Cure Alzheimer's FUND
targeting breakthrough research

Drug Development Strategy: Three Points of Attack

"We have developed a number of compounds and are currently testing them with the hopes of narrowing the list down to one or two clinical candidates," says Dr. Wagner.

In view of an emerging consensus on how Alzheimer's disease develops and progresses, the Cure Alzheimer's Fund Research Consortium aggressively is focusing on three opportunities for possible intervention—at the early stage of the disease, the middle stage and the late stage. This comprehensive strategy addresses the whole picture of how Alzheimer's disease develops and progresses, and attacks all three points simultaneously.

What we know

For too long, Alzheimer's research has been distracted by arguments over "plaques" vs. "tangles." Some thought the key to treatment was clearing plaques, while others argued that eliminating tangles would cure the disease. Most researchers now agree it is necessary to attack both plaques and tangles, as well as other elements of the pathology, to stop the disease's progression.

The Research Consortium now shares the understanding that Alzheimer's is a vicious cycle of destruction that begins with the production of excessive beta-amyloid peptides (Abeta) that aggregate into clusters called "oligomers," then proceeds to the creation of tangles from the protein tau that originate inside cells but that recently have been shown to spread to other cells. Both of these create inflammation in the brain, which stimulates more creation of Abeta, thus continuing a cycle that is deadly for brain cells. This destructive cycle can be envisioned as follows:

Intervention point A

Early stage

Ideally, this cycle would be stopped at what is thought to be its origin: the overproduction of the protein Abeta. This approach has been pursued broadly for a number of years, so far to little avail. Some drug candidates have proven too toxic; others were ineffective at safe doses. Recent research led by Robert Moir, Ph.D., of Massachusetts General Hospital (MGH) and funded by Cure Alzheimer's

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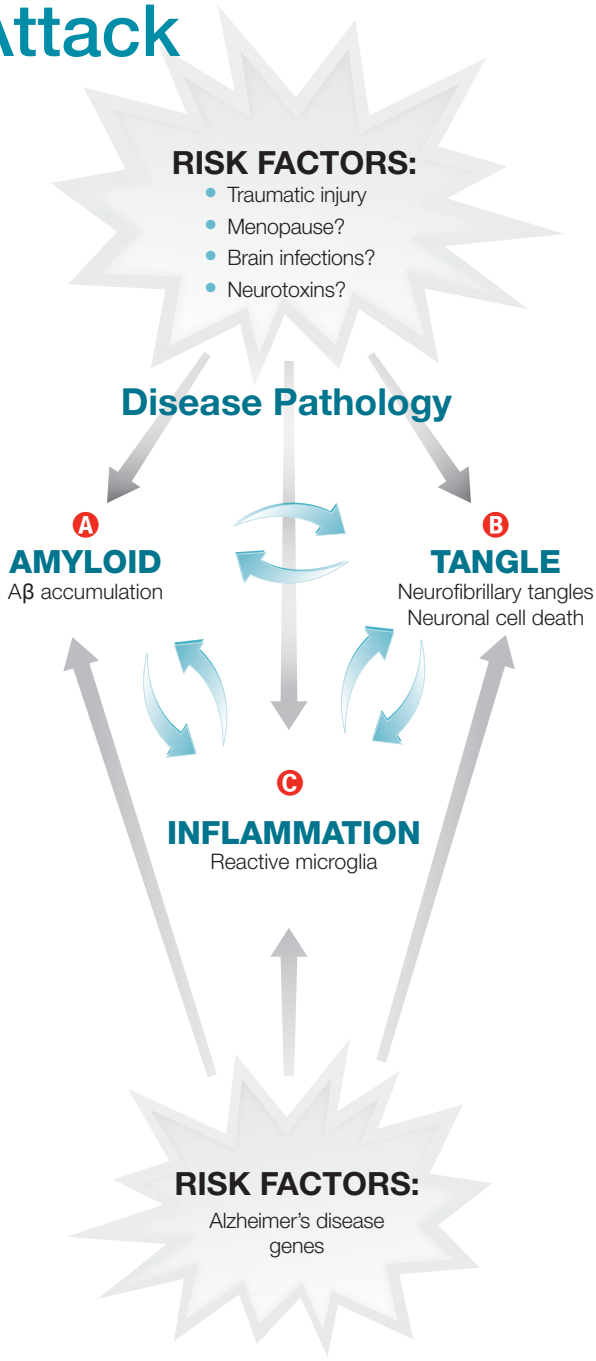


For full diagram, visit curealz.org/how-to-intervene

FEATURED RESEARCHER

Thomas C. Südhof, M.D.

