



DISCOVERIES II



**Cure Alzheimer's FUND**  
targeting breakthrough research



# The Human Brain is Magnificent. And Mysterious.

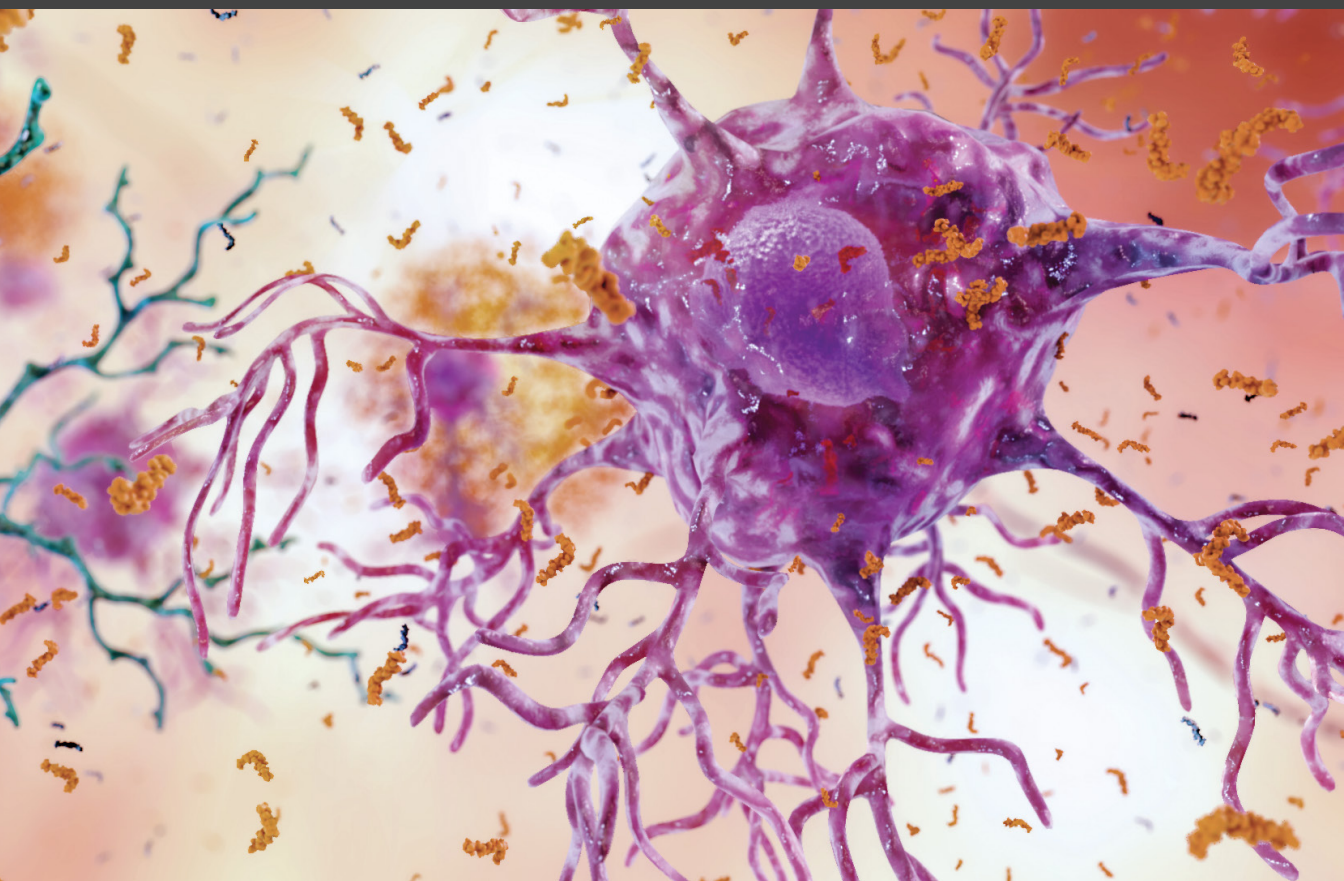
It is the wellspring of  
our existence, recording and  
cataloging our lives, and  
animating the way we breathe,  
move, laugh, touch, and feel.

