

CURE ALZHEIMER'S FUND

# Consortia

*“In the long history of humankind (and animal kind too) those who learned to collaborate and improvise most effectively have prevailed.”*

CHARLES DARWIN

1809 - 1882 | *English Naturalist*

## OUR MISSION

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

---

In 2004, the founders of Cure Alzheimer's Fund (CureAlz) embraced as a core tenet that the best way to accelerate potential therapies against Alzheimer's disease (AD) would be to support fundamental proof-of-concept research into its causes. They recognized that established ideas and orthodox approaches could find funding within the traditional system, but that scientists with well-reasoned but unique or unconventional ideas regarding the contributing factors to Alzheimer's disease struggled to obtain the funding necessary to test their hypotheses. A founding principle of Cure Alzheimer's Fund is the sharing of information and collaboration among researchers who receive a grant from CureAlz. Through this cooperative effort, researchers benefit from the findings and input of others, accelerating the growth of knowledge. Our funded researchers actively engage across subdisciplines and institutions to build research partnerships and contribute significantly to a better understanding of Alzheimer's disease.

Cure Alzheimer's Fund historically has supported innovative research projects with grants at the \$100,000 to \$300,000 level that have the potential to add significant new understanding of Alzheimer's pathology to the field. While CureAlz will continue to support these new high-risk, high-potential standalone efforts, advances in understanding Alzheimer's disease have warranted larger-scale investigations within specific areas of the science. The consortia model provides for these initiatives with an expanded level of collaboration. This document provides a summary of each of our five consortia:

- ▶ Alzheimer's Disease Drug Discovery & Development (AD4)
- ▶ Fleming APOE
- ▶ Brain Entry & Exit
- ▶ Collaboration to Infer Regulatory Circuits and to Uncover Innovative Therapeutic Strategies (CIRCUITS)
- ▶ Neuroinflammation

---

# Alzheimer's Disease Drug Discovery & Development (AD4) Consortium

The AD4 Consortium is testing large libraries of FDA-approved drugs and natural products to identify any that could be beneficial against Alzheimer's disease in a number of different ways. This approach—repurposing—offers significant time and cost advantages over developing a new drug from scratch, a process that for neurology drugs has been estimated to take several billion dollars and 15 years. Drugs approved by the FDA for other diseases already have undergone significant safety testing and have a body of information available for them; natural products have not necessarily undergone the same amount of analysis, but already are being consumed safely.

The AD4 Consortium's approach to screening repurposing candidates has been empowered by its use of the CureAlz-funded Alzheimer's in a Dish™ (ADiD) model. This human-derived 3D system models the key cell types and blood-brain barrier making up the Alzheimer's environment in the human brain. It has been optimized to allow high-throughput screening of 96 different compounds at a time. Each candidate is being assessed by AD4 for its ability in ADiD to reduce amyloid beta and tau pathology, as well as to regulate neuroinflammation. Candidates with powerful impact then are studied to discern the likely mechanism of action for this impact and their ability to get into the brain. Artificial intelligence and in silico drug screening are applied to the strongest candidates to determine whether other drugs or chemical compounds might achieve the same mechanism of action with even better profiles on other dimensions, suggesting even stronger candidates in turn.

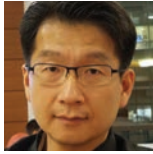
To date, the consortium has successfully analyzed a 2,640-compound drug library, narrowing it down to eight very strong candidates based on their potency in reducing the pathological hallmarks of Alzheimer's disease. In addition, 803 natural products have been reviewed for their effect on tau pathology, yielding 14 natural compounds of interest. These candidates are now with a CureAlz task force with appropriate pharmacological and clinical trial expertise for further prioritization as drug candidates for AD clinical trials.

## **FUNDING TO DATE**

In total, \$7,673,500 has been distributed to support 33 research projects.