Avram Goldstein Professor in the School of Medicine and Professor of Molecular & Cellular Physiology, Psychiatry & Behavioral Science, and Neurology & Neurological Sciences, Stanford University; Nobel Prize Winner in Physiology or Medicine, October 2013

When Dr. Thomas Südhof first learned he had won the Nobel Prize last October, he could not have been more surprised. "Are you serious?" were the first words out of his mouth.

When someone is awarded the Nobel Prize, he or she is called first at home with the news, and then again soon afterward. The second call is recorded so winners have time to prepare what they want to say. But Dr. Südhof never received the first call. So when he first heard the good news, he was caught completely off guard. "I was driving in the middle of Spain on my way to a conference and I was a little lost," he admits. "At first I was a little skeptical when I got the call," Südhof says, but he quickly realized the truth. "I was utterly surprised and, needless to say, delighted." Later he said, "Every scientist dreams of this. It's quite amazing." Dr. Südhof was awarded the prize for his work in synaptic transmission together with Randy Schekman, Ph.D., of the University of California, Berkeley, and James E. Rothman, Ph.D., of Yale University.

Early days

Südhof was born in Göttingen, Germany, in 1955. He was the second of four children, with an older sister and two younger brothers. As a child he had many different interests, including music. "My bassoon teacher, Herbert Tauscher, taught me that the only way to do something right is to practice and listen for hours and hours. I believe that my training in classical music imbued me with a sense of focus and hard work that is a prerequisite for creativity," says Dr. Südhof.

He graduated from the Hannover Waldorf School in 1975 and went on to medical school at the RWTH Aachen University, Harvard University and then the University of Göttingen. "I became interested in science as a serious endeavor when I was in medical school," explains Südhof. "I discovered how helpless we are as physicians in treating people because we don't actually understand how diseases arise. The brain is a very important organ and we really know very little about how it works. Brain diseases may not always be life threatening, but the most prevalent—schizophrenia, Parkinson's and Alzheimer's—impose an enormous burden on the population."

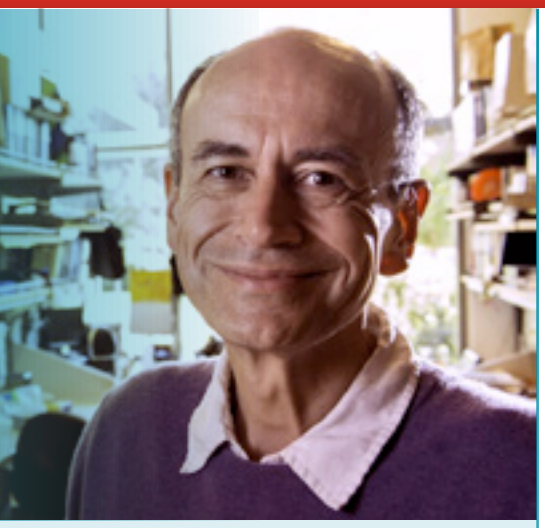
Südhof obtained a medical degree in 1982. He became familiar with neuroscience when he performed research for his doctoral degree at the Max Planck Institute for Biophysical Chemistry. His thesis dealt with the release of hormones from adrenal cells, a model of neurotransmitter release. To deepen his knowledge of biochemistry and molecular biology, Dr. Südhof moved to the United States in 1983, where he began postdoctoral training in the department of molecular genetics at the University of Texas. There, Dr. Südhof worked under Michael Brown, M.D., and Joseph Goldstein, M.D., to describe the role of the LDL receptor in cholesterol metabolism, for which Brown and Goldstein were awarded the Nobel Prize in Physiology or Medicine in 1985. Dr. Südhof completed his training in 1986 and became an investigator at the Howard Hughes Medical Institute. He then started his own laboratory at the University of Texas Southwestern Medical Center, where he focused on the presynaptic neuron for 25 years.