For centuries, scientists have worked to gain insight into the vast secrets of the human brain. There is much we do not know—but we do know that its seemingly endless neural connections hold the very essence of that which makes us human.

Alzheimer's disease ravages more than memories. The disease destroys the physical structure of the brain, eventually rendering it incapable of even basic functions. The disease can progress over a long period of time; in fact, its development can often be measured in decades rather than in years.

Cure Alzheimer's Fund was started in 2004 with a single goal in mind: To eradicate Alzheimer's disease. To achieve this, we focus on fundamental scientific research—the crucial (and sometimes unconventional) thinking we believe will unlock the secrets of the disease—and illuminate the path to a cure. Projects we funded have contributed significantly to furthering our understanding of Alzheimer's disease, disrupted conventional wisdom, and changed the industry's approach to the science.

Research is the only path to a cure.



---

# The Main Elements of the Pathology of Alzheimer's Disease

Many molecular and cellular changes occur in the brain of a person with Alzheimer's disease. These changes can be observed in 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 and are formed from the breakdown of a larger protein, 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 the protein tau that collects inside neurons. Healthy neurons, in part, are supported internally by structures called microtubules. In healthy neurons, tau normally binds to and stabilizes 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, harming 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.

# Things You Should Know

We have organized the research studies to begin with those that represent investigations of genes (CD33, ZBTB7C, APOE), and continue with topics including diagnostic tools, exercise, the gut connection and more. Throughout this document, you will notice certain terms that may not be familiar. Below is a list of those terms, along with simple definitions. While reading about each scientific study, it is important to know that almost all of the lab work is performed using specialized mice unless otherwise noted. The work we fund provides the necessary fundamental proof-of-concept results that often lead to additional phases in the scientific process.

---

## Glossary of Key Terms

### A P O E 4

One of the variants of the APOE gene, the APOE4 gene is the second-highest risk factor for developing Alzheimer’s disease. First is old age.

### A S T R O C Y T E S

Astrocytes are star-shaped glial cells with many brain functions, including nourishing neurons.

### B L O O D - B R A I N   B A R R I E R

“Blood vessels are critical to deliver oxygen and nutrients to all of the tissues and organs throughout the body. The blood vessels that vascularize the central nervous system (CNS) possess unique properties, termed the blood–brain barrier, which allow these vessels to tightly regulate the movement of ions, molecules, and cells between the blood and the brain.” (National Institutes of Health—National Library of Medicine)

## GENE

The basic unit of inheritance, passed from parents to offspring; a gene contains specific physical and biological traits.

## GLIAL

Support cells that hold neurons in place and have a variety of functions, including facilitating neurotransmission and immune response.

## LYMPHATICS

A network of vessels carrying lymphatic fluid and immune cells.

## MICROGLIA

A type of glial cell that acts as the primary line of defense and immunity for the brain.

## NEURONS

Specialized impulse transmitting cells that are the fundamental working units of the brain and nervous system.

## NEURODEGENERATION

Progressive atrophy and loss of neurons.

## PATHOLOGY

Structural and functional changes that result in disease.

## PROTEIN

Biomolecules made of chains of amino acids with numerous functions in cells, tissues and the body.

## SYNAPSE

The junction between two neurons and the location of the transmission of nerve impulses.



# Alzheimer's Genome Project Leads to New Therapeutic Target

CD33 has the distinction of being the first gene identified as a result of the CureAlz Alzheimer's Genome Project™, back in 2008. CD33 carries the genetic code for receptors found on microglia cells, which normally clear away neurological debris, including plaques and tangles.

Neuroinflammation plays a key role in Alzheimer's disease (AD) pathology. With Alzheimer's progression, CD33 receptors become overexpressed in the brain. This overexpression has been shown to decrease the uptake and clearance of amyloid beta in microglial cell cultures. Gene therapy targeted at CD33 in mouse models decreased the levels of CD33 mRNA (a good indication that the number of CD33 receptors on microglial was also decreased), amyloid beta accumulation and neuroinflammation. The earlier the intervention was administered, the better the outcome. Gene therapy targeted at reducing the levels of CD33 may yield a potent new therapy for the treatment and prevention of AD.

