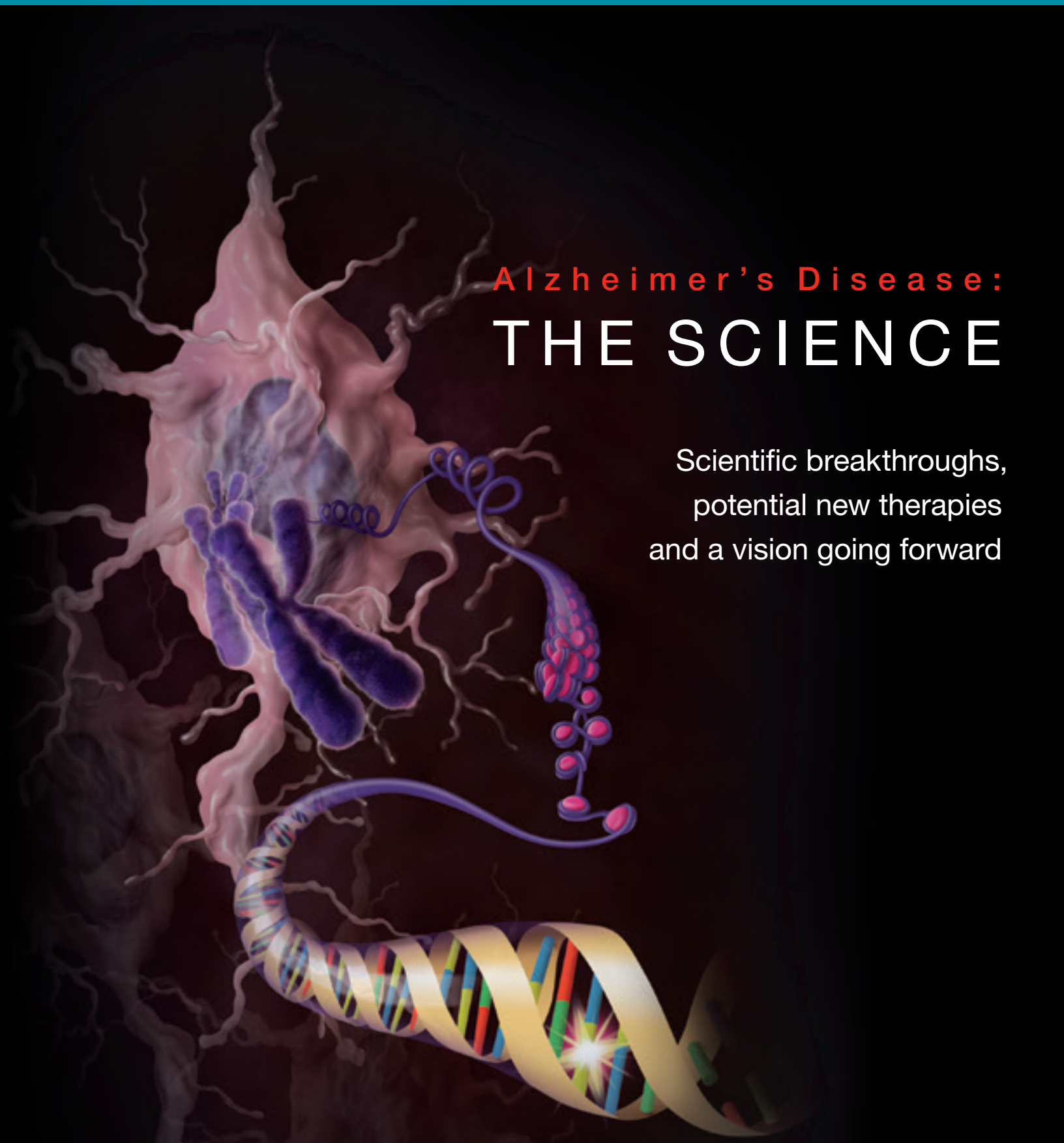
2014 EDITION



Alzheimer's Disease:
THE SCIENCE

Scientific breakthroughs,
potential new therapies
and a vision going forward

Cure Alzheimer's FUND

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Scientific breakthroughs,
potential new therapies
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10 YEARS OF LEADING RESEARCH

Knowledge of the science of Alzheimer's disease has advanced markedly during the last 10 years. We believe the strategic, philanthropic investment by Cure Alzheimer's Fund in leading research has contributed significantly to a dovetailing of genetic, biomarker, imaging and drug development efforts that brings us much closer to effective therapeutics.

Our goal not only is to devise therapies that can benefit patients now, but also to prevent future cases of Alzheimer's disease via a program of early prediction, early detection and early prevention. On our 10th anniversary, we are proud to offer this update on the progress toward eradicating Alzheimer's disease.

I. What is Alzheimer's?

Alzheimer's is the most common cause of dementia worldwide, affecting more than 5 million individuals in the United States alone.

It is a progressive disease of the brain that develops slowly over time, leads to increasingly serious cognitive decline associated with the presence of plaques and tangles in the brain, and it eventually is fatal. Alzheimer's primarily affects the elderly, but also can emerge as an early-onset form in middle age. With more than 70 million aging baby boomers, Alzheimer's disease has the capacity to single-handedly collapse the U.S. health care system in the coming decade. Dramatic gains in human longevity have resulted in life expectancies into the 70s, 80s and 90s, with an associated increased risk of Alzheimer's. Roughly 13 percent of those ages 65 and older have AD; this skyrockets to around 50 percent for those 85 years and older.

The Human and Financial Toll

While there are, of course, many serious health threats to the elderly, Alzheimer's is the only major health threat on the rise AND the one toward which we have by far the least-sophisticated medical response. The financial costs also are terrifying, reaching more than $200 billion *annually* in the United States (more than $600 billion worldwide). These numbers inevitably will increase significantly along with the number of cases, threatening to bankrupt national health care systems.

A History of Research

Modern research efforts began in 1984 with the discovery of beta-amyloid protein (Abeta) as the chief protein component of the Alzheimer's "plaques." In 1986, another protein, tau, was discovered to be the primary component of the "tangles." The first Alzheimer's-related gene, which codes for the amyloid precursor protein (APP), was discovered in 1987 by Dr. Rudy Tanzi and others.[1,2,3,4] In 1995, two other Alzheimer's genes, presenilin 1 and 2, also were discovered by Dr. Tanzi and others. Although mutations in these genes are rare, inheriting a mutation in one of them inevitably leads to the early onset of Alzheimer's. A fourth gene, APOE-e4, was found to be a common genetic risk factor in 1993. Together, these four genes strongly reinforced the so-called "amyloid hypothesis," which states that beta-amyloid is the key factor initiating the development of the disease. Also beginning in 1993, a series of drugs treating the symptoms of Alzheimer's, but not the progression—Cognex, Aricept, Razadyne, Exelon and Namenda—were approved by the U.S. Food and Drug Administration (FDA), but none has been able to modify disease progression. In 1999, researchers were able to prevent the development of plaques in genetically modified mice by injecting them with a beta-amyloid-based "vaccine." This gave a boost to therapeutic research. Dozens of compounds since have been investigated and tested, including many following the vaccine model, and several have gotten to FDA Stage III efficacy trials. However, no currently available drug has been shown to stall the progress of Alzheimer's pathology.