---

**AD4 CONSORTIUM: FUNDED RESEARCHERS**



SE HOON CHOI | PH.D.  
MASSACHUSETTS GENERAL HOSPITAL



LUISA QUINTI | PH.D.  
MASSACHUSETTS GENERAL HOSPITAL



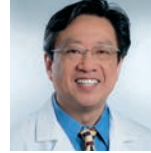
ANA GRICIUC | PH.D.  
MASSACHUSETTS GENERAL HOSPITAL



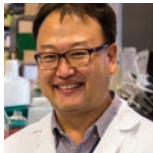
\*RUDY TANZI | PH.D.  
MASSACHUSETTS GENERAL HOSPITAL



ROGER KAMM | PH.D.  
MASSACHUSETTS INSTITUTE OF  
TECHNOLOGY



STEPHEN T.C. WONG | PH.D.  
HOUSTON METHODIST



DOO YEON KIM | PH.D.  
MASSACHUSETTS GENERAL HOSPITAL



WEIMING XIA | PH.D.  
BOSTON UNIVERSITY SCHOOL  
OF MEDICINE



JOSEPH PARK | PH.D.  
MASSACHUSETTS GENERAL HOSPITAL

\*Chair



# Fleming APOE Consortium

The E4 variant of the APOE gene is the strongest genetic risk factor for Alzheimer's disease that develops after age 65: a person carrying two copies has a lifetime risk of an Alzheimer's diagnosis more than 10 times higher than someone carrying two copies of the E3 variant. On the other hand, the E2 variant reduces risk of Alzheimer's, yet increases risk of cerebral amyloid angiopathy (CAA), a frequent comorbidity with AD. Substantial data inform us that APOE variants differentially affect amyloid plaque accumulation and clearance, tau tangle formation and neuroinflammation, non-AD hallmarks of aging and the porosity of the blood-brain barrier, yet the mechanisms by which these effects arise are not understood.

The Fleming APOE Consortium is bringing together experts across the various dimensions of AD affected by APOE to develop a better understanding of these mechanisms. The group is considering, among other questions, how different APOE variants affect microglial behavior; whether apoE produced in the body impacts the health of the brain; how genetic sex and APOE interact; and whether the structure of APOE particles in our blood might tell us about our risk and level of AD pathology in our brain. Expanding our understanding of the role of APOE will lead to new and more effective diagnostic tools, and therapeutics to slow, reverse or prevent Alzheimer's disease.

## FUNDING TO DATE

In total, \$5,947,308 has been distributed to support 23 research projects.

## FLEMING APOE CONSORTIUM: FUNDED RESEARCHERS



RANDALL BATEMAN | M.D.  
WASHINGTON UNIVERSITY SCHOOL  
OF MEDICINE IN ST. LOUIS



\*DAVID HOLTZMAN | M.D.  
WASHINGTON UNIVERSITY SCHOOL OF  
MEDICINE IN ST. LOUIS



GUOJUN BU | PH.D.  
MAYO CLINIC JACKSONVILLE



JEAN-PIERRE ROUSSARIE | PH.D.  
BOSTON UNIVERSITY SCHOOL  
OF MEDICINE



OLEG BUTOVSKY | PH.D.  
BRIGHAM AND WOMEN'S HOSPITAL



CHERYL WELLINGTON | PH.D.  
UNIVERSITY OF BRITISH COLUMBIA



\*\*PAUL GREENGARD | PH.D.  
ROCKEFELLER UNIVERSITY

\*Chair of the APOE consortium

\*\*Deceased in 2019

---

# Brain Entry & Exit Consortium

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

The consortium's members bring cutting-edge expertise to the study of these interconnected structures. They are examining how the blood-brain barrier must be selective, rather than simply exclusive, and how clearance of debris through the meningeal lymphatics system is vital to immune communication between the brain and periphery. They also are assessing how cerebrospinal fluid flow dynamics affect both exit and entry, and how it may be altered in AD as amyloid beta pathology builds up. The only drug currently FDA approved for its impact on AD pathology is delivered from the blood across the blood-brain barrier; it then tags amyloid beta for clearance from the brain. The work of the Brain Entry & Exit Consortium offers a powerful opportunity to identify new therapeutic possibilities and improve those already in development.

## **FUNDING TO DATE**

In total, \$1,959,673 has been distributed to support 10 research projects.