*Ana Griciuc, Ph.D., Casey Maguire, Ph.D., and Rudy Tanzi, Ph.D., all of Massachusetts General Hospital*

<https://bit.ly/3MjuwBU>

# Women & Alzheimer's: The ZBTB7C Gene

Evidence suggests that sex-specific risk factors may contribute to women developing AD at twice the rate of men. In a study scanning the whole genome of more than 2,000 individuals from 605 families, four novel sex-specific AD genes were identified that had opposite effects on AD risk for men and women. Variations in three of these genes increased AD risk in men but seemed to be protective in women. However, the strongest association with AD risk was with the ZBTB7C gene, variants of which conferred high risk for women but protection for men. The type of protein that the ZBTB7C gene encodes has been shown to play a role in blood-brain barrier function, potentially linking increased female risk of AD to the state of the brain's vasculature.

*Lars Bertram, M.D., University of Lübeck; Winston Hide, Ph.D., Beth Israel Deaconess Medical Center; Christoph Lange, Ph.D., Harvard Medical School; and Rudolph Tanzi, Ph.D., Massachusetts General Hospital*

<https://bit.ly/3CI0oBk>

# New Insights Into APOE4 and the Blood-Brain Barrier

APOE4 causes the breakdown of the blood-brain barrier (BBB) in areas of the brain critical for learning and memory. The BBB is an important boundary that protects the brain from harmful substances like pathogens and toxins. BBB dysfunction is an early biomarker of cognitive decline and its future severity.

We now have a better understanding of how APOE4 leads to BBB breakdown. Among other cells, the BBB contains endothelial cells, which regulate what can pass through the barrier, and pericytes, which keep the BBB healthy. These cells become damaged in APOE4 carriers. As these cells malfunction and die, the BBB becomes compromised.

This leads to synaptic damage, which alters the ability of neurons to communicate with one another. The result of this cascade of damage is behavioral changes and cognitive decline.

*Berislav Zlokovic, M.D., Ph.D., University of Southern California*

<https://bit.ly/3fQCNkD>

# Removing Astrocytic APOE4 May Benefit Late-Stage AD

APOE4 is the strongest genetic risk factor for late-onset AD, and patients who are APOE4 carriers may develop the disease at an earlier age. Compared with other APOE variants, the expression of APOE4 significantly increases the likelihood of amyloid beta accumulation and neuronal loss, decreases brain volume and increases glial inflammatory signals. In the absence of APOE, however, these consequences appear less frequently, suggesting that APOE4 is a precipitating factor. Although APOE is secreted by both astrocytes and microglia in the brain, previous studies have shown that astrocytic APOE particles are larger and contain more lipids than microglial-derived APOE. As a result, some researchers have wondered whether astrocytic-derived APOE might be playing a unique role in the brain, and if reducing APOE4 in astrocytes may benefit the brain by preventing neuronal damage, curbing neuroinflammation, reducing amyloid beta plaques and preserving cognitive function.

*Oleg Butovsky, Ph.D., Brigham and Women's Hospital; and David Holtzman, M.D., and Jason Ulrich, Ph.D., both of Washington University School of Medicine in St. Louis*

<https://bit.ly/3SXUPzK>

# A Rare Variant of APOE3 Reduces Risk of Developing AD

The rare APOE3-Jacksonville (APOE3-Jac) variant, named after the city in which it was discovered, significantly lowers a person's risk for developing AD. The function of the APOE protein is to bind and transport lipids, including cholesterol, and mediate fat metabolism. The APOE3-Jac variant has a mutation in its lipid-binding region that allows it to transport more cholesterol and other lipids critical for membrane homeostasis and synaptic function; it increases the amount of healthy fats in the brain. The mutation also keeps APOE3-Jac from clumping together and forming aggregates.

The result of APOE3-Jac's enhanced lipid-carrying capacity and reduced self-aggregation is a decrease in AD pathology. There are fewer amyloid beta plaques and damaged neurons and less evidence of neuroinflammation. This data opens the door for potential therapies targeting APOE-mediated lipid metabolism and APOE self-aggregation to decrease AD pathology.