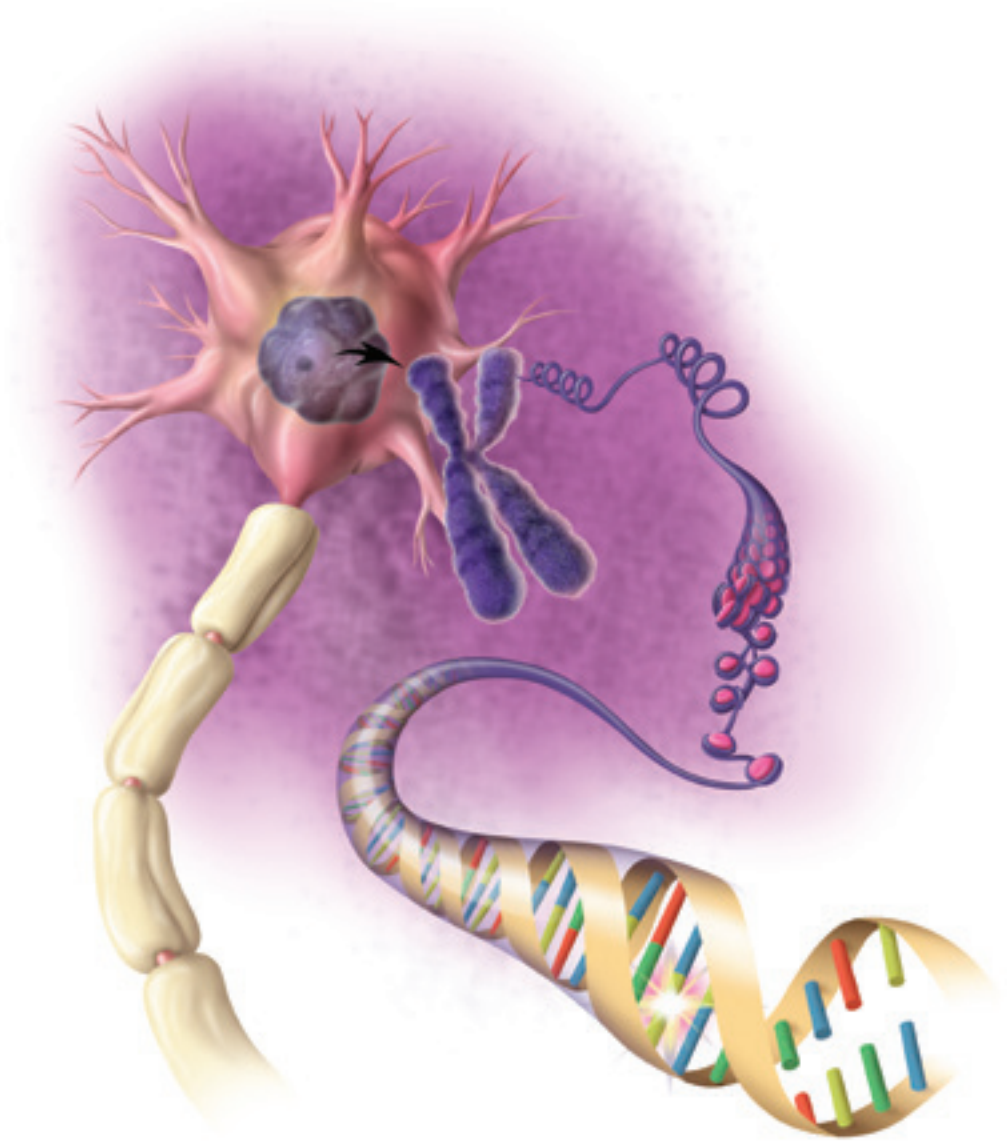
II. 10 Years of Leading Research: A Summary of Cure Alzheimer's Fund's Contributions

When Cure Alzheimer's Fund (CAF) was created in late 2004, our mission was to end the disease by: 1) identifying all risk genes; 2) using those genes to reveal underlying disease mechanisms; and 3) aggressively pursuing potential therapies based on the knowledge gained from AD genes. While we have not yet stopped the disease, we have, without question, come much closer to the goal line through substantial progress in these three key benchmarks.

Genetics: The Alzheimer's Genome Project™

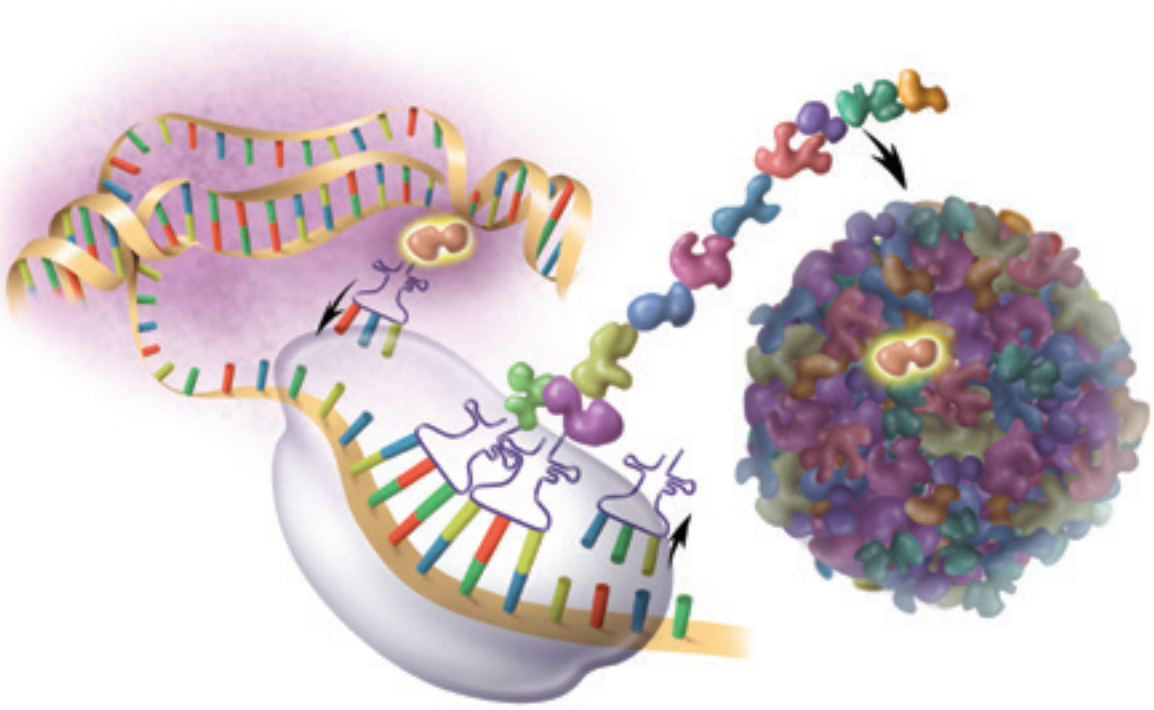
While the original four Alzheimer's disease genes have taught us most of what we know about the disease, they represent only a relatively small percentage of the genes responsible for Alzheimer's inheritance. Cure Alzheimer's Fund has dedicated substantial resources to identifying the full complement of Alzheimer's genes. The Alzheimer's Genome Project™ was first up, launched in 2005. The first phase of this study led to the identification of more than 100 new Alzheimer's candidate genes, and was named by TIME magazine/ CNN to be one of the Top 10 Medical Breakthroughs of 2008. This was also the *first* large-scale study of the human genome specific to Alzheimer's disease and the first to report novel AD genes with statistical significance.

To keep track of these results, Cure Alzheimer's Fund supports an online database originally established in Tanzi's laboratory called "AlzGene" (www.alzgene.org) that systematically catalogs all of the reported Alzheimer's genes and publicly provides all of the details on the studies. Phase 2 of the AGP is focused on using genes in neurons using disease models in mice. These studies have led to several new insights into the disease, including how these genes contribute to nerve cell abnormalities and death that is brought on by beta-amyloid. Additionally, a critical step was taken to identify not just which genes are associated with Alzheimer's risk, but also all of the DNA variants and mutations in those genes that increase or decrease risk for late-onset Alzheimer's disease. This was accomplished by Whole Geneome Sequencing (WGS), which was used to read the entire genome of individuals with AD—all 3 billion base pairs of DNA across all 46 chromosomes. This allowed us to identify nearly 1,000 new genetic mutations in more than 50 different Alzheimer's and frontotemporal lobar dementia genes, all of which functionally cause or protect against the disease.