Dr. Südhof's work is unique because, prior to his discoveries, the majority of neuroscience research had focused on the *post*synaptic neuron and its role in learning and memory. But Dr. Südhof revealed the role of *pre*synaptic neurons in neuropsychiatric illnesses and helped to advance knowledge of mechanisms behind such poorly understood diseases and conditions as Alzheimer's, schizophrenia and autism.

In 2008, Dr. Südhof moved to Stanford University, where he serves as the Avram Goldstein Professor in the School of Medicine as well as a professor of molecular and cellular physiology, psychiatry and behavioral sciences, and neurology and neurological sciences. As a neuroscientist, he continues to "work on how the brain works," he says. "It's quite an amazing organ with billions of billions of nerve cells that constantly talk to each other. We have been trying to shed light on how the cells send information to each other at the synapse, which is like a little nano computer." And his contributions have been significant.

Cure Alzheimer's Fund

Dr. Südhof joined the Cure Alzheimer's Fund (CAF) Research Consortium in July 2010 and was named to CAF's Scientific Advisory Board (SAB) in 2013. The role of the SAB is to ensure the scientific integrity of proposals submitted for funding and advise the board of directors about the broad directions of research that will lead most effectively to controlling and ending the disease. While Dr. Südhof doesn't focus on Alzheimer's disease specifically, nor has he received



funding from CAF to date, his work on the brain is highly relevant.

"My personal view," explains Südhof, "is although it's absolutely crucial to get to a cure, and I fully support that goal, we need a better understanding of the pathogenesis of Alzheimer's disease. We live in a time when science is in peril. More and more funds are devoted toward large projects that in the end are not that productive. There needs to be balance with smaller projects that support individual laboratories, like mine. My hope is that Cure Alzheimer's Fund will gain a better understanding of how Alzheimer's develops. We have a lot of genes and risk factors, but we don't know how they conspire to cause the disease."

Personal life

Dr. Südhof is married and has two small children, ages 4 and 3. He enjoys spending time with his family when he's not working. "My wife is a full-time professor, so we try to share as much of the work as we can. She is a neuroscientist, like me, and she works on different aspects of synaptic transmission." They met at a conference, but they've never actually worked together. "Before we had children we used to go to movies, museums, concerts and travel, but now more than 80 percent of my free time is spent taking care of my family," explains Dr. Südhof. Despite how busy he is, Dr. Südhof is well-known for his productivity. He says, "I cannot tell you how much I enjoy what I do. I will always consider it an enormous privilege to be a scientist." ■

DRUG STRATEGY
Three Points of Attack

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Fund has shown the Abeta protein is an important and integral part of the innate immune system, and therefore maintaining an appropriate balance of the protein rather than eliminating it may be the right therapeutic approach.

Consortium researchers are pursuing a number of ways to control Abeta production and clearance. Perhaps the most promising research is taking place in the University of California, San Diego lab of Steven Wagner, Ph.D., and the MGH lab of Rudy Tanzi, Ph.D. Their approach has been to develop drugs to modulate an enzyme called gamma secretase, which is a critical contributor to Abeta production. Their effort has been so successful that the compounds they have developed have been adopted by the National Institutes of Health (NIH) as part of its fast-track, high-priority "Blueprint" program.

"We're making excellent progress," reports Wagner. "We have developed a number of compounds and are currently testing them with the hopes of narrowing the list down to one or two clinical candidates." Tanzi echoes this optimism, saying, "We are hopeful that this project will lead to our gamma secretase modulators in clinical trials over the next year or so."

Intervention point B

Middle stage

In concert with efforts to contain Abeta in the earliest possible stage, consortium members also are pursuing strategies that would zero in on the formation and spread of tau tangles. Foremost among these is the effort led by consortium member David Michael Holtzman, M.D., based at Washington University in St. Louis, who recently demonstrated breathtakingly positive results in a proof-of-concept study aimed at stopping the aggregation and spread of tau in the middle stages of the disease.