---

**BRAIN ENTRY & EXIT CONSORTIUM: FUNDED RESEARCHERS**



HELENE BENVENISTE | M.D., PH.D.  
YALE UNIVERSITY SCHOOL OF MEDICINE



ROGER KAMM | PH.D.  
MASSACHUSETTS INSTITUTE  
OF TECHNOLOGY



SE HOON CHOI | PH.D.  
MASSACHUSETTS GENERAL HOSPITAL



\*JONATHAN KIPNIS | PH.D.  
WASHINGTON UNIVERSITY SCHOOL  
OF MEDICINE IN ST. LOUIS



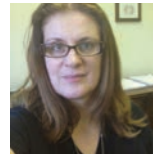
RICHARD DANEMAN | PH.D.  
UNIVERSITY OF CALIFORNIA, SAN DIEGO



FERNANDA MARQUES | PH.D.  
MINHO UNIVERSITY SCHOOL  
OF MEDICINE



ALI ERTÜRK | PH.D.  
HELMHOLTZ MUNICH



LAURA SANTAMBROGIO | M.D., PH.D.  
WEILL CORNELL MEDICINE



FANNY HERISSON | M.D., PH.D.  
MASSACHUSETTS GENERAL HOSPITAL



ALLEN TANNENBAUM | PH.D.  
STONY BROOK UNIVERSITY

\*Chair

---

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

We have long known that advancing age and family history are the strongest risk factors for late-onset Alzheimer's disease. What science has only recognized in the last two decades, however, is that the two interact—and their impact must be understood together. Although the genes we inherit from our parents—our genetics—do not change, and every cell carries the same DNA, the way and amounts that our DNA is translated into proteins—our epigenetics—is different in different cells, and can and does change with our life experience. Regulatory genes do not themselves encode proteins, but instead affect the expression of protein-encoding genes. CIRCUITS—the Collaboration to Infer Regulatory Circuits and Uncover Innovative Therapeutic Strategies—is investigating how the expression of regulatory genes differs in health and disease, at different stages of disease, and in different cell types and brain regions in these contexts.

The Alzheimer's Genome Project™ (AGP), headed by Dr. Rudy Tanzi and funded by CureAlz, has identified many gene variants impacting either risk of Alzheimer's or age of onset. Some of these variants—such as APOE4—are of genes that encode specific proteins; in that case, ApoE4. However, the majority of these risk variants are in regulatory genes. CIRCUITS is developing an extraordinary repository of information about how regulatory genes change gene expression over our lifespan in different cells and brain regions, how these changes differ in those who will or have developed Alzheimer's disease, and how the risk variants identified by AGP relate to these changes. In a disease like Alzheimer's, in which our risk increases as our bodies accumulate experience, and in which our genetics affects our risk but does not define it, understanding how epigenetic regulation ties experience to DNA is vital to understanding where and how to intervene.

## **FUNDING TO DATE**

To date, \$6,825,149 has been distributed to support 23 research projects.

---

**CIRCUITS: FUNDED RESEARCHERS**



LARS BERTRAM | M.D.  
UNIVERSITY OF LÜBECK



\*MANOLIS KELLIS | PH.D.  
MASSACHUSETTS INSTITUTE  
OF TECHNOLOGY



JOSEPH R. ECKER | PH.D.  
THE SALK INSTITUTE



ANDREAS PFENNING | PH.D.  
CARNEGIE MELLON UNIVERSITY



WINSTON HIDE | PH.D.  
BETH ISRAEL DEACONESS MEDICAL  
CENTER



RUDY TANZI | PH.D.  
MASSACHUSETTS GENERAL HOSPITAL



BRADLEY T. HYMAN | M.D., PH.D.  
MASSACHUSETTS GENERAL HOSPITAL



\*LI-HUEI TSAI | PH.D.  
MASSACHUSETTS INSTITUTE  
OF TECHNOLOGY



RUDOLF JAENISCH | M.D.  
MASSACHUSETTS INSTITUTE  
OF TECHNOLOGY

\*Chair

# Neuroinflammation Consortium

Neurons were the cell type of focus for Alzheimer’s research for decades; after all, they die off in large numbers over the course of the disease and are considered the primary cells for memory and other cognitive brain activity. However, when large-scale genetic sequencing of Alzheimer’s patients became possible, the field discovered that the genetics of neurons are not primary for most cases of Alzheimer’s. Of the common protein-encoding genes with variants that affect risk of Alzheimer’s disease, more than half are primarily expressed not in neurons, but in microglia, astrocytes and peripheral myeloid cells.