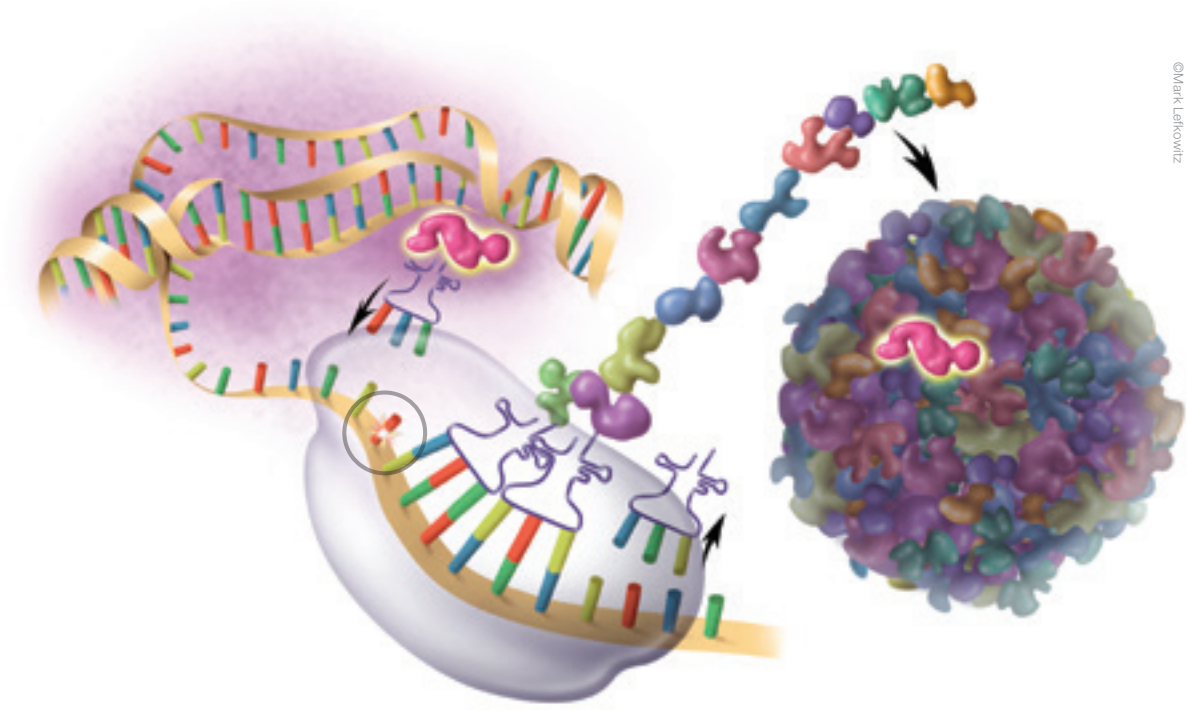


▲ Figure 1. What is a Gene?

Approximately 35,000 genes provide the blueprints for the roughly 350,000 proteins made in the human body. Genes are chemically made of deoxyribose nucleic acid (DNA), first described by Jim Watson and Francis Crick in the late 1950s. DNA is packaged into 46 different chromosomes, such as the X-shaped one shown here. Chromosomes are found in the nucleus at the center of the cell, in this case, a nerve cell. The structure of DNA resembles a double helix consisting of chemicals called nucleotides (bases). The bases are named by letters: A (red), T (green), C (blue) and G (yellow). A on one strand always binds to T on the other, and C always to G. There are two pairs of 23 chromosomes, 1–22 and either X or Y. Each parent gives you a set, making a total of 46 per cell. Most, but not all, genes provide the blueprint used by cells of the body to make a protein. A protein is made up of a chain of 20 different amino acids arranged in different combinations, which in a given protein may number in the thousands. To make proteins, DNA is used to create RNA. Proteins then are assembled in RNA-based factories called "ribosomes," which read the "genetic code" originally contained within the DNA for a particular gene in the nucleus of a cell. The RNA in the ribosome then guides the assembly of the protein from amino acids. The protein later is processed in various organelles within the cell to achieve its final configuration. Some proteins serve as the building blocks of the body, while others carry out specific functions. While most genes provide the template for a protein, some serve to regulate the activity of other genes without making proteins, e.g., by only making RNA. For example, some genes make "microRNAs" that can control the activity of other genes.



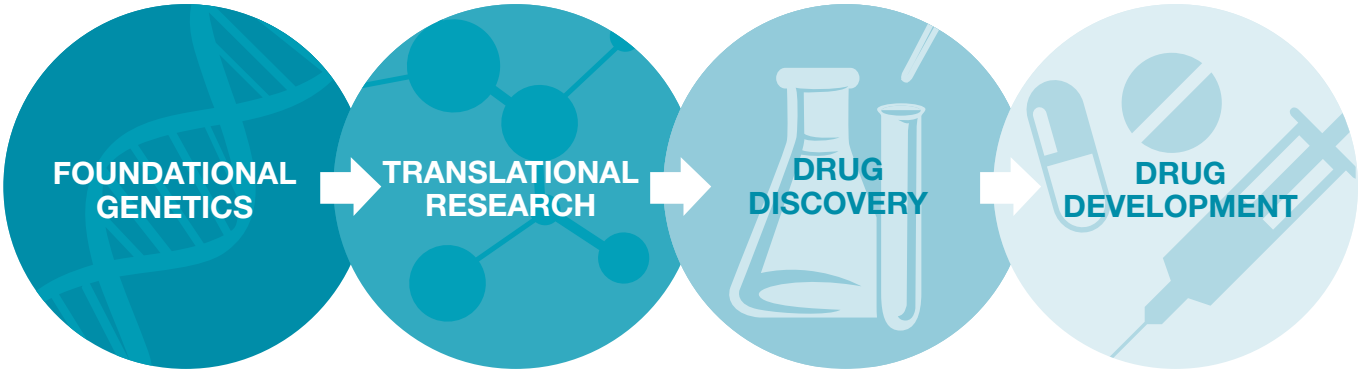
In identifying these new gene mutations, Dr. Tanzi and his team effectively have identified the biological linchpins (key causal agents) that drive Alzheimer's pathology in the brain. Cure Alzheimer's Fund-supported studies on some of these genes already are under way (PICALM in Dr. Berislav Zlokovic's (USC) lab, CD33 in Dr. Tanzi's lab and CR1 in Dr. Cindy Lemere's (Harvard Medical School) lab). Studies on new genes, including ABCA7 and TREML2, are being designed. With the data collection of the Whole Genome Sequencing completed, Tanzi and colleagues have entered Phase 3 of the Alzheimer's Genome Project: determining the precise biological mechanisms by which the new AD genes influence risk for the disease.



▲ Figure 2. From Gene to Protein.

Approximately 4 percent of our DNA makes up genes that provide blueprints for making proteins. A protein is made up of a chain of 20 different amino acids and can vary from just a few amino acids (called a peptide) or thousands of them. The DNA double-stranded helix first makes RNA, a single-stranded version of DNA in which one of the bases is substituted for another (U instead of T). RNA-based factories called "ribosomes" (grey globule) then guide the production of the protein. If a gene carries a defect in the DNA, e.g., a single base of the wrong type, this can lead to the production of a defective protein that does not function correctly. In the example above, the protein on the left (multicolored sphere) received one amino acid (small yellow bow) while the defective protein on the right received a different amino acid in that position (pink squiggle). This was caused by one single base change in the DNA (blue G substituted in DNA with red C—circled and marked with a small yellow star). This substitution leads to a similar change in the RNA that guides the amino acid chain that will make up the protein. The result is an altered protein with compromised function. In some cases, the altered protein will have no effect on one's health or predisposition to disease. In other cases, the altered protein either might directly cause or increase/decrease susceptibility for disease.

