
Cure Alzheimer's FUND
targeting breakthrough research

Alzheimer's disease was first documented over 110 years ago. At the time, little was known about the disease, and for the next 80 years, only a meager amount of additional information was discovered.

Our founders, frustrated by the slow pace of research, came together and leveraged their experience in venture capital and business to create Cure Alzheimer's Fund. They designed the Fund to dramatically accelerate Alzheimer's research, make bold bets, and focus exclusively on finding a cure. Founders Jacqui and Jeff Morby, Henry McCance, and Phyllis Rappaport built the new organization around several key principles:

—Fund the world's leading Alzheimer's researchers

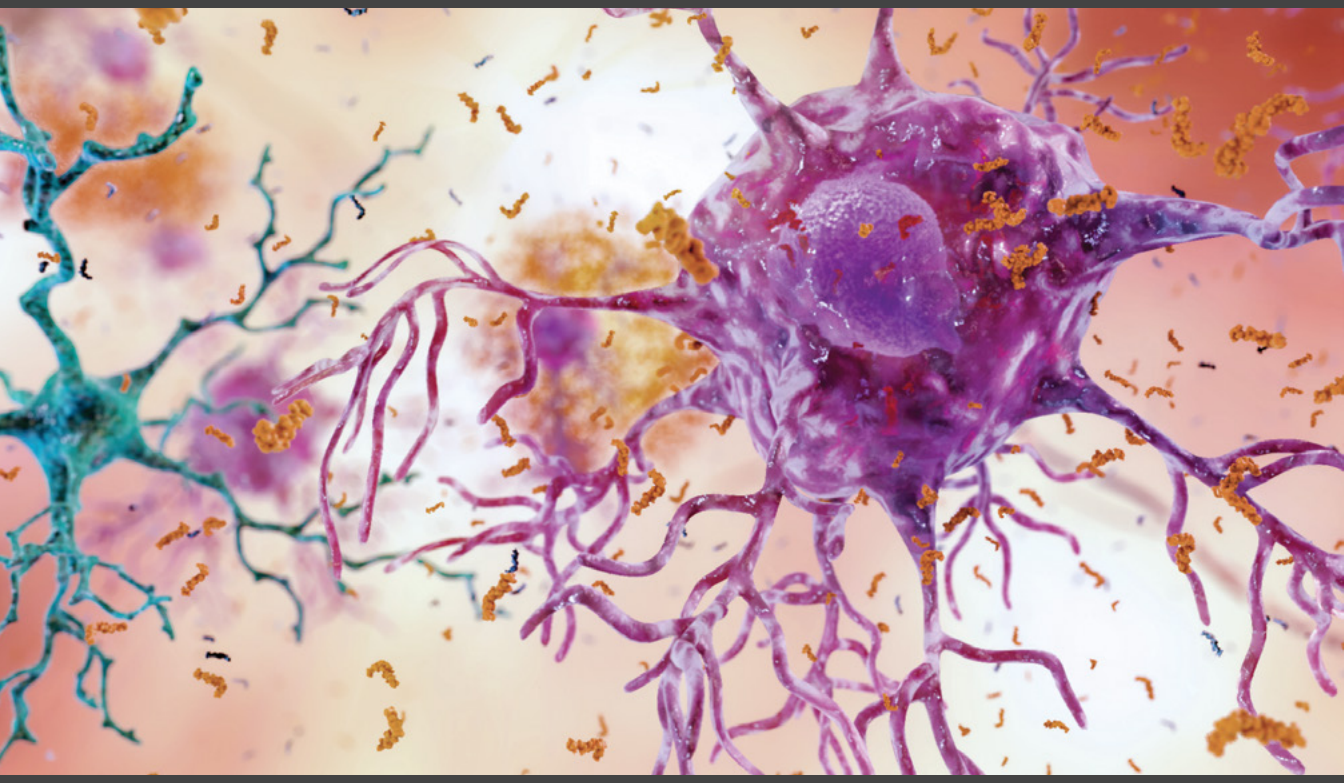
—Provide rapid review & approvals of grant requests

—Insist on collaboration among funded scientists

—The board of directors pays for all overhead expenses so that 100% of all donations go directly to research

Since our inception in 2004, we have been relentlessly focused on providing research grants to the worlds' leading scientists searching for a cure for Alzheimer's. We are honored to work with scientists who are passionate in their pursuit to rid our world of this disease. Their work has resulted in over 450 published papers, and many of the funded projects have resulted in significant breakthroughs—including findings that have altered the course of the research of Alzheimer's disease by changing the discovery pathways.