These cells are the primary immune cells of the central nervous system. The proteins they express participate in innate immune pathways rather than in amyloid or tau pathways. They survey the brain, respond rapidly to pathological conditions, and maintain homeostasis in the healthy brain by isolating and cleaning up debris, from invading pathogens to cellular byproducts to amyloid beta plaques. However, their behavior can become mistargeted, degrading healthy synapses and neurons, eventually causing most of the neurodegeneration and cognitive loss seen

in AD. Better understanding of both healthy and pathogenic neuroinflammation is thus integral to redressing the damage that translates into AD symptoms.

The researchers in the Neuroinflammation Consortium are building the first comprehensive map of immune and neural cell state changes in Alzheimer’s disease to uncover how the different microglial states relate to other neural cells in vulnerable brain regions. Since gene expression differs for microglia in various states of activation, the group hypothesizes that imaging and fluid biomarkers tied to the proteins expressed in these states could indicate when someone is in an early stage of the disease, potentially in time to intervene. To achieve this map, the members of the consortium are developing new markers for specific microglial functional states; better knowledge of the biological function of the AD risk gene variants; computational tools to integrate genomic, biological, and proteomics data; and new imaging tools able to show the location and progression of neuroinflammation in a living brain. These tools will be shared across the Alzheimer’s disease field to accelerate research beyond this consortium.

## FUNDING TO DATE

To date, \$3,948,039 has been distributed to support 16 research projects.

## NEUROINFLAMMATION CONSORTIUM: FUNDED RESEARCHERS



MATHEW BLURTON-JONES | PH.D.  
UNIVERSITY OF CALIFORNIA, IRVINE



SANDEEP ROBERT DATTA | M.D., PH.D.  
HARVARD MEDICAL SCHOOL



CHRISTOPHER K. GLASS | M.D., PH.D.  
UNIVERSITY OF CALIFORNIA,  
SAN DIEGO



JACOB HOOKER | PH.D.  
MASSACHUSETTS GENERAL  
HOSPITAL



SHANE LIDDELOW | PH.D.  
NEW YORK UNIVERSITY  
LANGONE MEDICAL CENTER



\*BETH STEVENS | PH.D.  
BOSTON CHILDREN’S HOSPITAL

\*Chair



55,000

DONORS

73

FUNDED  
INSTITUTIONS

---

550

RESEARCH  
PROJECTS

818

RESEARCH PAPERS  
PUBLISHED

---

175

FUNDED  
RESEARCHERS

58,975

PAPER  
CITATIONS

---

\$130,000,000

RESEARCH FUNDED

## SUPPORT OUR RESEARCH

There are many ways to donate to the research of Alzheimer's disease:

- ▶ Online: you can donate directly from our website—please visit [www.CureAlz.org/giving/donate](http://www.CureAlz.org/giving/donate).
- ▶ By mail: Please make your check payable to Cure Alzheimer's Fund and mail to Cure Alzheimer's Fund, 34 Washington St., Suite 310, Wellesley Hills, MA 02481.
- ▶ By telephone: Please call 781-237-3800.
- ▶ Donor Advised Funds: Donors with funds held by Fidelity Charitable, Schwab Charitable or Great Kansas Community Foundation can use the DAF Direct form to

process donations directly from our website ([www.CureAlz.org/giving/ways-to-donate/](http://www.CureAlz.org/giving/ways-to-donate/).)

For all other Donor Advised Fund holders, please mail checks to Cure Alzheimer's Fund, 34 Washington St., Suite 310, Wellesley Hills, MA 02481.

- ▶ Planned giving: A number of planned giving options are available, some of which may provide tax incentives. Find more information by visiting [www.CureAlz.org/giving/ways-to-donate/](http://www.CureAlz.org/giving/ways-to-donate/).

To consider 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](mailto:LLyle@CureAlz.org), or by calling 781-237-3800.

---

100% of your donation goes directly to research.



---

RECOGNIZED FOR EXCELLENCE



Charity Navigator awarded Cure Alzheimer's Fund its highest rating of four stars, and has listed the organization in the top three percent of all charities for ten consecutive years.



GuideStar lists Cure Alzheimer's Fund as a platinum-level participant—its highest level of recognition.



Cure Alzheimer's Fund is an accredited charity and meets all 20 of the Better Business Bureau's standards for charity accountability.



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

---

100% of all donations go to research



WWW.CUREALZ.ORG | WWW.WOMENANDALZHEIMERS.ORG

34 Washington Street · Suite 310 · Wellesley Hills, Massachusetts 02481 · 781-237-3800

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 #52-239-6428