Holtzman's study, in collaboration with Washington University's Marc Diamond, M.D., assembled a variety of potential tau antibodies and introduced them into the brains of genetically engineered mice. Based on a hypothesis that the toxic form of tau gets "spit out" of nerve cells and subsequently "infects" other nearby healthy neurons, the study demonstrated that the antibodies were able to conclusively stop this spreading process; this subsequently led to cognitive improvements in the mice. Their study was published in the journal *Neuron* in September 2013. The results were "fantastic," commented the German Center on Degenerative Diseases' Eckhard Mandelkow, Ph.D., to the Alzheimer's Research Forum last September. "It explains why antibody therapy might work for tau pathology."

Intervention point C

Late stage

Consortium members also are pursuing efforts to curtail Alzheimer's-related brain inflammation. One of the most promising efforts involves an attempt to inhibit the activity of a gene called CD33. In 2008, Tanzi's group first discovered this gene's relationship to late-onset Alzheimer's in a large family-based, genome-wide association study (GWAS). In 2013, the group described in the journal *Neuron* the gene's regulation of immune-response microglial (helper) cells in the aging brain. Microglia normally clear away damaged and unwanted cells in the brain; if they are not functioning properly, damaging inflammation can occur. When Tanzi's group deactivated CD33 in AD mouse models, more Abeta was cleared away by the microglial cells, leading to diminished amyloid plaque burden and less inflammation.

The Tanzi lab is attempting to develop effective CD33 inhibitors by screening compounds and antibodies that inhibit CD33 function. The compounds showing the most promise will be tested in AD mouse models. "There's still some work to do here," says Tanzi, "but interrupting CD33 could turn out to be a powerful therapeutic strategy."

Following the science

"We follow the science, wherever it leads," says Cure Alzheimer's Fund Chairman Jeffrey Morby. "Alzheimer's is a complex disease and we're proud to support our Research Consortium in this multipronged effort to defeat it at each stage." ■

Want to learn more? David Holtzman, Rudy Tanzi and Steve Wagner will further discuss their research findings in an Alzstream video, moderated by David Shenk, available starting on March 20. The video will be posted at www.curealz.org and sent out via e-blast to everyone on our mailing list. If you would like to be added, please let us know at ***info@curealz.org****.*

Financial Update

	This Quarter	YTD*	Inception to Date
Fundraising	$3,695,690	$7,334,502	$37,481,611
Expenses paid for by the founders	$464,177	$1,564,322	$7,781,727
Funded research	$1,450,000	$4,576,000	$22,762,484

**Numbers shown are preliminary for the period.*

Research Update

Research funded during the fourth quarter of 2013

Project	Researcher	Distribution Amount
Characterization of the Pathological Significance of a Novel Type of Vascular Amyloid	Charles Glabe, Ph.D. University of California, Irvine	$100,000
Sleep and Tauopathies: Effect of an Anti-Tau Antibody	David Michael Holtzman, M.D. Washington University, St. Louis	$100,000
Whole Genome Sequencing	Rudy Tanzi, Ph.D. Mass General/Harvard University	$750,000
The Root of Alzheimer's Disease: Purification and Characterization of Amyloid-beta Oligomers from the Human Brain	David Brody, M.D., Ph.D. Washington University, St. Louis	$100,000
Vascular Regeneration Therapies for Alzheimer's Disease	Guojon Bu, Ph.D. Mayo Clinic, Jacksonville, Fla.	$100,000
The Roles of Eps Homology Domain (EHD) Proteins and Synaptic Activity in Axon Transport of the Alzheimer's Beta-Secretase BACE1 in the Brain, Year 2	Robert Vassar, Ph.D. Northwestern University	$100,000
Discovery of Alzheimer's Disease Blood Biomarkers Using Phage Display Technology	Yueming Li, Ph.D. Memorial Sloan-Kettering Cancer Center	$100,000
BACE1 Transcytosis in Alzheimer's Disease Pathogenesis, Year 2	Gopal Thinakaran, Ph.D. University of Chicago	$100,000
Total Distributed to Research for 4Q 2013		**$1,450,000**

Help us fund research with the highest probability of slowing, stopping or reversing Alzheimer's disease. Donations can be made through our website, www.curealz.org/donate, or sent directly to our office.