Here are a number
of those findings and
breakthroughs.



# 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 brain tissue under the microscope upon autopsy.

## AMYLOID PLAQUES

The amyloid plaques involved in Alzheimer's comes in several different molecular forms that collect between neurons. It is 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 that 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 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, 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 plaques 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. https://www.nia.nih.gov/health/what-alzheimers-disease

# Alzheimer's Genome Project™

The Alzheimer's Genome Project™ (AGP)—launched by Cure Alzheimer's Fund—was the first large-scale, family-based study of the human genome specific to Alzheimer's disease. The project screened DNA from over 400 Alzheimer's families and searched for genes that might increase risk for, or offer protection against, the disease. This was the first study to report novel Alzheimer's genes that reached statistical significance—the first phase of this study identified more than 100 candidate genes. The Alzheimer's Genome Project™ was listed in *TIME*'s Top 10 Medical Breakthroughs of 2008. It provided the foundation for other major genetic studies spearheaded by Cure Alzheimer's Fund, such as Whole Genome Sequencing and the Genes to Therapies program. Together, these studies are helping to complete the picture of the many genetic factors contributing to Alzheimer's disease, and are highlighting genes as candidates for intervention with therapeutics.

*Rudy Tanzi, Ph.D., Massachusetts General Hospital*

# The Toxic Effects of Apoe4 May Result from a Damaging Immune Response to Tau

The APOE gene is associated with the metabolism of fats in the human body. Having two copies of the epsilon 4 variant, APOE4, is the largest known risk factor for developing late-onset Alzheimer's disease. APOE4 exists in about 20% of the population and increases the risk of developing Alzheimer's disease by up to 12x. It also increases the brain's levels of amyloid, one of the prime suspects in the investigation into the causes of Alzheimer's. This study revealed the effect of APOE4 on the tau protein.

Once tau accumulates, the brain degenerates. When APOE4 is present, it amplifies the toxic function of tau, and may trigger the entire pathological cascade of neurodegeneration in the brain. In light of these findings, APOE4 has become a new target for the development of therapies.

*David Holtzman, M.D., Ph.D., Washington University School of Medicine*

# Converting the Harmful Apoe4 Gene to Neutral Apoe3

APOE is known to promote the accumulation of amyloid beta proteins in the brain. Using CRISPR gene editing technology, the harmful APOE4 gene was converted to the neutral APOE3 gene in the lab, alleviating Alzheimer's-related characteristics in neurons, glia, and stem cell tissue cultures. The long-term future use of gene editing to convert APOE4 to APOE3 in humans may provide a therapy that would diminish the characteristics of Alzheimer's disease.

*Li-Huei Tsai, Ph.D., Massachusetts Institute of Technology*

# Stem Cell Models and Familial Alzheimer's

A mutation in the Presenilin 1 gene is known to cause elevated levels of amyloid plaques and inflammation in those who had early-onset Alzheimer's disease. Cure Alzheimer's Fund created a consortium to develop models of familial Alzheimer's disease using stem cells that included the Presenilin 1 gene; this resulted in the identification of 14 other genes that potentially have a link to Alzheimer's disease. These genes are targets for further study and may help the scientific community to understand other elements of the pathology of the disease such as inflammation.

