoints in Immune Cells
Francesco Di Virgilio

Aging Cell
Effects of Cerebral Amyloid Angiopathy on the Brain Vasculome
Eng H. Lo

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 Lymphatic 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
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

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
Eckhard Mandelkow

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 Ca 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.

SRDJAN D. ANTIC, M.D.
University of Connecticut Health Center

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

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

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

HELENE BENVENISTE, M.D., PH.D.
Yale School of Medicine

MICHAEL A. BONAGUIDI, PH.D.
University of Southern California

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

ALEXANDRE BONNIN, PH.D.
University of Southern California
New Funded Researcher, 2022

RAJA BHATTACHARYYA, PH.D.
Massachusetts General Hospital; Harvard Medical School

MATHIEU BOURDENX, PH.D.
University College London, England
New Funded Researcher, 2022

STACI D. BILBO, PH.D.
Duke University
New Funded Researcher, 2022

PAOLA BOVOLENTA, PH.D.
Universidad Autónoma de Madrid, Spain

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

GUNNAR BRINKMALM, PH.D.
University of Gothenburg, Sweden
New Funded Researcher, 2022
ALEJANDRA CAMACHO-SOTO, M.D., M.P.H.S.
Washington University School of Medicine in St. Louis

OLEG BUTOVSKY, PH.D.
Brigham and Women’s Hospital; Harvard Medical School

COLETTE CYWES-BENTLEY, PH.D.
Brigham and Women’s Hospital; Harvard Medical School

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

SANDRO DA MESQUITA, PH.D.
Mayo Clinic, Jacksonville

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

ANNIE CIERNIA, PH.D.
University of British Columbia, Canada
New Funded Researcher, 2022

BART DE STROOPER, M.D., PH.D.
KU Leuven, Belgium; University College London, England
Research Leadership Group

MAARTEN DEWILDE, PH.D.
KU Leuven, Belgium

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

CASEY N. COOK, PH.D.
Mayo Clinic, Jacksonville
New Funded Researcher, 2022

MAUREN DE WILDE, PH.D.
KU Leuven, Belgium

LAURA M. COX, PH.D.
Brigham and Women’s Hospital; Harvard Medical School

MARC I. DIAMOND, M.D.
University of Texas Southwestern Medical Center
Research Leadership Group

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Northwestern University Feinberg School of Medicine

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Massachusetts General Hospital; Harvard Medical School
New Funded Researcher, 2022

FRANCESCO DI VIRGILIO, M.D.
University of Ferrara, Italy
VISHWA DEEP DIXIT, D.V.M., PH.D.
Yale School of Medicine

P. MURALI DORAISWAMY, M.B.B.S.
Duke University School of Medicine
Research Leadership Group

KAREN E. DUFF, PH.D.
University College London, England
Research Leadership Group

JOSEPH R. ECKER, PH.D.
Salk Institute for Biological Studies

MICHELLE E. EHRLICH, M.D.
Icahn School of Medicine at Mount Sinai

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

EVANDRO F. FANG, PH.D.
Akershus University Hospital, Norway
New Funded Researcher, 2022

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

CALEB E. FINCH, PH.D.
University of Southern California
Research Leadership Group

LIISA GALEA, PH.D.
Centre for Addiction and Mental Health, Canada

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

LI GAN, PH.D.
Weill Cornell Medicine
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Icahn School of Medicine at Mount Sinai

ANNA GREKA, M.D., PH.D.
Brigham and Women’s Hospital; Harvard Medical School; Broad Institute

ANA GRICIUC, PH.D.
Massachusetts General Hospital; Harvard Medical School

VINCE GROPPI, PH.D.
Oricula Therapeutics
Research Strategy Council

CHRISTIAN HAASS, PH.D.
German Center for Neurodegenerative Diseases (DZNE), Germany
Research Leadership Group

BENJAMIN M. HAMPSTEAD, PH.D., ABPP/CN
University of Michigan

OSKAR HANSSON, M.D., PH.D.
Lund University, Sweden
New Funded Researcher, 2022

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

WINSTON HIDE, PH.D.
Beth Israel Deaconess Medical Center; Harvard Medical School

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Massachusetts General Hospital; Harvard Medical School

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The Johns Hopkins University School of Medicine
Research Leadership Group

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Harvard Medical School
New Funded Researcher, 2022

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Weill Cornell Medical College

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Hong Kong University of Science and Technology (HKUST)
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Whitehead Institute; Massachusetts Institute of Technology

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Massachusetts General Hospital; Harvard Medical School
MATHIAS JUCKER, PH.D.
University of Tübingen, Germany; German Center for Neurodegenerative Diseases (DZNE)

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University of Tübingen, Germany

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Mayo Clinic, Jacksonville

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Massachusetts General Hospital; Harvard Medical School

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Washington University School of Medicine in St. Louis
Research Leadership Group

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Brigham and Women’s Hospital; Harvard Medical School

BRUCE LAMB, PH.D.
Indiana University School of Medicine
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MEYTAL LANDAU, B. PHARM, M.S.C., PH.D.
Technion, Israel Institute of Technology; Deutsches Elektronen-Synchrotron (DESY)
New Funded Researcher, 2022

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Harvard T.H. Chan School of Public Health
Research Leadership Group

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University of Virginia
Research Strategy Council

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Boston Children’s Hospital; Harvard Medical School

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TONG LI, PH.D.
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New Funded Researcher, 2022

YUEMING LI, PH.D.
Memorial Sloan Kettering Cancer Center
Research Leadership Group

STEFAN LICHTENTHALER, PH.D.
German Center for Neurodegenerative Diseases (DZNE); Technische Universität München (TUM)
New Funded Researcher, 2022

VIJAY K. KUCHROO, D.V.M., PH.D.
Brigham and Women’s Hospital; Harvard Medical School

CHRISTINA M. LILL, M.D., M.SC.
University of Münster, Germany; Imperial College London, England

SHANE A. LIDDELOW, PH.D.
New York University
Research Leadership Group

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

RICHARD B. LIPTON, M.D.
Albert Einstein College of Medicine
Ronaldo C. Petersen, M.D., Ph.D.
Mayo Clinic, Rochester
Research Leadership Group