For gifts of securities or direct wire transfers, please contact Tim Armour at 877-CURE-ALZ (287-3259) for further information.

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Mission

Fund research with the highest probability of preventing, slowing or reversing Alzheimer's disease.

Research Consortium

Develops and updates a "roadmap for research" for the most effective and efficient route to slowing, stopping and/or reversing Alzheimer's disease. Members research their own projects and recruit others whose work will hasten development of effective therapies for and prevention of Alzheimer's disease.

Rudolph E. Tanzi, *Ph.D., Chairman, Research Consortium; Harvard Medical School/Massachusetts General Hospital*
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Charles Glabe*, Ph.D., University of California, Irvine*
David Michael Holtzman*, M.D., Washington University, St. Louis*
Richard L. Huganir*, Ph.D., The Johns Hopkins University*
Virginia M.-Y. Lee*, Ph.D., M.B.A., University of Pennsylvania*
Roberto Malinow*, M.D., Ph.D., University of California, San Diego*
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Steven L. Wagner*, Ph.D., University of California, San Diego*
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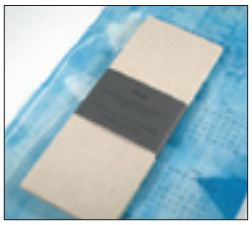
Thanks to all of you who have devoted your time, energy and money to end Alzheimer's disease. Together you raised more than $280,000 in 2013! *To find out more about the events below, visit curealz.org/events/archive.*

Making Every Day Count



Last year bookbinder and letterpress printer Maggie Campbell used her talents to create limited-edition handmade calendars to support Cure Alzheimer's Fund in honor of her mother-in-law, who was diagnosed with early-onset Alzheimer's at age 59. This year, Maggie has created another stunning collection, using dried Queen Anne's Lace from her home in Brooklyn, N.Y. Ten dollars from the sale of each calendar will be donated to Cure Alzheimer's Fund. To purchase one, visit: **www.campbellrawpress.com/collections/2013-holidays/products/cyanotype-2013-calendar**.

Bravelets

Stephanie and her mom

When bad news hits a family, everyone bonds together to be brave for each other. That's what happened in June 2011 when Stephanie Hansen of Austin, Texas, found out her mother had breast cancer. "I wanted to make something that my mom, dad, sister and I could all wear in the weeks leading up to my mom's mastectomy—a symbol that would help us all remember to be brave"—so Stephanie came up with the idea of Bravelets™. "They're more than just something to wear on your wrist, they're a symbol of hope, strength and courage," she says. Last fall the company created nine different styles of Bravelets to support Cure Alzheimer's Fund (CAF). The organization already has donated more than $2,500 to CAF. To purchase a Bravelet, please visit **www.bravelets.com/product/alzheimers-bracelet**.

Heroic Halloween Party

For the last 11 years Stephanie Moody, 46, has had a Halloween party at her barn in Boxford, Mass., with costumes, a band and all the usual festivities. But this year, after spending time with family friends Joanne and Brian O'Keefe and realizing they all shared a passion for fighting Alzheimer's disease, she changed her plans. "This year we decided that we should use the party as a way to give back," says Stephanie. Together they raised $4,500 for Cure Alzheimer's Fund in a Halloween bash certain to be remembered.

Motivating Words

Kelly Hulfachor

"*Imagine waking up in the morning and not knowing where you were or who the people around you are*," writes 16-year-old Kelly Hulfachor, a sophomore at South Elgin (Ill.) High School. Last fall, the students in Kelly's health class were asked to research a charity they believe "helps the greater good" and write a persuasive essay about it. Since Kelly's grandmother suffers from Alzheimer's disease, Kelly looked at several Alzheimer's organizations before choosing to write about Cure Alzheimer's Fund. "*Watching my grandma rapidly deteriorate from this disease has been heartbreaking*," Kelly wrote. She described the frightening realities of Alzheimer's disease and how CAF is focused on finding a cure. In the end, Kelly's essay was selected as one of the top three to be read aloud anonymously; the students then voted on which cause they wanted to raise money for. Kelly won and her high school donated more than $400 to Cure Alzheimer's Fund.