ROADMAP TO A CURE



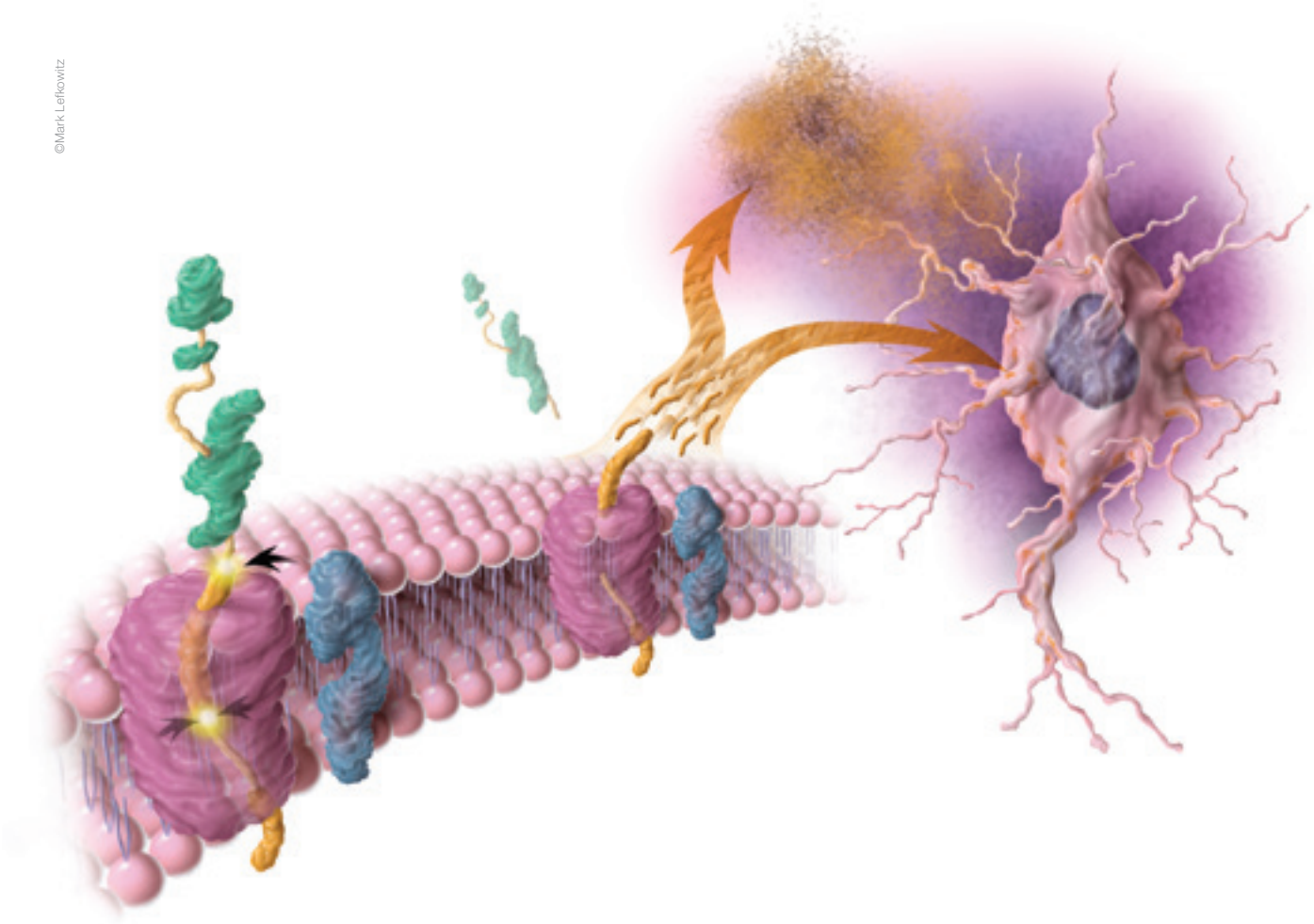
Mechanisms of Action

Using our genetic discoveries as guideposts, Cure Alzheimer's Fund has sponsored dozens of studies investigating the central mechanisms of action behind the disease.

For decades, it was thought Abeta only is made accidentally in the brain and is just residual "junk" generated by aberrant protein processing of APP. In fact, many in the Alzheimer's field still think this is the case. However, in research sponsored by Cure Alzheimer's Fund, Dr. Robert Moir at Massachusetts General Hospital (MGH) discovered that Abeta performs a vital function: it protects the brain from the impact of invasions by different pathogens, which it kills and sequesters. In other words, Abeta is part of our innate immune system, and is essential for the protection of the brain. However, it also can become the principal driver of Alzheimer's disease if defective genes produce too much of it, or if it is not cleared properly from the brain.

A new "alternative amyloid hypothesis" from the lab of Dr. Charles Glabe at the University of California, Irvine may help explain precisely how nerve cells die in Alzheimer's disease and how known genetic mutations initiate a chain reaction in this long process. The new approach is an "inside-out view" of Alzheimer's. The traditional view is that the protein fragment beta-amyloid aggregates into plaques outside neurons and subsequently causes stress and death to those neurons. Glabe's new hypothesis proposes the reverse order: beta-amyloid forms first within the neuron, causing cell death, which subsequently spurs the formation of neuritic plaques. This finding has therapeutic implications, because it suggests that gamma-secretase modulators of the type that are being developed by Research Consortium member Dr. Steven Wagner (see page 12) will be successful, as they will increase the secretion of soluble Abeta species and prevent the intraneuronal accumulation that leads to neuron death.

In other areas, Cure Alzheimer's Fund supported a consortium that allowed researchers to characterize different forms (oligomers) of Abeta. This study led to the discovery of the specific clumps of beta-amyloid that disrupt communication between nerve cells (synapses). These toxic amyloid oligomers now are being targeted with drug discovery with Cure Alzheimer's Fund backing.