*Guojun Bu, Ph.D., Independent*

<https://bit.ly/3rGUIC8>

# Benefit of Exercise for Cognitive Decline

As with our hearts, there is now evidence that exercise benefits our brains.

While we exercise, the hormone irisin is secreted by our muscles. This hormone modulates the metabolic processes and functioning of the nervous system and acts as an anti-inflammatory. When irisin was given to mice with significant AD pathology, the glial cells in the brain were activated to reduce neuroinflammation, resulting in improved cognition. Conversely, the removal of irisin erased the neuroprotective effects by altering the development and maturation of new neurons in the hippocampus, a region of the brain important for memory and cognitive functions, and the first region of the brain to develop AD pathology.

*Se Hoon Choi, Ph.D., Rudy Tanzi, Ph.D., and Christiane D. Wrann, Ph.D., all of Massachusetts General Hospital*

<https://bit.ly/3T3DOnI>

# Trem2 Antibodies Reduce AD Pathology

Microglia are the innate immune cells that reside in the central nervous system and remove unwanted particles and debris from the brain. TREM2 is a receptor found on microglia and its activation increases amyloid beta uptake; the effect is therefore neuroprotective. An antibody designed to increase TREM2 activation has shown therapeutic promise in the lab by decreasing the pathology of the disease. A single antibody injection induced microglia proliferation and converted them into an active state. Additional injections reduced plaque formation and the resulting damage to neurons. Phase 1 clinical trials of antibody activation of TREM2 are currently in process.

*Marco Colonna, M.D., Washington University School of Medicine in St. Louis*

<https://bit.ly/3Enzb3x>



# Gamma-Secretase Modulators for Alzheimer's Disease

Amyloid beta ( $A\beta$ ) is a key protein that forms into plaque bundles. It is cleaved from the larger amyloid precursor protein by gamma-secretase into shorter lengths ( $A\beta_{37}$ ,  $A\beta_{38}$ ) and longer lengths ( $A\beta_{40}$ ,  $A\beta_{42}$ ). The longer lengths of amyloid beta are more likely to clump together into toxic plaques.

Clinical trials more than a decade ago provided doses of a compound designed to completely inhibit the function of gamma-secretase. However, gamma-secretase has an important role in the brain, and blocking all of its natural and necessary activity resulted in significant negative side effects as well as an increase in cognitive decline.

With an increased understanding of the important role gamma-secretase has in the brain, CureAlz has funded studies to investigate the potential for a *modulator* of gamma-secretase (GSM). These novel agents alter the activity of gamma-secretase by selectively reducing levels of the longer, plaque-forming amyloid beta ( $A\beta_{42}$ ) in favor of the shorter, nontoxic forms. In the lab, the GSM, at low and safe doses, decreased plaque formation and neuroinflammation. The next stage, Phase I clinical trials, has been supported by a \$7 million grant from the National Institutes of Health.

*Rudy Tanzi, Ph.D., Massachusetts General Hospital; and Steven L. Wagner, Ph.D., University of California, San Diego*

<https://bit.ly/3MhOrAZ>

# A New Diagnostic Tool: PET Scans Of Gamma-Secretase in The Brain

The buildup of amyloid beta in the brain is facilitated by gamma-secretase. In the lab, a gamma-secretase modulator has been effective in reducing plaque buildup, resulting in improved cognition. However, little is known about the regional expression or distribution of gamma-secretase in the brain. A positron emission tomography (PET) tracer has been developed to visualize gamma-secretase for the first time in animal models. This tracer will lead to a better understanding of AD and also support the continuing development of drugs with more accurate targeting of gamma-secretase.

*Rudy Tanzi, Ph.D., Massachusetts General Hospital; and Steven L. Wagner, Ph.D., University of California, San Diego*

<https://bit.ly/3C9JDJm>

# Some Brains are Resilient to Alzheimer's Disease

Some individuals seem to be resilient to AD. Although these individuals develop the classic hallmarks of the disease—bundles of amyloid plaque and neurofibrillary tau tangles—they do not develop dementia symptoms in their lifetime.