Leonard Petrucelli, Ph.D.
Mayo Clinic, Jacksonville

Andreas R. Pfennig, Ph.D.
Carnegie Mellon University

Gerald B. Pier, Ph.D.
Brigham and Women’s Hospital; Harvard Medical School

Paola Pizzo, B.C.S., Ph.D.
University of Padova, Italy

Wolfram C. Poller, M.D.
Icahn School of Medicine at Mount Sinai
New Funded Researcher, 2022

Francisco J. Quintana, Ph.D.
Brigham and Women’s Hospital; Harvard Medical School
New Funded Researcher, 2022

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

Brad A. Racette, M.D.
Barrow Neurological Institute

Karen Reeves, M.D.
AZTherapies
Research Strategy Council

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

Scott J. Russo, Ph.D.
Icahn School of Medicine at Mount Sinai
New Funded Researcher, 2022

Katherine R. Sadleir, Ph.D.
Northwestern University Feinberg School of Medicine
New Funded Researcher, 2022

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

Ronald L. Schmaier, Ph.D.
The Johns Hopkins University School of Medicine
New Funded Researcher, 2022

Subhash Sinha, Ph.D.
Weill Cornell Medicine

Sangram S. Sisodia, Ph.D.
University of Chicago
Research Leadership Group

John Sondek, Ph.D.
University of North Carolina at Chapel Hill
ANDREW YANG, PH.D.
University of California, San Francisco
New Funded Researcher, 2022

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

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

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

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

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

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.

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<th>Grant Funding* by Project Age</th>
<th>$6,392</th>
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<td>Competitive Renewal/ Follow-on $1,920</td>
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<td>Non-competitive Renewal $15,028</td>
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**Number of New Investigators and Projects**

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<th>Number</th>
<th>% of Total</th>
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<td>New Named Investigators</td>
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<td>New Projects</td>
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<td>New Institutions</td>
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*Excludes Taconic and scientific meeting spending

**Project/Researcher**

**FOUNDATIONAL RESEARCH**

**GENETIC RISK FACTORS**

The Alzheimer’s Genome Project™
Rudolph E. Tanzi, Ph.D., Massachusetts General Hospital; Harvard Medical School

**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

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

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

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

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

Sex Differences in Alzheimer’s Disease Progression: Framingham Heart Study
P. Mural Doraiswamy, M.B.B.S., Duke University School of Medicine