*Sam Gandy, M.D., Ph.D., Mount Sinai*

# Alzheimer's in a Dish

Alzheimer's disease has been difficult to replicate in the laboratory environment. For the first time in 2014, a 3-dimensional model of Alzheimer's disease was developed in a Petri dish using a new and proprietary gel medium formula. Growing human cell cultures in a gel rather than a liquid provided for the 3-D structure of neurons in a real brain, allowing Alzheimer's pathology to develop in the dish just as it would in a living person. This has become an invaluable tool for research, as it provides for studies to be performed in shorter timespans and allows for the rapid screening of existing drugs for their effect on amyloid plaques and tau tangles. The recipe for the gel is available to all scientists so that Alzheimer's research can be accelerated, regardless of their affiliation with Cure Alzheimer's Fund.

The scientists were awarded the Smithsonian Ingenuity Award for this discovery; *The New York Times* noted Alzheimer's in a Dish as a "real game changer"; and Dr. Tanzi was recognized by *TIME* Magazine as one of The 100 Most Influential People in 2015.

*Rudy Tanzi, Ph.D., and Doo Yeon Kim, Ph.D., Massachusetts General Hospital*

# The (R)Evolution of Alzheimer's in a Dish

In 2018, the original Alzheimer's in a Dish—first used to culture neural stem cells—was updated to include the inflammatory factors known to contribute to neuroinflammation in Alzheimer's disease. Alzheimer's in a Dish now includes amyloid plaques, tau neuronal tangles, inflammation, and microglia. This provides for a more complete replication of the pathology of Alzheimer's disease in the laboratory.

*Rudy Tanzi, Ph.D., Massachusetts General Hospital and Hansang Cho, Ph.D., University of North Carolina*

# Dual Role of Amyloid as Harmful and Beneficial

Because amyloid plaques can build up in the brain and trigger a cascade response, leading to cognitive decline and neurodegeneration, they have previously been thought of as *only harmful*. As such, plaques have been the target of pharmaceutical companies in the development of drugs—remove amyloid plaques, the logic goes, and one can halt the destruction occurring in the brain as a result of Alzheimer's disease. All of these prospective drugs have failed.

New research is revealing that amyloid may play more nuanced part in the function of the brain. Evidence suggests that amyloid plays a role in innate immunity, and that it can protect against a wide range of infectious agents. Amyloid has the capacity to form fibrils that trap pathogens in an infected brain. As infections in the brain increase, the build-up of amyloid demonstrates the double-edged sword of this peptide. On the one hand, amyloid initially traps the infection, keeping the brain safe—on the other hand, this leads to an accelerated build-up of the plaque that can contribute to the pathology associated with Alzheimer's disease.

This would suggest that total clearance of amyloid from the brain is not an appropriate therapy; instead, it should be regulated and not removed completely.

*Rudy Tanzi, Ph.D., and Rob Moir, Ph.D., Massachusetts General Hospital*

# Sleep and Alzheimer's Disease

During sleep, the natural cleaning system of the brain goes into action, removing debris and toxic particles. Poor sleep is now associated with a buildup of amyloid and extended poor sleep causes the buildup of tau, another hallmark of the disease.

It turns out that, during wake cycles, amyloid accumulates in the brain. During sleep, cerebrospinal fluid rushes through the brain to clear out unwanted protein particles and debris. One study also pointed to orexin, a neurotransmitter that regulates the sleep cycle, as likely being involved in the production of increased levels of amyloid. This research helped both to identify orexin as a potential drug target, and to demonstrate the critical importance of adequate sleep in lowering risk for Alzheimer's disease.

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

# Estrogen, Menopause, and Alzheimer's Disease

Estrogen is a fundamental regulator of the metabolic system of the female brain and body. Within the brain, estrogen regulates the chemical that maintains cell-to-cell communication. During menopause, the decline in circulating estrogen contributes to a decline in brain cellular energy. Many researchers have proposed that the loss of estrogen may significantly contribute to cognitive decline and Alzheimer's disease risk in women. (It is worth pointing out that men also undergo age-related changes in hormones that contribute to their risk for dementia.)

Research now supports the idea that post-menopausal hormone therapy can modulate brain bioenergetics likely leading to the maintenance of cognitive function and reduced risk of Alzheimer's disease. (Any discussion of hormone therapy as a treatment strategy should take place with a doctor as estrogen receptors exist throughout the body, including in the breast and ovaries; as a result, hormone therapy could increase the risk for certain types of cancers in other places in the body.)