Studies suggest that resilience to the pathology may be associated with reduced levels of neuroinflammation, thought to be universal in symptomatic AD. Instead of promoting neuroinflammation, the essential immune cells in the brain—microglia and astrocytes—remain in their housekeeping state and do not become disease-associated despite a significant burden of amyloid plaques and tau tangles. Therefore, identifying predictive markers of resilience and understanding the underlying mechanisms involved may be key to therapeutically mimicking the brain's natural protection against amyloid beta and tau, and developing novel therapies for AD that preserve cognition.

*Teresa Gomez-Isla, M.D., Massachusetts General Hospital*

<https://bit.ly/3V9CKAu>



Sc 4  
SE/M  
SI 8

Sc 4  
SE/M  
SI 9

Sc 4  
SE/M  
SI 11

Sc 4  
SE/M  
SI 12

FH 17 head

FH 23 head

FH 30 head

FH 36 head

FH 43 head

# Potential Diagnostic Tool: Measuring Neuroinflammation in the Brain

Biomarkers are extremely important in clinical research. The measurement of each biomarker provides the information needed to determine the stage of disease, resulting in selection of individuals to qualify for clinical trials. Biomarkers also provide the data needed to evaluate how effective a treatment may be during the trial. For AD, biomarker tests are available to determine levels of amyloid beta and tau. However, neuroinflammation mediated by disease-associated microglia and astrocytes is now accepted as a central driver of neurodegeneration in AD, and therefore the identification of meaningful biomarkers for neuroinflammation is also of high clinical importance.

Using state-of-the-art protein detection technology in the lab, a recent study identified a panel of glial proteins in cerebrospinal fluid that show potential as fluid biomarkers for neuroinflammation in AD. These proteins were found to directly relate to the disease-associated states of microglia and astrocytes in the AD brain.

*Christian Haass, Ph.D., DZNE, Germany; and Mathias Jucker, Ph.D., and Stephan Kaeser, Ph.D., both of University of Tübingen*

<https://bit.ly/3yp1yL9>

# Identified: An Elusive Toxin That Damages Neurons

With unfavorable conditions, the normally helpful astrocytes can become inflammatory and release a substance that is toxic to neurons. In a breakthrough discovery after years of searching, researchers have identified the toxic substance as saturated lipids. These toxins induced the death of nearby injured neurons and contributed to neurodegeneration in the brain. Studies demonstrated that eliminating a key enzyme in the production of the lipid toxins made the astrocytes much less toxic. Targeting this enzyme may be of future therapeutic potential for AD.