**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

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

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

Genes to Therapies™ (G2T) Research Models and Materials
Taconic Biosciences

CURE ALZHEIMER’S FUND | ANNUAL REPORT 2022 27
<table>
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<th>Project/Researcher</th>
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<td><strong>CIRCUITS: Interpreting Alzheimer’s Disease-Associated Genetic Variation at Enhancer Regions</strong></td>
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<td>Andreas R. Pfenning, Ph.D., Carnegie Mellon University</td>
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<td><strong>CIRCUITS: Characterizing Epigenetic Biomarkers of Human Cognitive Aging</strong></td>
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<td>Lars Bertram, M.D., University of Lübeck, Germany</td>
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<td><strong>CIRCUITS: Impact of Genetic, Epigenetic and Cellular Variants on Alzheimer’s Disease Pathology</strong></td>
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<td>Rudolf Jaenisch, M.D., Whitehead Institute; Massachusetts Institute of Technology</td>
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<td>Joseph R. Ecker, Ph.D., Salk Institute for Biological Studies</td>
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<td><strong>TRANsLATIONAL RESEARCH</strong></td>
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<td><strong>Studies of Novel Alzheimer’s Disease Genes</strong></td>
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<td>Dissecting the Modulatory Roles of Interleukin-17 Receptor D in Alzheimer’s Disease</td>
<td>$201,250</td>
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<td>Jun Huh, Ph.D., Harvard Medical School</td>
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<td>Understanding and Mimicking the Biological Effects of the Phospholipase C-gamma-2 P522R Variant That Protects Against Alzheimer’s Disease</td>
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<td>Rik van der Kant, Ph.D., Amsterdam University Medical Centers, The Netherlands</td>
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<td><strong>ABCA7 Loss of Function in Aging and Alzheimer’s Disease</strong></td>
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<td>Takahisa Kanekiyi, M.D., Ph.D., Mayo Clinic, Jacksonville</td>
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<td>In Vivo Characterization of a Loss-of-Function GGA3 Rare Variant Associated with Alzheimer’s Disease</td>
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<td>Giuseppina Tesco, M.D., Ph.D., Tufts University School of Medicine</td>
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<td><strong>Single Nucleus RNA Sequencing Analysis of ACE1 R1284Q Knock-in Mice</strong></td>
<td>$246,804</td>
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<td>Robert Vassar, Ph.D., Northwestern University Feinberg School of Medicine</td>
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<td>David M. Gate, Ph.D., Northwestern University Feinberg School of Medicine</td>
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<td>Leah K. Cuddy, Ph.D., Northwestern University Feinberg School of Medicine</td>
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<td>Functional Basis for Novel Protein Kinase C-eta K56R Mutation in Alzheimer’s Disease</td>
<td>$172,500</td>
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<td>Alexandra C. Newton, Ph.D., University of California, San Diego</td>
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<td>Exploring the Therapeutic Potential of Clusterin in a Preclinical Model of Alzheimer’s Disease</td>
<td>$201,250</td>
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<td>Alban Gaultier, Ph.D., University of Virginia</td>
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<td><strong>Studies of Amyloid Precursor Protein (APP) and Amyloid Beta</strong></td>
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<td>Structural Mimicry in Microbial and Antimicrobial Amyloids Connected to Neurodegenerative Diseases</td>
<td>$200,760</td>
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<td>Meytal Landau, B. Pharm, M.S.C., Ph.D., Technion, Israel Institute of Technology; Deutsches Elektronen-Synchrotron (DESY)</td>
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<td>Effects of Depalmitoylation and ACAT Inhibition on Axonal Amyloid Beta Generation Via MAM-Associated palAPP</td>
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<td>Raja Bhattacharyya, Ph.D., Massachusetts General Hospital; Harvard Medical School</td>
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<td>Rudolph E. Tanzi, Ph.D., Massachussetts General Hospital; Harvard Medical School</td>
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<td>Secreted Frizzled Related Protein 1 (SFRP1) as a Therapeutic Target and Diagnostic/Prognostic Factor in Alzheimer’s Disease</td>
<td>$172,500</td>
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<td>Paola Bovolenta, Ph.D., Universidad Autónoma de Madrid, Spain</td>
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<td>Air Pollution and Alzheimer’s Disease Risk Interact with Premature Aging of Neural Stem Cells and Apolipoprotein E Alleles</td>
<td>$219,535</td>
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<td>Caleb E. Finch, Ph.D., University of Southern California</td>
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<td>Michael A. Bonaguidi, Ph.D., University of Southern California</td>
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<td><strong>Studies of Tau</strong></td>
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<td>Alzheimer’s Disease Tau Consortium: How Do Soluble Tau Species Replicate</td>
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<td>Bradley T. Hyman, M.D., Ph.D., Massachusetts General Hospital; Harvard Medical School</td>
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<td>Alzheimer’s Disease Tau Consortium: The Role of Amyloid Beta-Induced Membrane Damage in Tau Pathology</td>
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<td>Katherine R. Sadier, Ph.D., Northwestern University Feinberg School of Medicine</td>
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<td>Robert J. Vassar, Ph.D., Northwestern University Feinberg School of Medicine</td>
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<td>Alzheimer’s Disease Tau Consortium: Impact of Tau Mutations and Amyloid Beta on Tau Post-Translational Modifications and Conformation</td>
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<td>Karen E. Duff, Ph.D., University College London, England</td>
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<td><strong>Alzheimer's Disease Tau Consortium: Deep Mass Spectrometry Profiling of Tau Aggregates in Alzheimer's Disease and Other Tauopathies</strong>&lt;br&gt;Henrik Zetterberg, M.D., Ph.D., University of Gothenburg, Sweden&lt;br&gt;Gunnar Brinkmalm, Ph.D., University of Gothenburg, Sweden</td>
<td>$287,500</td>
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<td><strong>Alzheimer's Disease Tau Consortium: Role of VCP/p97 in Tau Prion Replication</strong>&lt;br&gt;Marc I. Diamond, M.D., University of Texas Southwestern Medical Center</td>
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<td><strong>Characterization of Tau Pathology Heterogeneity Across the Alzheimer’s Disease Spectrum</strong>&lt;br&gt;Oskar Hansson, M.D., Ph.D., Lund University, Sweden&lt;br&gt;Rik Ossenkoppele, Ph.D., Amsterdam University Medical Centers, The Netherlands; Lund University, Sweden</td>
<td>$201,250</td>
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<td><strong>Properties of Tau in Posterior Cortical Atrophy</strong>&lt;br&gt;Bradley T. Hyman, M.D., Ph.D., Massachusetts General Hospital; Harvard Medical School&lt;br&gt;John R. Dickson, M.D., Ph.D., Massachusetts General Hospital; Harvard Medical School</td>
<td>$172,500</td>
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<td><strong>RNA as a Determinant of Tau Seeding</strong>&lt;br&gt;Marc I. Diamond, M.D., University of Texas Southwestern Medical Center</td>
<td>$230,000</td>
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<td><strong>Targeting Tauopathies with Antisense Oligonucleotides to Synaptogyrin-3</strong>&lt;br&gt;Patrik Verstreken, Ph.D., VIB-KU Leuven, Belgium</td>
<td>$215,625</td>
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<td><strong>Using Long-Read Sequencing to Investigate the MAPT Locus and Transcripts in Neurodegeneration</strong>&lt;br&gt;John Hardy, Ph.D., University College London, England</td>
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<td><strong>Toxic Effects of Extracellular Tau Oligomers on Neurons</strong>&lt;br&gt;George S. Bloom, Ph.D., University of Virginia</td>
<td>$198,932</td>
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<td><strong>Investigating the Role of Tau Protein in Neuronal Senescence Induction and Maintenance</strong>&lt;br&gt;Miranda E. Orr, Ph.D., Wake Forest University School of Medicine</td>
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<td><strong>STUDIES OF APOLIPOPROTEIN E (APOE)</strong>&lt;br&gt;APOE Consortium: APOE4-mediated Dysfunction of CD8 T-Cell-Microglia Crosstalk in Alzheimer’s Disease&lt;br&gt;Oleg Butovsky, Ph.D., Brigham and Women's Hospital; Harvard Medical School</td>
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<td><strong>APOE Consortium: Modulation of Selective Neuronal Vulnerability in Alzheimer’s Disease by Apolipoprotein E</strong>&lt;br&gt;Jean-Pierre Roussarie, Ph.D., Boston University School of Medicine</td>
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<td><strong>APOE Consortium: Assessing the Added Diagnostic Value of Peripheral Apolipoprotein E Protein Levels in Current Blood-Based Biomarker Assays for Central Nervous System Amyloidosis</strong>&lt;br&gt;Randall J. Bateman, M.D., Washington University School of Medicine in St. Louis</td>
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<td><strong>APOE Consortium: Effect of Cholesteryl Ester Transfer Protein Activity on Amyloid and Cerebrovascular Pathologies in Animal Models of Alzheimer’s Disease</strong>&lt;br&gt;Cheryl Wellington, Ph.D., University of British Columbia, Canada</td>
