



DISCOVERIES





WE'RE HERE TO

Cure Alzheimer's

Alzheimer's disease was discovered over 110 years ago. Little was known about the disease and little more was learned.

Our founders, frustrated by the slow pace of research into Alzheimer's disease, decided to leverage their experience in venture capital and corporate start-ups and build a fund designed specifically to accelerate research, make bold bets, and focus on finding a cure. To this end, Jacqui and Jeff Morby, Henry McCance, and Phyllis Rappaport insisted on four key principles to best ensure success:

- **Fund the world's leading Alzheimer's researchers**
- **Provide rapid review and approvals for submitted grants**
- **Insist on collaboration among funded scientists**
- **The board of directors pays for all overhead expenses so that 100% of donations go directly to research**

Since our inception in 2004, our steadfast focus has been providing research grants to the world's leading scientists researching Alzheimer's disease. To date, Cure Alzheimer's Fund has contributed nearly \$60,000,000 to Alzheimer's research. We are honored to work with scientists who are passionate in their pursuit to rid our world of this debilitating disease. Many of the funded projects have resulted in significant breakthroughs in developing a better understanding of Alzheimer's disease and getting closer to a cure.

We are pleased to share some of our findings and breakthroughs.



2017

The Most Toxic Effects of APOE4 May Result from a Damaging Immune Response to Tau

Discovered in 1993, APOE4 exists in about 20% of the population and increases the risk of developing Alzheimer's disease by up to twelve times. It increases levels of amyloid in the brain, which is one of the prime suspects for the cause of Alzheimer's. A new study, conducted by David Holtzman and his team at Washington University School of Medicine in St. Louis, revealed that APOE4 and its effect on the tau protein might be critical in understanding how Alzheimer's disease develops. "Once tau accumulates, the brain degenerates. What we found was that when APOE4 is there, it amplifies the toxic function of tau, which means that if we can reduce APOE4 levels we may be able to stop the disease process," said Holtzman.

2016

Dual Role of Amyloid as Protector and Instigator

Research conducted by Rob Moir, Ph.D., and Rudy Tanzi, Ph.D., of Massachusetts General Hospital uncovered the likely role of infection in Alzheimer's disease. Moir and Tanzi showed that amyloid plaques, a hallmark of Alzheimer's, might form as an immune response to pathogens in the brain. This discovery shows that Alzheimer's pathology begins with a weakened blood-brain barrier that, with age, may allow pathogens to permeate – triggering an exaggerated immune response. The study also showed that amyloid may also have a role in protecting the healthy brain and that future therapies for the disease should probably regulate amyloid beta and not remove it completely.

The Microbiome of the Gut and Alzheimer's

Sam Sisodia, Ph.D., of the University of Chicago, performed the first-ever study to characterize the relationship between Alzheimer's disease and microbiome in the gut (the makeup of microorganisms in the digestive tract). His work found that altering the composition of the gut microbiome in mice 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.

Air Pollution and Alzheimer's

Caleb Finch, Ph.D., at the University of Southern California also determined in his study that air pollution might have a role in elevating the risk for Alzheimer's disease. Finch's study cited nanoparticles emitted from vehicle exhaust as potential threats. He estimates that pollution from such particles contributes to at least 5% of all Alzheimer's cases. Finch was awarded a multi-year grant from the National Institutes of Health to continue investigating this subject.

2014

Alzheimer's in a Dish

For many reasons, Alzheimer's disease has been difficult to replicate in the laboratory environment. Doo Yeon Kim, Ph.D., and Rudy Tanzi, Ph.D., at Massachusetts General Hospital developed a 3-dimensional model of Alzheimer's disease in a Petri dish using a new and proprietary formula for a gel medium. By growing human cell cultures in a gel rather than a liquid, Kim and Tanzi were able to better replicate the 3D 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 affiliation with Cure Alzheimer's Fund. Drs. Kim and Tanzi 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* among its "100 Most Influential People" in 2015.

Building New Nerve Cells in the Brain *mGluR2/3 Blocker Drug*

Building on previous work performed by the Cure Alzheimer's Fund Stem Cell Consortium, Sam Gandy, M.D., Ph.D., at the Icahn School of Medicine at Mt. Sinai conducted studies on a drug called an "mGluR2/3 blocker," which stimulates the creation of new nerve cells in the brain. Promising pilot results of the drug in mice helped the project secure \$1 million in funding from the Veteran's Administration for additional study.