More research is being conducted to explore exactly why women are at increased risk for developing Alzheimer's disease and whether targeting declining estrogen levels could afford protection against the development of Alzheimer's disease.

*Lisa Mosconi, Weill Cornell Medicine*

# Cholesterol and Alzheimer's Disease

Although the brain is the organ with the highest cholesterol content, almost all of the cholesterol in the brain is actually synthesized in the brain; high levels of cholesterol can be a risk factor for Alzheimer's disease. An enzyme called ACAT in the cholesterol pathway can increase production of amyloid, resulting in the buildup of amyloid plaque bundles in the brain. A mechanism of action was identified called *palmitoylation* that accounts for the relationship between ACAT and increased toxic production of amyloid plaques. Further studies have revealed that ACAT inhibitors reduced brain cholesterol in the lab, but also led to increased incidence of stroke and heart attack.

*Dora Kovacs, Ph.D., Massachusetts General Hospital*

# Evidence of the Link Between Alzheimer's and Herpes

Two independent studies have demonstrated that viruses—and two strains of herpes in particular—are involved in Alzheimer's disease. One study demonstrated that the herpes virus influenced the activity of many human genes—including several that affect the risk of Alzheimer's. The damage is particularly bad in the brain samples of those who have the APOE4 gene. The second study found that amyloid could become over-activated by infections such as herpes and form plaques in an attempt to protect the brain. The research suggests that amyloid may work alongside the immune system in responding to infections and other pathogens in the brain.

*Rudy Tanzi, Ph.D. and Rob Moir, Ph.D. Massachusetts General Hospital, and Sam Gandy, M.D., Ph.D., Mount Sinai*

# Exercise May Generate New Neurons in the Brain

Imagine a future where the beneficial effects of exercise could be recreated in a brain ravaged by the cell loss, plaques, and tangles associated with Alzheimer's disease. To this end, it would be crucial to first determine the biochemical changes that could improve memory in a brain experiencing the early stages of dementia. A giant step forward uncovered how exercise and neurogenesis work collaboratively to enhance the likelihood that new neurons will survive to play a role in protecting against cognitive decline.

*Rudy Tanzi, Ph.D., and Se Hoon Choi, Ph.D., Massachusetts General Hospital*

# Certain Types of Neurons May be Vulnerable to Disease

There are approximately 100 distinct types of neurons in the human brain whose function is to communicate messages rapidly and precisely with other cells. One characteristic that defines these cells is whether or not they are classified as excitatory or inhibitory. An excitatory neuron increases the likelihood that an action potential—critical in cell-to-cell communication—will fire, whereas inhibitory neurons dampen neural activity. Excitatory neurons are more likely to be impaired in early Alzheimer's disease, but the reason for the vulnerability has not been known.

A new study shows that excitatory neurons are more susceptible to neurodegeneration; this study includes data indicating that tau accumulates selectively in excitatory neurons leading to increased vulnerability to Alzheimer's disease in these cells. One of the genes identified is called BAG3. BAG3 is known to regulate the process by which the cell removes waste products. Reducing levels of BAG3 in neurons led to increased accumulation of tau; conversely, increasing levels of BAG3 protected neurons from tau. This study provides crucial evidence for the underlying cellular processes contributing to selective vulnerability of different neurons to tau pathology.

*Karen Duff, Ph.D., Columbia University*

# The Role of Brain Vasculature in Neurodegenerative Disorders

A vast network of arteries, capillaries, and veins is required to keep the 86 billion neurons in the brain functioning properly. Lab studies show that amyloid plaques and tau lead to blood vessel abnormalities and a breakdown of the blood-brain barrier. This vascular dysfunction appears to precede the full pathology of Alzheimer's disease. Individuals with early cognitive dysfunction develop damage to the capillaries of the brain, and to the blood-brain barrier, regardless of the levels of accumulation of amyloid plaques or tau tangles. A new model of biomarkers has been suggested that links brain vascular changes to neurodegeneration.