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<td><strong>APOE Consortium: Role of APOE Isoforms in Immune Responses in a Model of Tauopathy</strong>&lt;br&gt;David M. Holtzman, M.D., Washington University School of Medicine in St. Louis</td>
<td>$345,000</td>
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<td><strong>Establishing the Molecular and Cellular Mechanisms and Biomarkers of APOE4-mediated Susceptibility to Tau-related Cognitive Impairments</strong>&lt;br&gt;Joel Blanchard, Ph.D., Icahn School of Medicine at Mount Sinai</td>
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<td><strong>Sex Matters: Understanding the Influence of Sex and Apolipoprotein E (APOE) Genotype on Hippocampal Plasticity and Cognition</strong>&lt;br&gt;Liisa Galea, Ph.D., Centre for Addiction and Mental Health, Canada</td>
<td>$170,200</td>
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<td><strong>STUDIES OF THE IMMUNE RESPONSE IN ALZHEIMER’S DISEASE</strong>&lt;br&gt;Neuroimmune Consortium: Biomarker Tool Development&lt;br&gt;Jacob M. Hooker, Ph.D., Massachusetts General Hospital; Harvard Medical School</td>
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<td><strong>Neuroimmune Consortium: Understanding the Consequences of Noncoding Alzheimer’s Disease Risk Alleles on Microglia Function</strong>&lt;br&gt;Beth Stevens, Ph.D., Boston Children's Hospital; Harvard Medical School; Broad Institute</td>
<td>$300,000</td>
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<td><strong>Neuroimmune Consortium: Assessing the Links Between the MS4A Risk Genes, Microglia and Alzheimer’s Disease</strong>&lt;br&gt;Sandeep Robert Datta, M.D., Ph.D., Harvard Medical School</td>
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<td><strong>Neuroimmune Consortium: Investigation of Alzheimer’s Disease Risk Alleles in Astrocytes—Focus on Cholesterol Transport and Microglia Interactions</strong>&lt;br&gt;Shane A. Liddelow, Ph.D., New York University</td>
<td>$115,000</td>
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<td><strong>Neuroimmune Consortium: Examining the Role of Human Microglia in the Transition</strong></td>
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<td><strong>Between Parenchymal and Vascular Amyloid Beta Pathology</strong></td>
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<td>Mathew Blurton-Jones, Ph.D., University of California, Irvine</td>
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<td><strong>Neuroimmune Consortium: Leveraging Enhancer Landscapes to Decode Alzheimer’s</strong></td>
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<td><strong>Disease Risk Alleles in Microglia</strong></td>
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<td>Christopher K. Glass, M.D., Ph.D., University of California, San Diego</td>
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<td><strong>Elucidating the Role of Soluble Epoxide Hydrolase and Arachidonic Acid</strong></td>
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<td><strong>Metabolism in Neuroinflammation and Alzheimer’s Disease</strong></td>
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<td>Hui Zheng, Ph.D., Baylor College of Medicine</td>
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<td><strong>Systems Integration and Therapeutics Translation in Alzheimer’s</strong></td>
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<td>Alison M. Goate, D.Phil., Icahn School of Medicine at Mount Sinai</td>
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<td>Edoardo Marcora, Ph.D., Icahn School of Medicine at Mount Sinai</td>
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<td><strong>Role of Checkpoint Molecule TIM-3 in Regulating Microglia in Alzheimer’s</strong></td>
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<td>Vijay K. Kuchroo, D.V.M., Ph.D., Brigham and Women’s Hospital; Harvard Medical</td>
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<td><strong>Revealing New Genes and Pathways at the Intersection of Lipotoxic and Genetic</strong></td>
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<td><strong>Risk for Alzheimer’s Disease</strong></td>
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<td>Anna Greka, M.D., Ph.D., Brigham and Women’s Hospital; Harvard Medical School;</td>
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<td>Beth Stevens, Ph.D., Boston Children’s Hospital; Harvard Medical School; Broad</td>
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<td><strong>Contributions of IL-34 Signaling to Microglial Function and Alzheimer’s</strong></td>
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<td><strong>Pathology in Mice</strong></td>
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<td>Staci D. Bilbo, Ph.D., Duke University</td>
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<td><strong>Microglial-Specific INPSSD Knockdown Modulates Behavior, Amyloidosis and</strong></td>
<td>$217,327</td>
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<td><strong>Tauopathy in Alzheimer’s Mouse Models</strong></td>
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<td>Samuel E. Gandy, M.D., Ph.D., Icahn School of Medicine at Mount Sinai</td>
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<td>Michelle E. Ehrlich, M.D., Icahn School of Medicine at Mount Sinai</td>
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<td><strong>Human Brain CD33 Ligand, Receptor Protein Tyrosine Phosphatase Zeta (RPTP)S3L,</strong></td>
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<td><strong>Limits Microglial Phagocytosis and Contributes to Alzheimer’s Disease</strong></td>
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<td>Ronald L. Schnaar, Ph.D., The Johns Hopkins University School of Medicine</td>
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<td>Tong Li, Ph.D., The Johns Hopkins University School of Medicine</td>
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<td><strong>The Role of Astrocyte-Derived Toxic Lipids Mediating Degeneration in Alzheimer’s</strong></td>
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<td><strong>The Role of Interferon-Induced Transmembrane Protein 3 (IFITM3) and Gamma-</strong></td>
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<td><strong>Secretase in Microglia</strong></td>
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<td>Yueming Li, Ph.D., Memorial Sloan Kettering Cancer Center</td>
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<td><strong>Prenatal Inflammation Effects on Blood-Brain Barrier Function and Alzheimer’s</strong></td>
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<td><strong>Disease-Related Pathologies Across the Lifespan</strong></td>
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<td>Alexandre Bonnin, Ph.D., University of Southern California</td>
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<td><strong>Extracellular ATP is a Key Factor in Promoting Alzheimer’s Disease Neuroin</strong></td>
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<td>Paola Pizzo, B.C.S., Ph.D., University of Padova, Italy</td>
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<td>Francesco Di Virgilio, M.D., University of Ferrara, Italy</td>
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<td><strong>Targeting a Master Innate Immune Adaptor Molecule in Alzheimer’s</strong></td>
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<td>John R. Lukens, Ph.D., University of Virginia</td>
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<td><strong>Investigating the Contribution of Astrocytic-Dependent Inflammation on</strong></td>
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<td><strong>Amyloid-Induced Tau Pathology</strong></td>
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<td>Gilbert Gallardo, Ph.D., Washington University School of Medicine in St. Louis</td>
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<td><strong>Contribution of Skull Bone Marrow-Derived Cells to Alzheimer’s</strong></td>
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<td>Jonathan Kipnis, Ph.D., Washington University School of Medicine in St. Louis</td>
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<td><strong>Role of Microglia in Degradation and Trimming of Alzheimer’s Amyloid Beta</strong></td>
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<td>Frederick R. Maxfield, Ph.D., Weill Cornell Medical College</td>
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<td><strong>Role of Secreted Protein Acidic and Rich in Cysteine (SPARC) in Immunometabolic</strong></td>
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<td><strong>Control of Age-Related Inflammation</strong></td>
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<td>Vishwa Deep Dixit, D.V.M., Ph.D., Yale School of Medicine</td>
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<td><strong>Neuroimmune Connectome Perturbations in Alzheimer’s Disease</strong></td>
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<td>Francisco J. Quintana, Ph.D., Brigham and Women’s Hospital; Harvard Medical School</td>
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<td><strong>STUDIES OF ALTERNATIVE NEURODEGENERATIVE PATHWAYS</strong></td>
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<td><strong>Brain Entry and Exit Consortium: Crosstalk of Central Nervous System Barriers</strong></td>
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<td><strong>and Clearance Routes in Homeostasis and Alzheimer’s Disease</strong></td>
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<td>Jonathan Kipnis, Ph.D., Washington University School of Medicine in St. Louis</td>
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<td><strong>Brain Entry and Exit Consortium: Biochemical and Functional Analysis of</strong></td>
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<td><strong>Cerebrospinal Fluid and Lymph Following Changes in Brain Fluid Dynamics</strong></td>
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<td>Laura Santambrogio, M.D., Ph.D., Weill Cornell Medical College</td>
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<td><strong>Brain Entry and Exit Consortium: Identifying the Blood-Brain Barrier Changes During Alzheimer's Disease</strong>&lt;br&gt;Richard Daneman, Ph.D., University of California, San Diego</td>