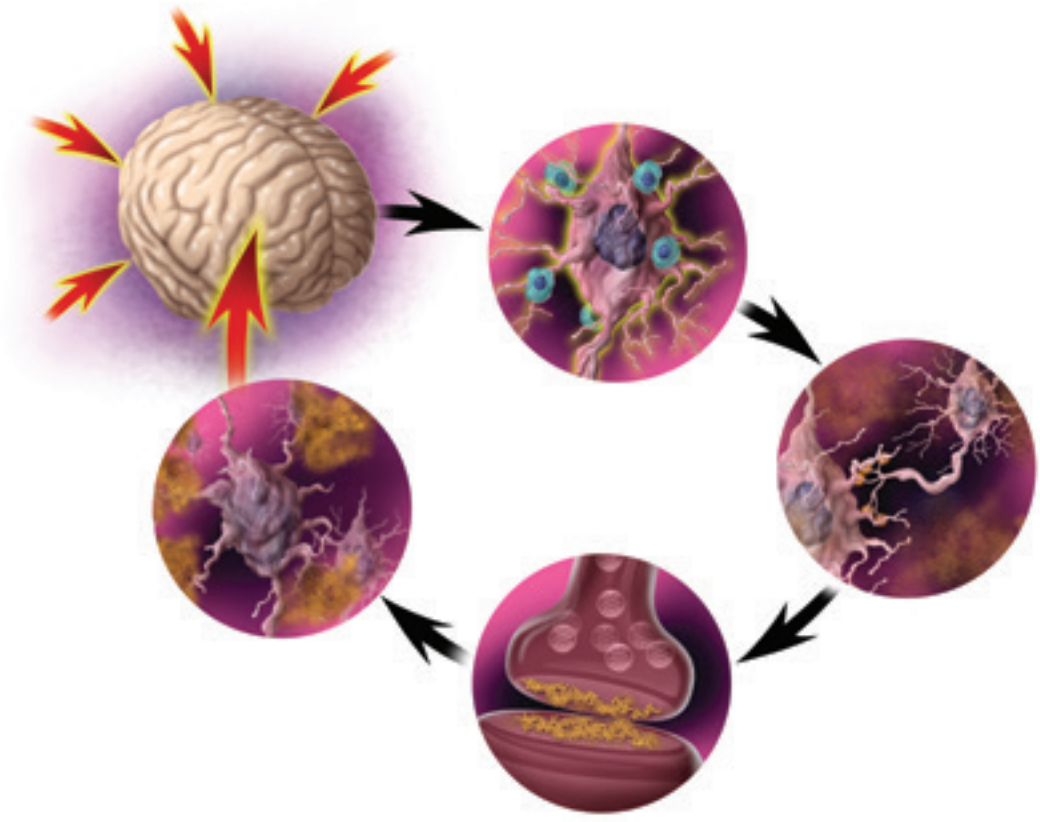


▲ Figure 3. Processing of APP to Produce Abeta, the Principle Component of Beta-amyloid in the Brains of Alzheimer's Patients.

APP (on the left) is shown inserted inside a nerve cell membrane (shown as parallel arrays pink spheres representing lipids). The green portion of APP is outside of the nerve and the red portion is inside. Abeta is depicted by the yellow portion in the membrane (between the outer green and inner red portions). APP in the cell normally is cleaved into two pieces by an enzyme called alpha-secretase (not shown). A smaller fraction of APP can be cleaved by beta-secretase (blue molecule in nerve cell membrane to the right of APP). This generates the raw material for Abeta production. Next, the APP stub left behind in the membrane is cleaved by gamma-secretase (purple blob in membrane). Gamma-secretase uses the "presenilins" to carry out the cleavage of APP. Presenilin 1 and 2 are produced by the early-onset familial AD genes, PSEN1 and PSEN2. If excess Abeta is produced, it can accumulate into clumps called oligomers that interfere with nerve cell function, impair synaptic communication between synapses, induce nerve cell death and create beta-amyloid deposits, such as senile plaques and brain blood vessel amyloid.

Finally, Dr. Doo Kim at MGH recently was able to recapitulate the amyloid plaque and neurofibrillary tangle pathology of AD in a Petri dish for the first time, using induced pluripotent stem cells (iPS cells). These "Alzheimer's in a dish" models can be created quickly for a variety of tests—much cheaper and faster than using transgenic mice for testing. Furthermore, the system can be customized to one's own personal genetics, as each new drug is tested to get an idea of whether a specific drug will work in that individual.

Having learned much about the pathway that leads to disease, together with the genes responsible, we now can proceed to look for chemical compounds that correct the defects. In other words, we can try to fix what is broken.



▲ Figure 4. Insults and Injuries to the Brain Trigger the Brain's Immune System and Abeta Accumulation in a Vicious Cycle.

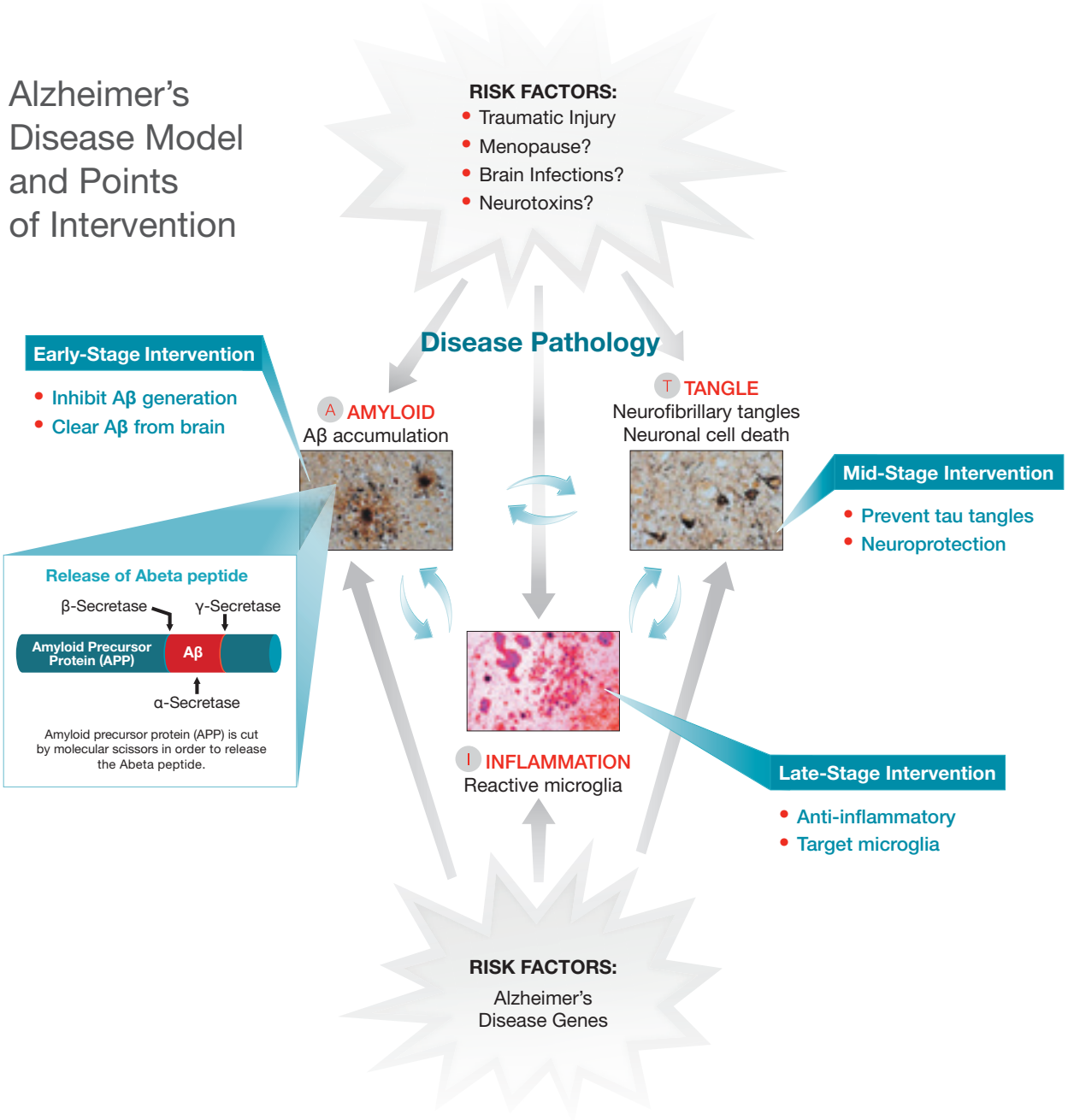
When the brain experiences any form of injury (red arrows), such as exposure to neurotoxins, stroke, transient ischemia, traumatic brain injury or an infection, excess Abeta is produced and accumulates in the brain. This can lead to inflammation and proliferation of glial cells (blue spheres in upper panel). While glial cells can help clear Abeta, inflammation can increase Abeta production and, consequently, the formation of excessive Abeta oligomers (yellow squiggles), which then can impair neurotransmission at synapses (right and bottom panels) where nerve cells communicate as part of the brain's neural network. The oligomers go on to form fibrils and amyloid plaques (left panel). Excess beta-amyloid can act as an insult that once again triggers the brain's immune system, inflammation and, thus, more Abeta production. This leads to a vicious cycle of Abeta accumulation and insult to the brain. Eventually this leads to neurodegeneration and dementia.