Something to Smile About

A decade ago, Drs. Brent and Christie McDonald, now in their mid-30s, started a family dental practice in McCordsville, Ind. They had met at Indiana University in 1997 and share a passion for dentistry—and unfortunately, also a family history of Alzheimer's disease. The McDonalds knew they wanted to do something to help fight the disease, but they weren't exactly sure what. When "Family Feud" came to Indianapolis seeking contestants, Christie had found that something. The McDonalds were invited to audition for the show, and two weeks later went to Atlanta to play the game. "We all agreed that if we were selected, we would donate our winnings to an Alzheimer's disease charity as a tribute to our family members who fought and are fighting the disease," Brent said. On Nov. 26 and 27, 2013, the show aired and the McDonalds won a remarkable $20,520—all of which they generously donated to Cure Alzheimer's Fund.

Pictured left to right: Brent McDonald, Christie McDonald, Steve Harvey, Lorie Brinson (Christie's sister), Tim Goodpaster (father of Christie and Lorie), and Karmen Fink (cousin of Christie and Lorie).

"Your donations this year have made a big difference in our progress toward finding a cure for Alzheimer's disease. Your passion, your energy and your generosity are an inspiration to all of us to work even harder to end this terrible disease. Thank you all for your leadership and support."

—Tim Armour, chairman and CEO, Cure Alzheimer's Fund

Also in 2013...

5th Grade Fundraiser, *Nelson Everts,* Sherborn, Mass. • **7th Annual Hay Harbor Tennis Tournament, *Diane Fiske and Hay Harbor participants,*** Fishers Island, N.Y. • **Dick Hollander Open™, *Josh and Jake Akman,*** Laytonsville, Md. • **DKJ Golf Tournament, *Gregg and Bruce Johnson,*** Reading, Mass. • **10K Swim, *Greg Wellman Jr.,*** Kingsport, Tenn. • **"The Ups and Downs of Living with Alzheimer's," *Charlie Collier,*** Hillsboro, Fla.; Wellesley, Mass.; Boston • **Boynton Beach Golf Tournament, *Ellen Cohen and the Women's Golf League,*** Boynton Beach, Fla. • **Benefit Concert, *Ki Oh and band members,*** Cleveland • **Marathon, *Ann Bulson, Kristen Adrien and Travis Song,*** Boston • **4th Annual Running 4 Answers Fun Run/Walk, *Barbara Geiger and Carolyn Mastrangelo,*** Roseland, N.J. • **Mountain Lake Golf Tournament, *Jonathan Powell and members of Mountain Lake Golf Club,*** Lake Wales, Fla. • **School Fundraiser, *Nate Levine and Kyle Brown,*** Fremont, N.H. • **Half-Marathon, *Kim Chan,*** Newport Beach, Calif. • **Branchburg Race Against Alzheimer's, *Mike Napoli and friends,*** Branchburg, N.J.

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Memories of the World

Last year Alvaro Barbera, 28, quit his job in advertising to pursue an effort closer to his heart. Alvaro's grandfather had spent 14 years fighting Alzheimer's disease, and passed away in 2008 at age 79. "He was an amazing character with a great sense of humor, but his personality soon vanished and his identity was stolen," Alvaro said. In November 2013, Alvaro set out with his backpack and camera on a journey from Canada to Argentina to collect people's best memories in an effort to raise awareness for the disease—one story at a time—in a project he calls *Memories of the World—A Journey of Hope to End Alzheimer's*. "There is a lack of awareness and understanding of the disease, especially among young people." To support his cause, please visit **www.memoriesoftheworld.org/hope/**.

See more Hero stories on page 5 »

"Spending time with my family for Thanksgiving is always a very happy memory."
—New York City

"My uncle died this year. I used to visit him with my dogs. He was in a home and he had Alzheimer's. I used to bring my dogs and he used to call them his grandchildren. The dogs knew exactly where his room was."
—Montreal

"I just came from seeing my stepmother who has Alzheimer's. She grabbed me from the cheeks, looked me in the eyes and she saw me."
—Toronto