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<td><strong>Brain Entry and Exit Consortium: Central Nervous System Fluid Homeostasis and Waste Clearance in Alzheimer's Disease Characterized by MRI</strong>&lt;br&gt;Helene Benveniste, M.D., Ph.D., Yale School of Medicine&lt;br&gt;Allen R. Tannenbaum, Ph.D., State University of New York at Stony Brook</td>
<td>$286,404</td>
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<td><strong>Neuroinflammation Contributions to Alzheimer's Disease: Role of the Choroid Plexus</strong>&lt;br&gt;Maria K. Lehtinen, Ph.D., Boston Children's Hospital; Harvard Medical School&lt;br&gt;Liisa Myllykangas, M.D., Ph.D., University of Helsinki, Finland</td>
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<td><strong>Turning Up Mitophagy to Blunt Alzheimer's Tau Pathologies</strong>&lt;br&gt;Evandro F. Fang, Ph.D., Akershus University Hospital, Norway</td>
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<td><strong>Immunotherapies Targeting the Microbiota to Prevent Cognitive Decline in Alzheimer's Disease</strong>&lt;br&gt;Gerald B. Pier, Ph.D., Brigham and Women's Hospital; Harvard Medical School&lt;br&gt;Colette Cywes-Bentley, Ph.D., Brigham and Women's Hospital; Harvard Medical School&lt;br&gt;Cynthia A. Lemere, Ph.D., Brigham and Women's Hospital; Harvard Medical School</td>
<td>$183,562</td>
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<td><strong>Targeting the Microbiome and Innate Immunity in Alzheimer's Disease</strong>&lt;br&gt;Howard L. Weiner, M.D., Brigham and Women's Hospital; Harvard Medical School&lt;br&gt;Laura M. Cox, Ph.D., Brigham and Women's Hospital; Harvard Medical School</td>
<td>$201,250</td>
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<td><strong>Stress and Neurovascular-Immune Networks in Alzheimer's Disease</strong>&lt;br&gt;Scott J. Russo, Ph.D., Icahn School of Medicine at Mount Sinai&lt;br&gt;Wolfram C. Poller, M.D., Icahn School of Medicine at Mount Sinai</td>
<td>$172,500</td>
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<td><strong>Neuroprotective Effects of the Exercise Hormone Irisin in Alzheimer's Disease</strong>&lt;br&gt;Se Hoon Choi, Ph.D., Massachusetts General Hospital; Harvard Medical School&lt;br&gt;Christiane Wrann, D.V.M., Massachusetts General Hospital; Harvard Medical School</td>
<td>$345,000</td>
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<td><strong>Circadian Perturbations of the Vasculome and Microgliome in Alzheimer's Disease</strong>&lt;br&gt;Eng H. Lo, Ph.D., Massachusetts General Hospital; Harvard Medical School</td>
<td>$200,417</td>
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<td><strong>Harnessing Meningeal Lymphatics and Immunity to Alleviate APOE4-Induced Brain Dysfunction</strong>&lt;br&gt;Sandro Da Mesquita, Ph.D., Mayo Clinic, Jacksonville</td>
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<td><strong>Alzheimer's Disease Pathophysiology Alters the Level of Electrical and Chemical Synapse Coupling in the Network of GABAergic PV+ Interneurons Early in Disease Course</strong>&lt;br&gt;Srdjan D. Antic, M.D., University of Connecticut Health Center&lt;br&gt;Riqiang Yan, Ph.D., University of Connecticut Health Center</td>
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<td><strong>Cellular Vulnerability to Aging in Alzheimer's Disease</strong>&lt;br&gt;Mathieu Bourdenx, Ph.D., University College London, England&lt;br&gt;Karen E. Duff, Ph.D., University College London, England</td>
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<td><strong>Gut Microbiota, Endothelial Dysfunction and Tau-Mediated Cognitive Impairment</strong>&lt;br&gt;Giuseppe Faraco, M.D., Ph.D., Weill Cornell Medical College&lt;br&gt;Costantino Iadecola, M.D., Weill Cornell Medical College</td>
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<td><strong>Temporal Relationships Between Gut Dysbiosis and Microglia Cell Activation Following Antibiotic Treatment</strong>&lt;br&gt;Sangram S. Sisodia, Ph.D., University of Chicago</td>
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<td><strong>Role of the Circulating Exerkine GPLD1 in Ameliorating Alzheimer's Disease Pathology</strong>&lt;br&gt;Saul Villeda, B.S., Ph.D., University of California, San Francisco</td>
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<td><strong>Understanding How Human Brain Vascular Cells Mediate Genetic Risk for Alzheimer's Disease</strong>&lt;br&gt;Andrew Yang, Ph.D., University of California, San Francisco</td>
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<td><strong>Identifying the Sex-Specific Roles of the Gut Microbiome-Brain Axis in a Mouse Model of Amyloid Beta Amyloidosis</strong>&lt;br&gt;Sangram S. Sisodia, Ph.D., University of Chicago</td>
<td>$210,871</td>
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<td><strong>DRUG DISCOVERY</strong></td>
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<td><strong>DRUG SCREENING AND LEAD DRUG EVALUATION PROJECTS</strong></td>
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<td>Alzheimer’s Disease Drug Discovery and Development Consortium: Blocking Synaptotoxicity in Alzheimer’s Three-Dimensional Models</td>
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<td>Weiming Xia, Ph.D., Boston University</td>
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<td>Alzheimer’s Disease Drug Discovery and Development Consortium: Modulating CD33 Function and Neuroinflammation as a Therapeutic Approach for Alzheimer’s Disease</td>
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<td>Ana Griciuc, Ph.D., Massachusetts General Hospital; Harvard Medical School</td>
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<td>Alzheimer’s Disease Drug Discovery and Development Consortium: Uncovering the Molecular Mechanism of Selected Drug Candidates Derived from Systematic Alzheimer’s Drug Repositioning</td>
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<td>Stephen T.C. Wong, Ph.D., Houston Methodist Research Institute; Weill Cornell Medicine</td>
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<td>Alzheimer’s Disease Drug Discovery and Development Consortium: High-Throughput Drug Screening for Alzheimer’s Disease Using Three-Dimensional Human Neural Culture Systems</td>
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<td>Doo Yeon Kim, Ph.D., Massachusetts General Hospital; Harvard Medical School</td>
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<td>Luisa Quinti, Ph.D., Massachusetts General Hospital; Harvard Medical School</td>
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<td>Stimulating Synaptic Proteasome Activity for the Treatment of Alzheimer’s Disease</td>
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<td>Hermann Steller, Ph.D., The Rockefeller University</td>
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<td>A Transcriptional Rejuvenation Signature for Alzheimer’s Disease</td>
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<td>Tony Wyss-Coray, Ph.D., Stanford University</td>
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<td>Identification of CD33 Antagonists</td>
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<td>Subhash Sinha, Ph.D., Weill Cornell Medicine</td>
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<td>Development of Human cGAS Inhibitors to Treat Alzheimer’s Disease</td>
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<td>Li Gan, Ph.D., Weill Cornell Medicine</td>
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<td>Subhash Sinha, Ph.D., Weill Cornell Medicine</td>
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<td>Small Molecule Activators of PLC-gamma-2 as Novel Therapeutics for Alzheimer’s Disease</td>
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<td>Qisheng Zhang, Ph.D., University of North Carolina at Chapel Hill</td>
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<td>Kenneth Pearce, Ph.D., University of North Carolina at Chapel Hill</td>
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<td><strong>DRUG DELIVERY AND ENABLING TECHNOLOGIES</strong></td>
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<td>Novel Entry Routes for Therapeutic Biologicals to the Brain</td>
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<td>Maarten Dewilde, Ph.D., KU Leuven, Belgium</td>
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<td>Bart De Strooper, M.D., Ph.D., KU Leuven, Belgium; University College London, England</td>
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<td><strong>PRECLINICAL AND CLINICAL DRUG DEVELOPMENT</strong></td>
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<td><strong>PRECLINICAL DRUG DEVELOPMENT</strong></td>
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<td>Combined Hormone Therapy as a Novel Treatment for Alzheimer’s Disease in the Face of a Metabolic Challenge: Influence of Sex and Genotype</td>
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<td>Liisa Galea, Ph.D., Centre for Addiction and Mental Health, Canada</td>
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<td>Annie Ciernia, Ph.D., University of British Columbia, Canada</td>
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<td><strong>CLINICAL TRIAL DESIGN</strong></td>
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<td>Application of Machine Learning Methods in Alzheimer’s Disease Clinical Trials</td>
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<td>Ali Ezzati, M.D., Albert Einstein College of Medicine</td>
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<td>Richard B. Lipton, M.D., Albert Einstein College of Medicine</td>
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<td>Scientific Meeting Support</td>
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<td>Genes to Therapies™ (G2T), Alzheimer’s Disease Drug Discovery and Development (AD4) and General Scientific Support</td>
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<td>Wilma Wasco, Ph.D., Massachusetts General Hospital; Harvard Medical School</td>
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<td><strong>SCIENTIFIC MEETINGS AND SUPPORT</strong></td>
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**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.