"Inside-Out" Amyloid Hypothesis

The Amyloid Hypothesis argues that increases of the amyloid beta protein in the brain triggers a series of events that leads to the pathology and development of Alzheimer's disease. Charles Glabe, Ph.D., at University of California Irvine advanced an "alternative amyloid hypothesis" to describe how Alzheimer's disease progresses. Glabe found evidence that amyloid plaques may actually form on the interior of cells, not the exterior as had been the belief. Glabe's model may help to explain why plaques cause cell death, and bring us closer to identifying exactly where and how Alzheimer's disease causes damage to the brain.

Stem Cell Models and Familial Alzheimer's

Presenilin 1 is a gene known to cause early-onset Alzheimer's. Cure Alzheimer's Fund created a Stem Cell 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 science community to understand the different aspects of the pathology of the disease such as inflammation.



2013

Preventing the Buildup of Amyloid Formation *ADAM10 Gene Mutations*

Rudy Tanzi, Ph.D., and Jaehong Suh, Ph.D., of Massachusetts General Hospital identified two previously unknown mutations in the ADAM10 gene, which is linked with late-onset Alzheimer's disease. Their research suggests that the ADAM10 gene codes for an enzyme that helps to prevent the formation of amyloid beta, the protein that makes up the amyloid plaques seen in Alzheimer's. A mutation of the ADAM10 gene diminishes activity of this enzyme, leading to increased buildup of amyloid beta. By identifying a potential trigger of Alzheimer's pathology, Tanzi and Suh opened up new therapeutic targets for the disease.

Cholesterol and Alzheimer's

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 beta, an important component in the buildup of plaque bundles that are part of the Alzheimer's pathology. In 2013, Dora Kovacs, Ph.D., at Massachusetts General Hospital identified a mechanism of action called "palmitoylation" that accounts for the relationship between ACAT and increased toxic amyloid production. Kovacs' team then moved to test two existing drugs, inhibitors of the ACAT enzyme, for their effectiveness against Alzheimer's.

Clearing Amyloid Beta *CD33 Variant*

In a study co-funded by Cure Alzheimer's Fund and the National Institutes of Mental Health, Rudy Tanzi, Ph.D., showed 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 causes amyloid to be cleared more quickly and is actually protective against the disease. Tanzi first identified the gene as part of the Alzheimer's Genome Project™, an effort started by Cure Alzheimer's Fund in 2008 to identify all genes connected to Alzheimer's disease.

Air Pollution and Alzheimer's

Research by Sam Gandy, M.D., Ph.D., at the Icahn School of Medicine at Mt. Sinai revealed that nickel nanoparticles found in air pollution increased the amyloid levels of certain peptides in the brain that are also found at elevated levels in Alzheimer's disease. Gandy's work prompted further investigation into how genetic and environmental factors interact to cause Alzheimer's.

2012

General Anesthetics and Alzheimer's Disease

In 2012, Zhongcong Xie, M.D., Ph.D., of Massachusetts General Hospital published a study on the safety of two common anesthetics, isoflurane and desflurane. He found that while desflurane is safe in elderly patients, isoflurane could induce cell death and increase levels of amyloid beta – both prominent in Alzheimer's pathology. Xie's research provided valuable insight to health care providers and broadened our understanding of the risk factors involved with general anesthesia and Alzheimer's disease.

2009

Sleep and Alzheimer's Disease

David M. Holtzman, M.D., of Washington University in St. Louis uncovered a link between sleep deprivation and Alzheimer's disease. Holtzman found that amyloid plaques appeared earlier and more frequently in the brains of mice deprived of sleep than in mice with normal sleep patterns. The 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.

2005 and ongoing

Alzheimer's Genome Project

Launched in 2005 by Rudy Tanzi, Ph.D., and Cure Alzheimer's Fund, the Alzheimer's Genome Project™ (AGP) 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 Magazine'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, as well as highlighting genes as candidates for intervention with therapeutics.

Help us find a cure.



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.

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