III. Next Steps: Therapies in Progress

The model developed by Cure Alzheimer's Fund in recent years allows for three basic strategies for intervention:

1. An early-stage intervention, inhibiting the production of the Abeta protein and/or clearing it from the brain after it forms.
2. An early- to mid-stage intervention that would inhibit the formation of tau tangles and protect neurons from undue stress.
3. A late-stage intervention that would fight inflammation and thus slow down or even stop the disease process. (This intervention also can be used prophylactically.)

Alzheimer's Disease Model and Points of Intervention



Cure Alzheimer's Fund is simultaneously pursuing all three of these strategies. Here is a detailed summary of our current efforts:

Gamma-Secretase Modulators

The most promising class of anti-amyloid agents has been those targeting the production of Abeta in the brain. The two enzymes that cleave APP to produce Abeta are beta-secretase and gamma-secretase. Pharmaceutical companies have been attempting to make drugs that will inhibit these enzymes and, in so doing, reduce Abeta generation in the brain. Early efforts to target gamma-secretase-utilized drugs are known as gamma-secretase inhibitors (GSI). Likewise, beta-secretase inhibitors (BSI) have entered into clinical trials for AD. While the BSIs still are being tested in patient trials, the GSIs that have been tested in clinical trials thus far unfortunately have failed due to safety problems. Safer alternatives to GSIs are gamma-secretase modulators (GSMs), which only block gamma-secretase cleavage of APP as opposed to all enzyme activity. Ibuprofen and other nonsteroidal anti-inflammatory drugs (NSAIDs) were proposed early on to specifically block gamma-secretase cleavage of APP while allowing the enzyme to continue clipping its other target proteins.

Beginning in 1999, Drs. Steve Wagner (University of California, San Diego) and Rudy Tanzi screened for new classes of GSMs. In 2008, they published studies of a powerful new class of GSMs in the journal Neuron. This entirely new class of drugs was able to reach the brain and was safe and very potent in animal studies using transgenic Alzheimer's mice. Since that time, Cure Alzheimer's Fund has supported the development of these drugs. In 2011, the National Institutes of Health (NIH) included these GSMs as one of only seven highly prestigious "blueprint" grants. The hope is to get this promising new class of drugs approved for human clinical trials by 2015.

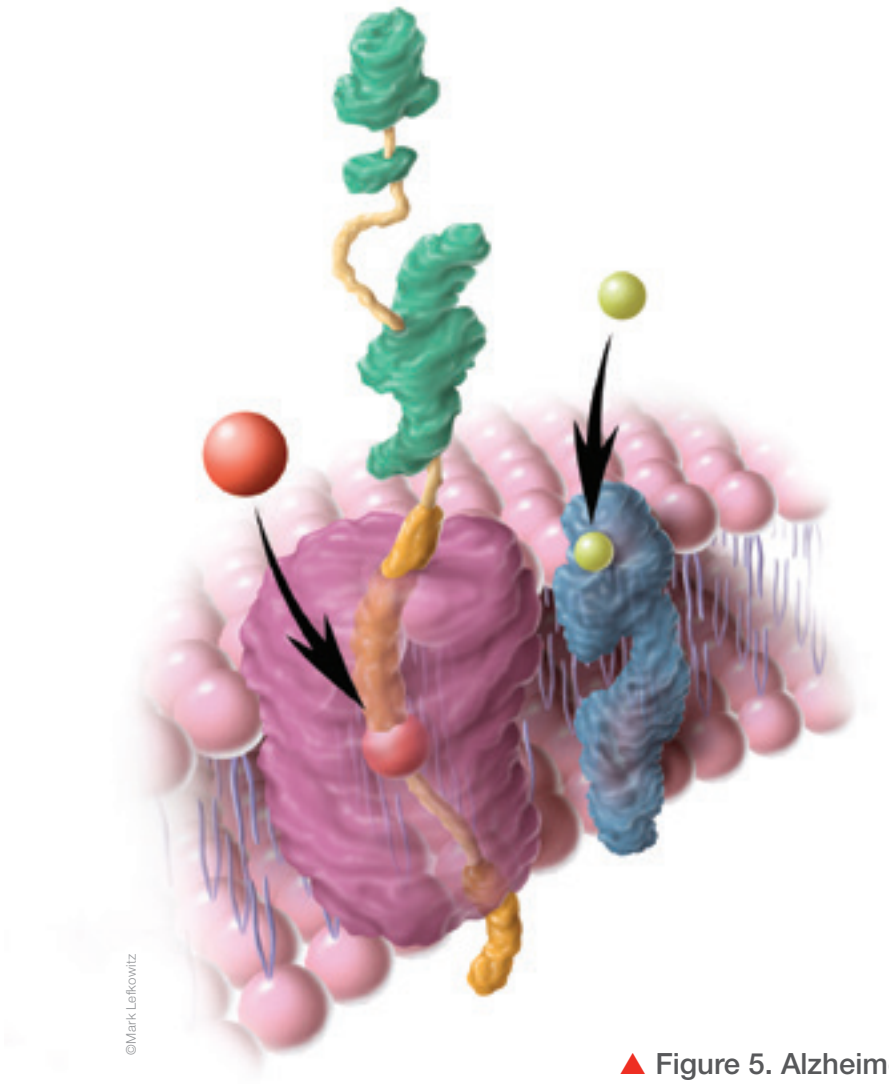
The achievement of NIH support for GSMs is an example of CAF's "leverage" and the potential for public/private partnerships. Our $700,000 in funding yielded $10 million of NIH drug development funding. These multimillion-dollar grants allow the NIH to act in the capacity of a pharmaceutical company to help get promising drugs from the lab bench to human clinical trials.

BACE Inhibitors

The enzyme beta-secretase (BACE1) is an attractive and important drug target for Alzheimer's disease—it is involved in the first steps in the generation of the pathogenic Abeta. Drs. Robert Vassar and Gopal Thinakaran have been funded by Cure Alzheimer's Fund to assess important details of how BACE1 functions in neurons, with the ultimate goal of designing safe and effective therapeutic approaches that target this enzyme and decrease the generation of Abeta.

ACAT Inhibitors

Cure Alzheimer's Fund is supporting the development of cholesterol-targeting drugs known as "ACAT inhibitors" by Dr. Dora Kovacs at MGH. These drugs, which aim to safely lower Abeta generation in the brain, are distinct from cholesterol-lowering drugs like statins (e.g., Lipitor) and reduce the generation of Abeta by regulating how APP is trafficked and processed inside nerve cells. Several novel forms of these drugs are being tested now in animal models of Alzheimer's disease in Dr. Kovacs' laboratory. The goal is to eventually get the best and safest ones into human clinical trials.



▲ Figure 5. Alzheimer's Drugs Aimed at Lowering the Generation of Abeta.

The two enzymes that cleave APP to produce Abeta are beta-secretase (blue) and gamma-secretase (purple). Drug companies have been actively engaged in developing drugs that will inhibit these enzymes as a way to reduce Abeta generation in the brain. The green ball is a drug called a beta-secretase inhibitor. The red ball is either a gamma-secretase inhibitor or gamma-secretase modulator.