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
Christina M. Lill, M.D., M.Sc., University of Münster, Germany; Imperial College London, England
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
Mathias Jucker, Ph.D., University of Tübingen, Germany; German Center for Neurodegenerative Diseases (DZNE)
Stephan A. Kaeber, 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 Immunocyte 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.

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...
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.
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.

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.

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.

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.

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 Fukimoto 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
Gunvar 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
Oskar Hansson, M.D., Ph.D., Lund University, Sweden
Rik Ossenkoppele, Ph.D., Amsterdam University Medical Centers, The Netherlands; Lund University, Sweden

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
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

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

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
Patrik Verstreken, Ph.D., VIB-KU Leuven, Belgium

“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 can counteract memory loss. If we are successful, we will have created a new class of drugs that interfere 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, reassert 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 (xcTauO). 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**  
**Miranda E. Orr, Ph.D., Wake Forest University School of Medicine**

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

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
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: 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

Alison M. Goate, D.Phil., Icahn School of Medicine at Mount Sinai
Edoardo Marcora, Ph.D., Icahn School of Medicine at Mount Sinai

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

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

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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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Michelle E. Ehrlich, M.D., Icahn School of Medicine at Mount Sinai

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.

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.

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 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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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 neuropathological 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.

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
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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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.
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-AB 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.
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.

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.
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.