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

# Who Knew? The Brain Has a Drain to Remove Debris?

In healthy humans, the cerebrospinal fluid (CSF) is renewed approximately four times per day, and the skull is lined with membranes that protect the brain and spinal cord. More than 200 years ago, it was speculated that the brain was also protected by lymphatic vessels whose purpose is, among other things, to transport bacteria and debris to the lymph nodes to be destroyed and eliminated from the body. In 2018, the hypothesis of the existence of lymphatic vessels in the brain was confirmed using state-of-the-art imaging technology.

In aging adults, impaired function of lymphatic vessels can lead to accelerated accumulation of toxic amyloid beta in the brain. The traditional model for how the CSF drained was directly challenged when the scientists injected molecular tracers into the CSF and demonstrated that the drainage occurred through the lymphatic vessels—demonstrating a new route for clearing molecules from the brain. The presence of a "brain drain" is now understood to be critical for maintaining intracranial pressure and removing waste.

*Jony Kipnis, Ph.D., University of Virginia School of Medicine*

# The Microbiome of the Gut and Alzheimer's

The first-ever study to characterize the relationship between Alzheimer's disease and the microbiome of the gut (the makeup of microorganisms in the digestive tract) found that altering the composition of the gut microbiome in the lab could lead to lower levels of amyloid plaques in the brain. Further research in this area may identify species of bacteria that exacerbate or protect against Alzheimer's pathology, and enhance our understanding of how changes in the gut can affect the brain in humans.

*Sam Sisodia, Ph.D., The University of Chicago*

# Air Pollution and Alzheimer's

Research revealed that nickel nanoparticles found in air pollution increased the amyloid levels in the brain that are also found at elevated levels in Alzheimer's disease. This work prompted further investigation into how genetic and environmental factors interact to cause Alzheimer's. A separate study determined that air pollution might play a role in elevating the risk for Alzheimer's disease citing nanoparticles emitted from vehicle exhaust as potential threats.

*Sam Gandy, M.D., Ph.D., Mount Sinai and Caleb Finch, Ph.D., University of Southern California*