CLR01

Dr. Gal Bitan at The David Geffen School of Medicine at UCLA has been focusing on developing CLR01, a "molecular tweezer," as a therapeutic drug for Alzheimer's disease and other amyloidoses (conditions involving the buildup of insoluble amyloid proteins). Initial studies show administration of low doses of CLR01 leads to a significant reduction of Abeta and tau in mouse models. Bitan also has conducted trials on its safety and pharmacokinetics—the study of the effects of the drug on the body. The results are promising, and point toward moving on to the next step of this study, which will be to optimize the administered dose of the drug and examine its effect on prevention of Alzheimer's-associated brain pathology in mouse models.

Real-time Animal Testing

Cure Alzheimer's Fund Research Consortium members Drs. David Holtzman (Washington University, St. Louis) and Roberto Malinow (University of California, San Diego) also are testing currently approved drugs for their potential ability to regulate the production and clearance of Abeta in transgenic mouse models of Alzheimer's disease. Those researchers have developed a unique technology that allows scientists to view the impacts of drugs directly on Abeta in synapses (of transgenic mice) in "real time"—a major advance in Alzheimer's drug testing.

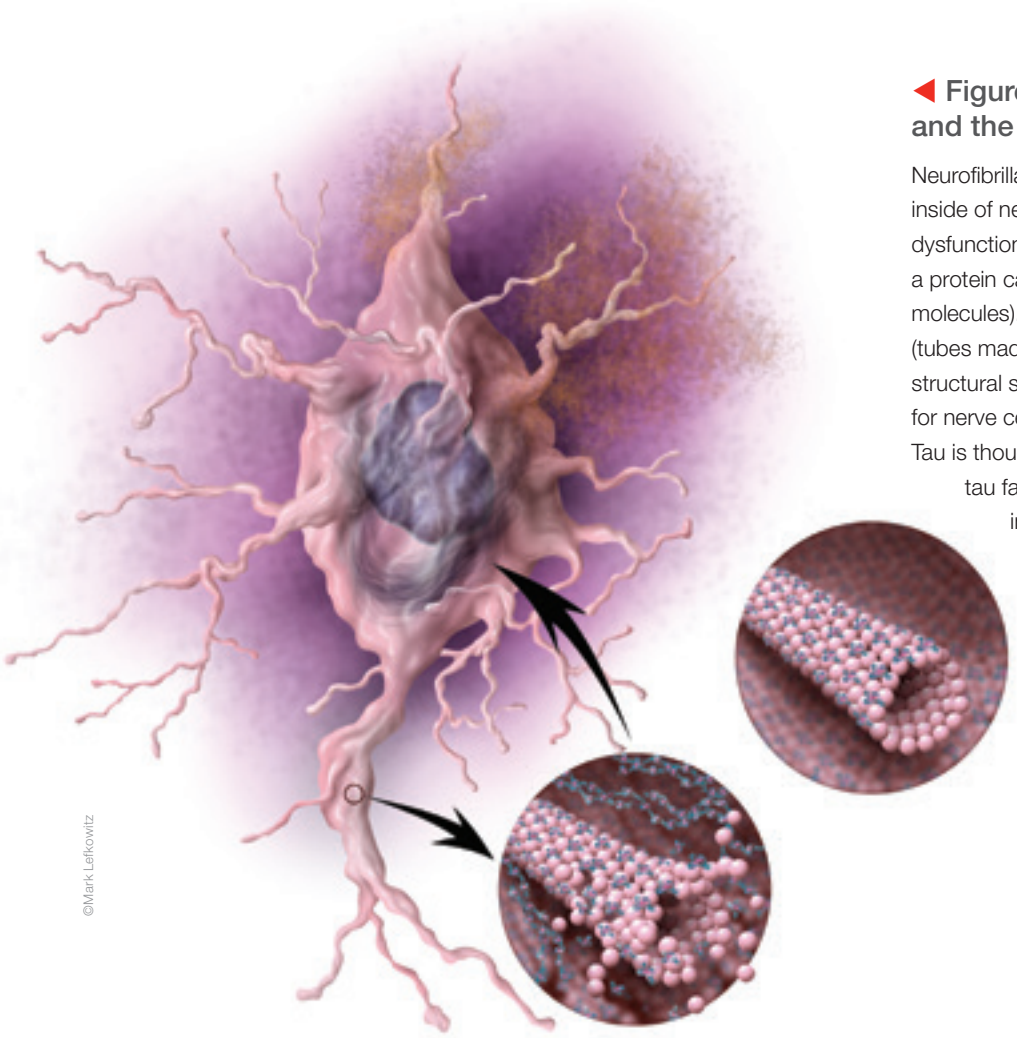
Stem Cell Consortium

Stem cells are the least mature cells in the body and they can be treated with a defined cocktail of factors that can cause maturation of cells into specific and discrete cell types. With a new tool called induced pluripotent stem (iPS) cells, it now is possible to take skin cells from adults and return them to this immature state. By redirecting skin cells from Alzheimer's patients and turning them into nerve cells, we are able to study adult Alzheimer's neurons (nerve cells) in the lab. These Alzheimer's neurons can be studied either in a dish or by transplanting them into the brains of host mice. These models provide an extreamly useful tool, because they allow for the study of cells that are specifically from patients with Alzheimer's disease, as opposed to generic cells used in typical cell culture models.

Under the leadership of Dr. Sam Gandy of the Icahn School of Medicine at Mount Sinai, we have been able to put together one of the most powerful stem cell research projects in the world. The team includes Dr. Scott Noggle (New York Stem Cell Foundation), Dr. Kevin Eggan (Harvard University, Howard Hughes Medical Institute), Dr. Doo Kim (Harvard Medical School, MGH with Dr. Tanzi), Dr. Tamir Ben-Hur (Hebrew University Hadassah Medical School) and Dr. Marc Tessier-Lavigne (The Rockefeller University). The Cure Alzheimer's Fund Stem Cell Consortium focuses on creating stem cells from normal skin tissue obtained from Alzheimer's and control patients, converting those stem cells into specialized brain cells, and then experimenting with those cells to learn more about the disease mechanisms and possible therapies.

A New Blood Test

A promising new blood test, which has the potential to accurately diagnose Alzheimer's disease in individuals and significantly advance drug testing and research on the disease, has been developed through grant funding by Cure Alzheimer's Fund. The test, known as Immunosignature (IS) and developed by a team led by UCLA neurologist Lucas Restrepo, uses a special method of fluorescent tagging of antibodies in the blood to recognize an identifiable binding pattern—or antibody "signature"—associated with Alzheimer's. If these results are confirmed, IS could be used to make diagnosis easier and swifter, and for researchers to test potential therapies much faster and more effectively.



◀ Figure 6. Tangle Formation and the Tau Protein.