<table>
<thead>
<tr>
<th>Project/Researcher</th>
<th>Distribution Amount</th>
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<tbody>
<tr>
<td><strong>FOUNDATIONAL RESEARCH</strong></td>
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<td><strong>GENETIC RISK FACTORS</strong></td>
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<tr>
<td><strong>Analytical and Statistical Tools for Sequence Analysis for Alzheimer’s Disease</strong>&lt;br&gt;Christoph Lange, Ph.D., Harvard T.H. Chan School of Public Health</td>
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<td><strong>BIOMARKERS, DIAGNOSTICS, AND STUDIES OF RISK AND RESILIENCE</strong></td>
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<td><strong>Understanding Human Brain Resilience to Alzheimer’s Pathology</strong>&lt;br&gt;Teresa Gomez-Isla, M.D., Harvard Medical School; Massachusetts General Hospital</td>
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<td><strong>Stable Isotope Labeling and Quantitative Mass Spectrometry Imaging of Alzheimer’s Disease Pathology in Human Brain</strong>&lt;br&gt;Katherine Schweyte, M.D., Ph.D., Washington University School of Medicine in St. Louis</td>
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<td><strong>BIOLOGICAL RESEARCH MATERIALS: NEW ANIMAL AND CELLULAR MODELS, AND HUMAN SAMPLES</strong></td>
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<td><strong>Targeted Recruitment of Underrepresented Americans for Brain Donation Registration</strong>&lt;br&gt;Brain Donor Project</td>
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<td><strong>EPigenetic FACTORS</strong></td>
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<td><strong>CIRCUITS: Collaboration to Infer Regulatory Circuits and Uncover Innovative Therapeutic Strategies—Production Group</strong>&lt;br&gt;Manolis Kellis, Ph.D., and Li-Huei Tsai, Ph.D., Massachusetts Institute of Technology; Broad Institute</td>
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<td><strong>TRANSLATIONAL RESEARCH</strong></td>
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<td><strong>STUDIES OF NOVEL ALZHEIMER’S DISEASE GENES</strong></td>
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<td><strong>The Role of Clusterin in Tau Pathology</strong>&lt;br&gt;John D. Fryer, Ph.D., Mayo Clinic, Arizona</td>
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<td><strong>STUDIES OF AMYLOID PRECURSOR PROTEIN (APP) AND AMYLOID BETA</strong></td>
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<td><strong>Interrogating Levetiracetam’s Impact on Amyloid Pathology and Presynaptic Proteostasis in Knock-in Mouse Models with Humanized Amyloid Beta</strong>&lt;br&gt;Jeffrey N. Savas, Ph.D., Northwestern University</td>
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<td><strong>The Nedd4-1 and PKCα Connection in Alzheimer’s Disease</strong>&lt;br&gt;Gentry N. Patrick, Ph.D., University of California, San Diego</td>
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<td><strong>STUDIES OF TAU</strong></td>
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<td><strong>Reversal of Tau Pathology by an Adenosine A1 Receptor Antagonist</strong>&lt;br&gt;Eva-Maria Mandelkow, M.D., Ph.D., Eckhard Mandelkow, Ph.D., and Anja Schneider, M.D., German Center for Neurodegenerative Diseases (DZNE)</td>
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<td><strong>Patient-Based Structural and Functional Biology of Tauopathies</strong>&lt;br&gt;Leonard Petrucelli, Ph.D., Mayo Clinic, Jacksonville</td>
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<td><strong>Influence of Plaque Vicinity on Microglial and Astrocyte Gene Expression; Role of Human Tau and TREM2</strong>&lt;br&gt;Frances A. Edwards, Ph.D., and John Hardy, Ph.D., University College London, England</td>
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<td><strong>Mechanisms of Tau Propagation Across the Plasma Membrane</strong>&lt;br&gt;Marc I. Diamond, M.D., University of Texas Southwestern Medical Center</td>
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<td><strong>STUDIES OF APOLIPOPROTEIN E (APOE)</strong></td>
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<td><strong>APOE Consortium: Counteracting Pathogenic Events in Alzheimer’s Disease with Peripheral or Central Apolipoprotein E</strong>&lt;br&gt;Takahisa Kanekio, M.D., Ph.D., Mayo Clinic, Jacksonville</td>
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<td><strong>Apolipoprotein E and Immunometabolism in Alzheimer’s Disease</strong>&lt;br&gt;Lance A. Johnson, Ph.D., Ramon Sun, Ph.D., and Josh Morganti, Ph.D., University of Kentucky</td>
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<td><strong>Protection Against APOE4 with Longevity-Promoting Interventions</strong>&lt;br&gt;Christian Pike, Ph.D., Caleb E. Finch, Ph.D., and Bérénice A. Benayoun, Ph.D., University of Southern California</td>
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<td><strong>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</strong>&lt;br&gt;Berislav V. Zlokovic, M.D., Ph.D., University of Southern California</td>
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<td><strong>STUDIES OF THE IMMUNE RESPONSE IN ALZHEIMER’S DISEASE</strong></td>
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<td><strong>The Role of MGnD-Neurodegenerative Clec7a+ Microglia in an Alzheimer’s Disease Mouse Model</strong>&lt;br&gt;Oleg Butovsky, Ph.D., Brigham and Women's Hospital</td>
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<td>Christian Haass, Ph.D., and Kai Schlepckow, Ph.D., German Center for Neurodegenerative Diseases (DZNE)</td>
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<td>Understanding the Mechanism Underlying Vaccination for Alzheimer's Disease</td>
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<td>Charles L. Greenblatt, M.D., Hebrew University of Jerusalem, Israel, Ofir N. Gofrit, M.D., Ph.D., Haddassah Medical Organization, Israel, and Benjamin Y. Klein, M.D., Hebrew University of Jerusalem, Israel</td>
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<td>VGF-Derived Peptide Therapy for Alzheimer's Disease: Studies of Mouse and Human TLOP-21 and its Receptor, C3aR1</td>
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<td>Michelle E. Ehrlich, M.D., and Stephen R. Salton, M.D., Ph.D., Icahn School of Medicine at Mount Sinai</td>
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<td>Tau and Amyloid Beta are Innate Immune Antimicrobial Peptides in the Brain</td>
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<td>William Eimer, Ph.D., Massachusetts General Hospital, Harvard Medical School</td>
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<td>T Cell Epigenetics in Alzheimer's Disease</td>
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<td>David M. Gate, Ph.D., Northwestern University Feinberg School of Medicine</td>
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<td>The Role of Astrocyte-Secreted Insulin-Like Growth Factor Binding Protein 2 (IGFBP2) in the Progression of Alzheimer's Disease</td>
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<td>Nicola J. Allen, Ph.D., Salk Institute for Biological Studies</td>
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<td>Understanding the Role of Natural Amyloid Beta-Specific B Cell Responses in Alzheimer's Disease Progression</td>
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<td>Marco Colonna, M.D., Washington University School of Medicine in St. Louis</td>
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<td>The Neuroprotective Gliarial Barrier: A Multicellular Reaction with Therapeutic Potential in Alzheimer's Disease</td>
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<td>Jaime Grutzendler, M.D., Yale School of Medicine</td>
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<td>STUDIES OF ALTERNATIVE NEURODEGENERATIVE PATHWAYS</td>
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<td>Disentangling the Role of Intracranial Arteriosclerosis in Alzheimer's Disease</td>
<td>$172,052</td>
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<td>Daniel Bos, M.D., Ph.D., Meihe Vernooij, M.D., Ph.D., Frank Wolters, M.D., Ph.D., Erasmus University Medical Center, The Netherlands, Geert Jan Biessels, M.D., Ph.D., UMC Utrecht Brain Center, The Netherlands, and Julia Neitzel, Ph.D., Harvard T.H. Chan School of Public Health</td>
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<td>Investigating Bone Marrow Hematopoesis as the Link Between Sleep Fragmentation and Vascular Inflammation in AD</td>
<td>$172,500</td>
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<td>Cameron McAlpine, Ph.D., and Filip K. Swirski, Ph.D., Icahn School of Medicine at Mount Sinai</td>
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<tr>
<td>Characterizing Gut Microbiome Synergy with Emphasis on Mycobiome and Its Impact on Alzheimer's Disease (AD) Pathology in AD Mouse Models</td>
<td>$250,000</td>
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<td>Deepak Kumar Vijaya Kumar, Ph.D., Nanda Kumar Navalpuru Shannumag, Ph.D., William Eimer, Ph.D., and Rudolph E. Tanzi, Ph.D., Massachusetts General Hospital</td>
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<td>Microbes and Alzheimer's Disease: Metagenomics on Saliva, Cerebrospinal Fluid, Blood and Brain</td>
<td>$350,000</td>
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<td>Nanda Kumar Navalpuru Shannumag, Ph.D., William Eimer, Ph.D., Deepak Kumar Vijaya Kumar, Ph.D., and Rudolph E. Tanzi, Ph.D., Massachusetts General Hospital</td>
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<td>Brain Entry and Exit Consortium: Human 3D Neurovascular Interaction and Meningeal Lymphatics Models with Application to Alzheimer's Disease</td>
<td>$215,000</td>
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<td>Se Hoon Choi, Ph.D., Massachusetts General Hospital, and Roger Kamm, Ph.D., Massachusetts Institute of Technology</td>
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<td>Effect of Gut Microbiome Dysbiosis on Neuroinflammation and Amyloid Beta Deposition: A Longitudinal Micro-PET Study in Alzheimer's Transgenic Mice</td>
<td>$168,434</td>
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<td>Sangram S. Sisodia, Ph.D., University of Chicago</td>
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<td>Neural Synaptic Circuit Changes During Alzheimer's Disease Progression</td>
<td>$172,500</td>
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<td>Huizhong W. Tao, Ph.D., University of Southern California</td>
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<td>Central Clock Influence on Alzheimer's Disease Pathogenesis</td>
<td>$154,701</td>
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<td>Geraldine J. Kress, Ph.D., Washington University School of Medicine in St. Louis</td>
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<td>DRUG DISCOVERY</td>
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<td>DRUG SCREENING AND LEAD DRUG EVALUATION PROJECTS</td>
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<td>Targeting Microglial TSG101 for Synaptic Protection and Cognitive Enhancement in Alzheimer's Disease</td>
<td>$172,500</td>
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<td>Seiko Ikezu, M.D., and Tsuneya Ikezu, M.D., Ph.D., Mayo Clinic, Jacksonville</td>
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<tr>
<td>Adult Human iNeurons: A Next-Generation Drug Screening Platform for Alzheimer's Disease</td>
<td>$229,249</td>
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<td>George S. Bloom, Ph.D., John S. Lazo, Ph.D., and Elizabeth R. Sharlow, Ph.D., University of Virginia</td>
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<tr>
<td>PRECLINICAL AND CLINICAL DRUG DEVELOPMENT</td>
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<td>PRECLINICAL DRUG DEVELOPMENT</td>
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<tr>
<td>Continuing Studies of the Effects of GSM 776890 Administration on Amyloid Species and Microgliosis in Older Alzheimer's Model Mice</td>
<td>$291,374</td>
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<tr>
<td>Kevin Rynearson, B.S., M.S., Ph.D., University of California, San Diego</td>
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</tbody>
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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
Eighteen Years of Growth:
Cure Alzheimer’s Fund’s investment in research continues to be driven by strong increases in overall contributions.
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 of Funds