# "Inside-Out" Amyloid Hypothesis

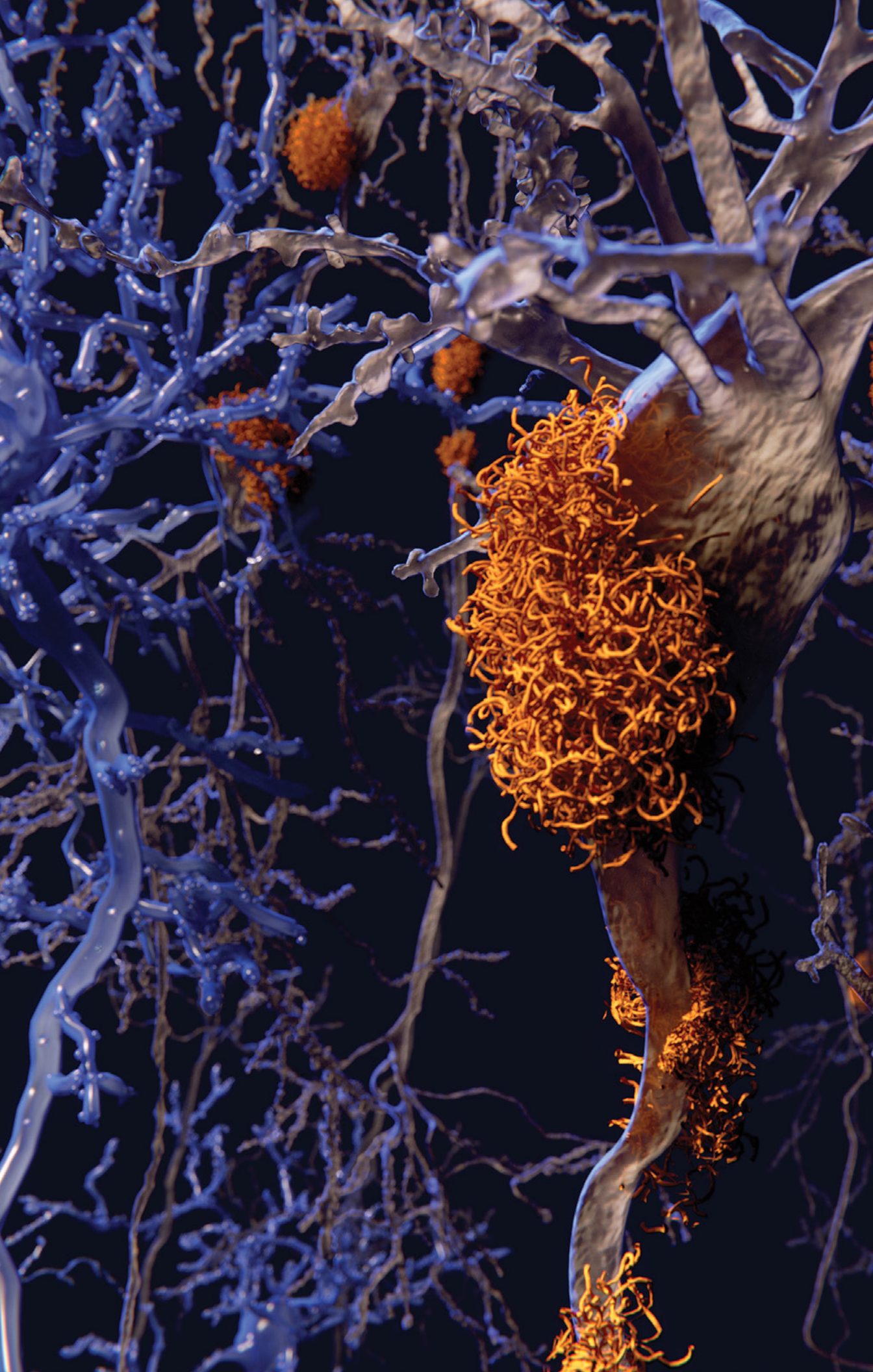
The "Amyloid Hypothesis" posits that increases of amyloid in the brain trigger a series of events that leads to the pathology and development of Alzheimer's disease. A different theory has been advanced to describe how Alzheimer's disease progresses. This discovery found evidence that amyloid plaques may actually form on the interior of cells, not the exterior, as had been the belief. The new model may help to explain why plaques cause cell death and it may bring us closer to identifying exactly where and how Alzheimer's disease causes damage to the brain.

*Charles Glabe, Ph.D., University of California Irvine*

# Preventing the Buildup of Amyloid in the Brain

Two previously unknown mutations in the ADAM10 gene have been identified; this gene is linked to late-onset Alzheimer's disease. The research suggests that the ADAM10 gene codes for an enzyme that helps to prevent the formation of the amyloid plaques seen in Alzheimer's. A mutation of the ADAM10 gene diminishes activity of this enzyme, leading to increased buildup of amyloid into the plaque bundles. Identifying this potential trigger of Alzheimer's pathology has made possible new therapeutic targets for the disease.

*Rudy Tanzi, Ph.D., and Jaehong Suh, Ph.D., Massachusetts General Hospital*



# Clearing Amyloid from the Brain

The CD33 gene is linked to amyloid pathology and the progression of Alzheimer's disease and studies show that excessive amounts of CD33 play a role in the development of late-onset Alzheimer's disease. A variant of the gene CD33 impedes the clearance of amyloid beta. However, a mutation of the gene also causes amyloid to be cleared more quickly and is actually protective against the disease.

*Rudy Tanzi, Ph.D., Massachusetts General Hospital*

# General Anesthetics and Alzheimer's Disease

A study of the safety of two common anesthetics, isoflurane and desflurane found that while desflurane is safe in elderly patients, isoflurane could induce cell death and increased levels of amyloid—both prominent in Alzheimer's pathology. The research provided valuable insight to health care providers and broadened our understanding of the risk factors involved with general anesthesia and Alzheimer's disease.

*Zhongcong Xie, M.D., Ph.D., Massachusetts General Hospital*

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.

Cure Alzheimer's FUND

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