*Shane Liddelow, Ph.D., New York University Langone Health*

<https://bit.ly/3VmY59M>

# Improving a Malfunctioning Brain Drain Clears Amyloid Plaques

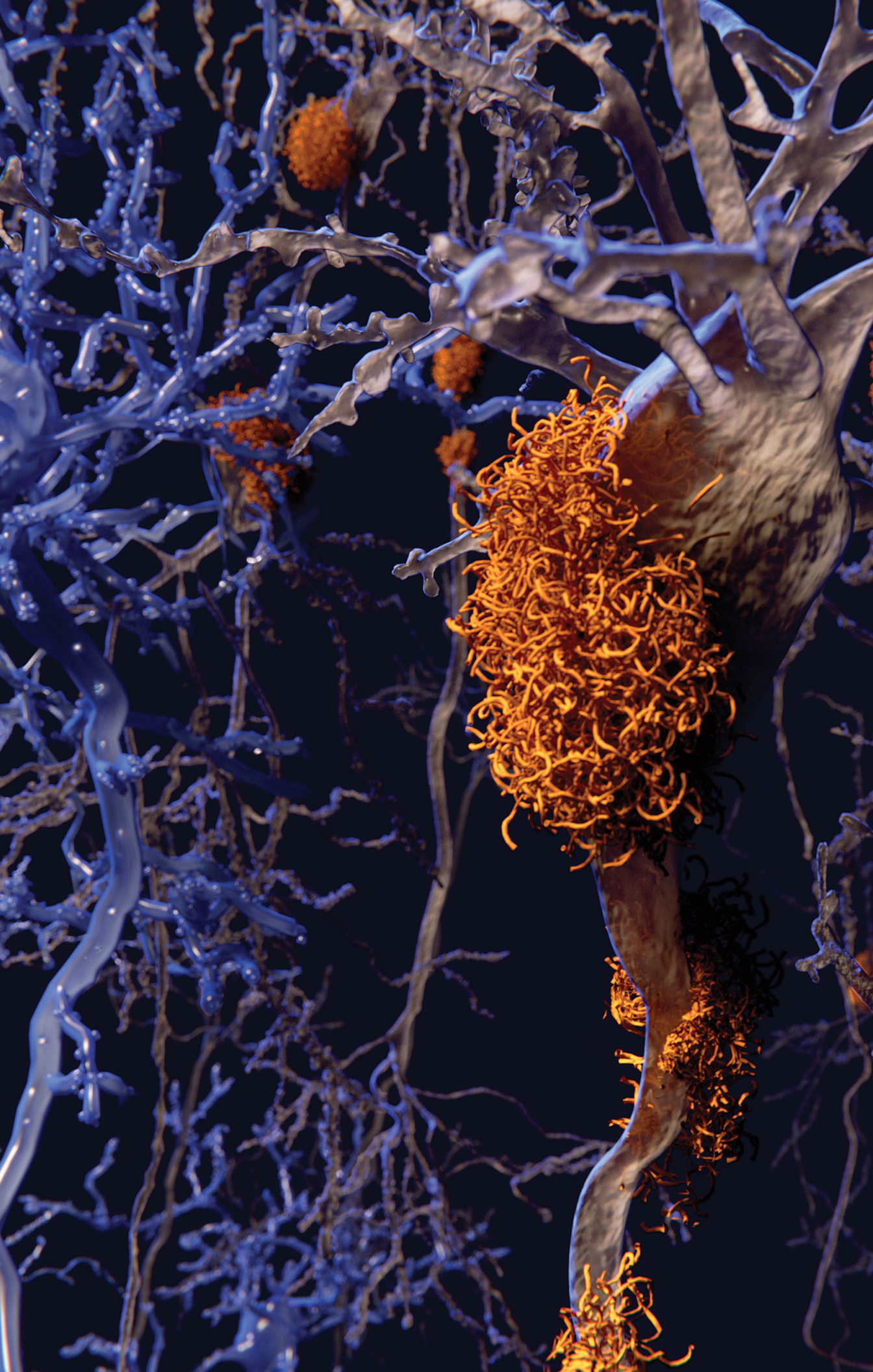
“The Central Nervous System (CNS) was historically considered as an immune privileged organ. Key factors contributing to immune privilege were considered to be the blood-brain barrier and the lack of lymphatic drainage of the CNS, which results in a physical disconnect with the immune system. Our lab has shattered the latter assumption by demonstrating the presence of meningeal lymphatics surrounding the brain borders that drain brain-derived molecules into the cervical lymph nodes.”

—Kipnis Lab website

When the lymphatics do not function properly, the impaired drainage that follows is suggested to aggravate AD pathology. A new study reveals that boosting the brain's meningeal lymphatics and drainage improves the clearance of amyloid plaques. The study also showed that improved lymphatic function increased the effectiveness of anti-amyloid immunotherapy.

*David Holtzman, M.D. and Jonathan Kipnis, Ph.D., both of Washington University School of Medicine in St. Louis*

<https://bit.ly/3Me2hEo>



# Altering the Gut Microbiome Impacts Amyloid in the Brain

There are four main groups of bacteria in the human gut, and the level of each type is constantly changing. This component of the human microbiome has an essential role in maintaining the body's normal functions, such as resistance to infection and inflammation. Advances in understanding the connection between the gut microbiome and the brain have brought to light that an imbalance in the diversity of gut microbes may trigger neuroinflammation in the brain. Short-term experimental treatment with high-dose antibiotics administered early in the life stage of specialized mice changed the composition of the microbiome and led to a significant reduction of amyloid beta later in life. Interestingly, the manipulation had an effect in male but not female mice. The research also suggests that the gut microbiome-brain connection relies on microglia. Depletion of microglia after the antibiotic treatment overturned the amyloid-reducing effect of the antibiotics and amyloid persisted.