- **51.6%** Individuals: $16,567,433
- **14.7%** Founders/Board/Trustees: $4,709,349
- **32.5%** Foundations/Trusts/Bequests: $10,436,172
- **1.2%** Corporations: $399,236

### Use of Funds

- **80%** Research Distributions and Support: $24,460,315
- **11.2%** Programs: $3,426,801
- **5.4%** Management and General: $1,032,769
- **3.4%** Fundraising: $1,662,785

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 Cash Flows

Cash Flows from Operating Activities:
- Contributions: $26,122,432
- Investment income: 63,064
  - Total received: 26,189,506
- 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

JACQUELINE C. MORBY
Founding Board Member
Senior Advisor of TA Associates
Co-Chairman of the Morby Family Charitable Foundation

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

ROBERT F. GREENHILL
Chairman and Founder
Greenhill & Company

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

TIM ARMOUR
President and Chief Executive Officer

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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 ANTONELLI
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
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
Bowiewie'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.

**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.
Some of the 130 volunteers and participants who helped make the first Race to Remember a success.

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.

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

“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/
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.
Cure Alzheimer’s Fund receives many gifts in memory or in honor from the families and friends of those with Alzheimer’s disease; these gifts are a reminder of the scale of Alzheimer’s disease and that a cure must be found.

Giving a gift in memory or in honor of a family member or friend is an extraordinary way to pay tribute to someone special in your life while supporting the mission of finding a cure. If you would like to designate a memorial gift, you can do so on our website, or by mail or telephone. We will gratefully acknowledge each gift by notifying the individuals you have designated without disclosing the amount of the donation. At your request, we also will publish memorial photos we receive to the In Memory section of our website at CureAlz.org/giving/in-memory/.

If you have any questions about our In Memory program, please contact Laurel Lyle, Vice President, Board Relations and Development Operations, at LLyle@CureAlz.org, or call 781-237-3800. Thank you.
Support Our Research

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

**Online Gifts**  
Make a secure gift online by credit card, PayPal or Venmo.

**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/](http://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.

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**Recognized for Excellence**

- Cure Alzheimer’s Fund has received the designation of Platinum level, the highest recognition offered by GuideStar.
- Cure Alzheimer’s Fund meets all 20 Better Business Bureau Standards for Charity Accountability.
- Cure Alzheimer’s Fund has been awarded the highest rating of 4 stars for 12 consecutive years.