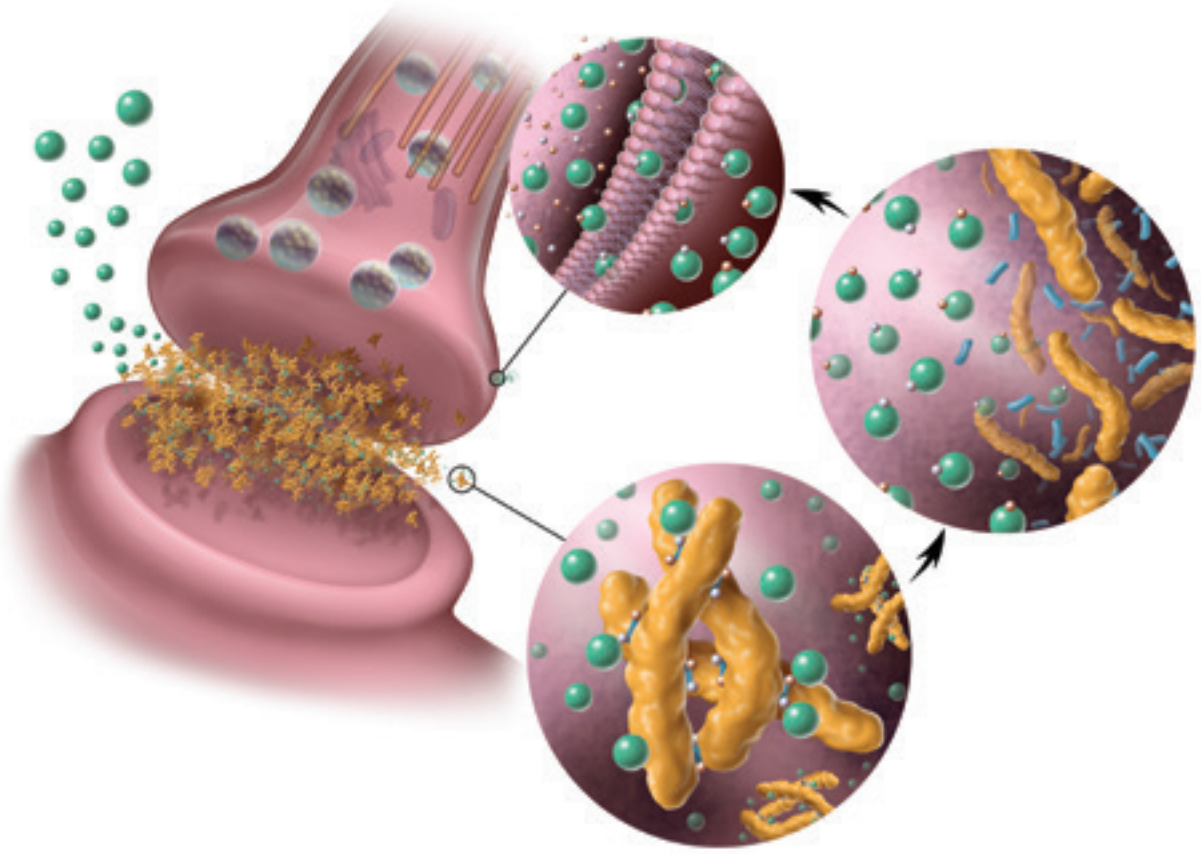
Neurofibrillary tangles (blue blob) choke the inside of nerve cells, eventually leading to their dysfunction and death. Tangles are made up of a protein called "tau." (small blue propeller-like molecules). Tau usually is bound to microtubules (tubes made of pink spheres). Microtubules provide structural support (known as the cytoskeleton) for nerve cells and their axons and dendrites. Tau is thought to stabilize the microtubules. As tau falls off of microtubules and clumps up into tangles (in blue), the microtubules unravel. As a result, the nerve cell loses its structural support and cannot operate properly. Eventually the nerve cell dies. While excessive beta-amyloid triggers Alzheimer's pathology, the formation of tangles is required for neurodegeneration and nerve cell death.

Tau Therapies

Preventing tau tangles from forming is another potential therapy for Alzheimer's. While beta-amyloid initiates the disease process, tangles subsequently must form in nerve cells to cause neurodegeneration and dementia. Thus far, no particularly promising anti-tangle drugs have been reported. However, pharmaceutical and biotech companies are working actively on this approach, including immunotherapy for the tau protein that makes up the tangles. Recently, it has been shown by Cure Alzheimer's Fund Research Consortium member Dr. Virginia Lee of the University of Pennsylvania, and investigators at Washington University, St. Louis, that tangle pathology can spread from one nerve cell to another. Thus, in addition to targeting Abeta, the tau protein most likely will have to be targeted in parallel for a drug cocktail to effectively treat and prevent Alzheimer's disease. One possibility under consideration is immunotherapy against tangles and the tau protein, similar to what is being tested for beta-amyloid. This is currently being pursued by Cure Alzheimer's Fund Research Consortium member Dr. David Holtzman at Washington University.

Metal Chaperones

Another therapeutic strategy for clearing Abeta out of the brain takes advantage of Dr. Tanzi's finding in the early '90s that copper and zinc are required to drive the aggregation of Abeta into oligomers and beta-amyloid deposits in the brain. This approach employs "metal chaperone" drugs that block the interaction of Abeta with copper and zinc and, in doing so, prevent Abeta aggregation. If Abeta does not aggregate, it is relatively easy for the brain to clear single Abeta proteins. These drugs also can pull these same metals away from beta-amyloid oligomers and deposits. This causes the deposits to dissolve into single Abeta proteins that readily are cleared from the brain. In addition, these drugs are able to take copper and zinc that previously was trapped by beta-amyloid and make these metals available for use once again in the brain. Copper and zinc are necessary for activities of many proteins involved in regulating gene activity and antioxidants that protect the brain. One leading candidate in this category is PBT2, which is being developed by Prana Biotechnology, a company founded in Tanzi's laboratory at MGH in 1997 (prior to the creation of Cure Alzheimer's Fund), and that currently is based in Melbourne, Australia.



▲ **Figure 7. Metal Chaperone Therapy for Treating Alzheimer's Disease.**

This therapeutic strategy for clearing Abeta out of the brain takes advantage of Dr. Tanzi's findings in the early '90s that copper and zinc are required to drive the aggregation of Abeta into oligomers and beta-amyloid deposits in the brain. This approach employs "metal chaperone" drugs (green spheres) that block the interaction of Abeta (yellow squiggles) with metals such as copper and zinc (blue rods and tiny golden spheres in right and bottom panels). This serves to prevent the aggregation of Abeta into oligomers and plaque. If Abeta does not aggregate, it rapidly is cleared out of the brain. These drugs also can pull these same metals away from beta-amyloid oligomers and deposits. This causes them to dissolve into single Abeta proteins that are cleared readily from the brain. In addition, these drugs are able to take copper and zinc that previously was trapped by beta-amyloid and make these metals available for use once again in cells in the brain (upper panel). Copper and zinc are necessary for activities of many proteins involved in regulating gene activity and antioxidants that protect the brain.

A Hopeful Summary

Our firm conviction is that in the coming years, we will witness the dovetailing of genetic, biomarker, imaging and drug development efforts that will bring us the therapeutics we all deserve. Our goal is not only to devise therapies that can benefit patients now, but also to prevent future cases of Alzheimer's disease via a program of early prediction, early detection and early prevention. On this, our 10th anniversary, we're proud that our multifaceted research efforts have brought us significantly closer to that day.

Endnotes

1 Goldgaber D., *et al*.: "Characterization and chromosomal localization of a cDNA encoding brain amyloid of Alzheimer's disease." Science 1987, 235(4791):877–80.

2 Kang J. *et al.*, "The precursor of Alzheimer's disease amyloid A4 protein resembles a cell-surface receptor." Nature 1987 325(6106):733–6.

3 Tanzi R.E., *et al.*, "Amyloid beta protein gene: cDNA, mRNA distribution, and genetic linkage near the Alzheimer locus." Science 1987, 235(4791):880–4.

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Thank you to our founders and board, researchers, advisory board, staff and funders for 10 years of leading research.

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Research Consortium

The volunteer members of the Research Consortium develop and update a "roadmap for research" for the most effective and efficient route to slowing, stopping and/or reversing Alzheimer's disease. Members contribute their own research projects consistent with that roadmap, as well as recruit others whose work will hasten development of effective therapies for and prevention of Alzheimer's disease.

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Scientific Advisory Board

Members of the Scientific Advisory Board (SAB) are invited independently of the Research Consortium to provide advice and counsel to Cure Alzheimer's Fund regarding the overall scientific soundness of the roadmap and to review individual grant proposals for consistency with the roadmap and with the objectives of Cure Alzheimer's Fund.

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