*Sangram Sisodia, Ph.D., The University of Chicago; and Rudolph Tanzi, Ph.D., Massachusetts General Hospital*

<https://bit.ly/3ErtlZQ>



# Blood Pressure Medication: a Future Treatment for AD?

The angiotensin-converting enzyme (ACE) causes blood vessels to narrow, increasing blood pressure. Patients with AD show higher levels of ACE in their brains. The Alzheimer's Genome Project identified rare variants of the angiotensin-converting enzyme (ACE) that were associated with AD. One of these mutations increased the levels of the ACE1 protein in neurons of the brain and induced neuroinflammation and neurodegeneration. This research investigates the relationship between neurodegeneration and ACE1, and the potential impact of FDA-approved blood pressure medications—ACE inhibitors—already proven safe as potential treatments for Alzheimer's disease.

*Leah Cuddy, Ph.D., Northwestern University; Winston Hide, Ph.D., Beth Israel Deaconess Medical Center; Rudolph Tanzi, Ph.D., Massachusetts General Hospital; and Robert Vassar, Ph.D., Northwestern University*

<https://bit.ly/3fKiTaF>

# Variation in Tau May Explain Why Some Patients Decline Faster

One of the many challenges presented by AD is that patients decline at very different rates. Scientists have recognized that the development of symptoms of the disease more closely correlates with the accumulation of tau tangles than with the accumulation of amyloid beta plaques, which typically peak before symptoms emerge. From the paper published in *Nature Medicine*, “These data suggest that different individuals with ‘typical’ AD may have distinct biochemical features of tau. These data are consistent with the possibility that individuals with AD, much like people with cancer, may have multiple molecular drivers of an otherwise common phenotype, and emphasize the potential for personalized therapeutic approaches for slowing clinical progression of AD.” Identifying differences in tau among patients, and their impact on the rates of severity of disease progression, sheds light on the potential for better prognostics and personalized therapy.

*Bradley Hyman, M.D., Ph.D., and Rudolph Tanzi, Ph.D., both of Massachusetts General Hospital*

<https://bit.ly/3SXVUri>

## WAYS TO DONATE

Cure Alzheimer's Fund is fortunate to have thousands of donors who make contributions of 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

You can donate directly from our website—please visit:  
[www.CureAlz.org/Giving/Donate](http://www.CureAlz.org/Giving/Donate).

## MAIL

If you prefer to make a donation by personal check, please make your check payable to: Cure Alzheimer's Fund. Our address is: Cure Alzheimer's Fund, 34 Washington St., Suite 310, Wellesley Hills, MA 02481.

## TELEPHONE

If you would like to make a donation by telephone, please call us at 781-237-3800. Our business hours are 9 a.m. to 5 p.m. ET. When calling after hours, please leave a message and we will return your call the next business day.

## DONOR ADVISED FUNDS

Donors with funds held by Fidelity Charitable, Schwab Charitable or Great Kansas Community Foundation may use the DAF Direct form on our website at [www.CureAlz.org/giving/donate](http://www.CureAlz.org/giving/donate) to process donations. For all other Donor Advised Fund holders, please mail checks to our office at: Cure Alzheimer's Fund, 34 Washington St., Suite 310, Wellesley Hills, MA 02481.

## PLANNED GIVING

We offer a number of planned giving options, some of which may offer tax incentives. These include bequests, qualified charitable distributions (QCDs), charitable gift annuities, charitable remainder trusts (CRTs), charitable lead trusts (CLTs) and gifts of retirement assets or life insurance policies.

To explore these and other ways to give, please visit:  
[www.CureAlz.org/Giving/Donate/](http://www.CureAlz.org/Giving/Donate/)  
or contact Laurel Lyle at [LLyle@CureAlz.org](mailto:LLyle@CureAlz.org),  
or call 781-237-3800.



## OUR MISSION

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

[WWW.CUREALZ.ORG](http://WWW.CUREALZ.ORG)

34 Washington Street • Suite 310 • Wellesley Hills, Massachusetts 02481 • 1.877.CURE.ALZ (1.877.287.3259)

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