



Alzheimer's: Focusing on the Big Picture

Modern science is, by necessity, built on specialization. A century ago, one man—Dr. Alois Alzheimer—knew everything there was to know about Alzheimer's disease. Today, thousands of Alzheimer's researchers specialize in neuroimaging, signaling, inflammation, stem cells, genetics and so on. It takes a village to cure this disease.

Dr. David M. Holtzman, Andrew B. and Gretchen P. Jones professor and chairman of neurology at Washington University in St. Louis, is one of the rare researchers who stands above this hyper-specialization. For more than 20 years, Holtzman has been a leader in Alzheimer's research in large part because of his breadth. While diving deeply into topics such as the neurobiology of the apoE protein and the molecular structure and metabolism of Abeta, he has labored to constantly stay connected to the many different pieces of the puzzle.

Holtzman, who is also the Paul Hagemann professor of neurology and developmental biology, the associate director of the Alzheimer's Disease Research Center and the scientific director of the Hope Center for Neurological Disorders, was this year awarded Washington University's Carl and Gerty Cori Faculty Achievement Award for "embody[ing] the ideals of individual and collaborative excellence." He is also a practicing neurologist who has found that seeing patients has led to a wider understanding of the disease. "I've always made sure that if I'm going to study something, it should be directly relevant to what's going on in human beings," he says. "That has led directly to some of our unique findings."

With his then post-doctoral fellow at the time, Randy Bateman, for example, Holtzman co-developed a technique to determine in a human being the synthesis

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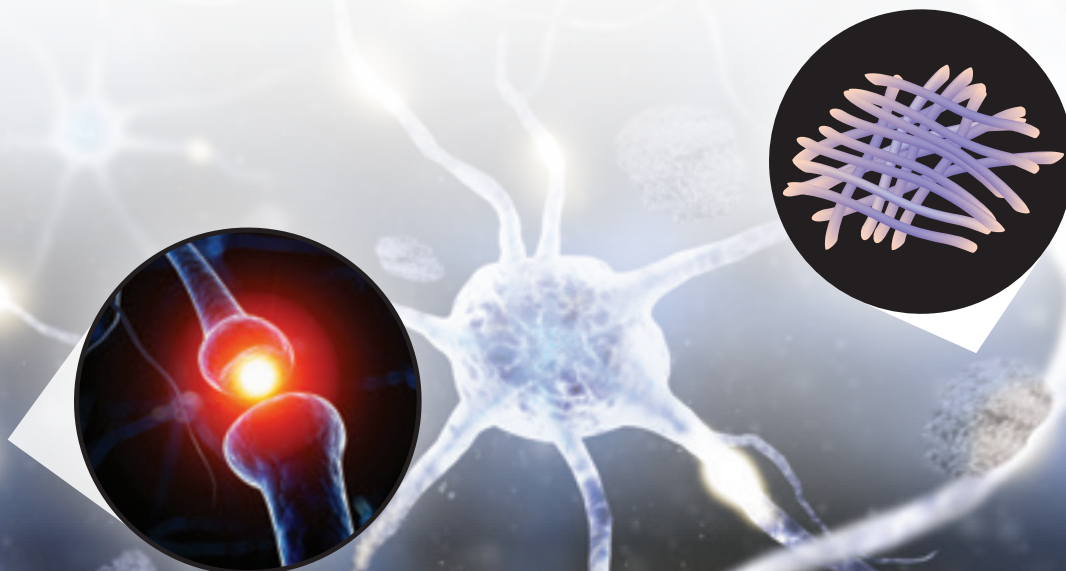
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FEATURED RESEARCHER

David Michael Holtzman, M.D.

***Andrew B. and Gretchen P. Jones Professor
and Chairman, Department of Neurology (primary);***

Professor of Developmental Biology;

***Director, Hope Center for Neurological Disorders and Hope Center
Program on Protein Aggregation and Neurodegeneration;***

***Associate Director, Knight Alzheimer's Disease Research Center,
Washington University School of Medicine, St. Louis***

Born and raised in St. Louis, Cure Alzheimer's Fund Research Consortium member David Holtzman grew up with a burning curiosity. At the age of 7 he watched his best friend's father, a veterinarian, dissect small animals. In grade school he participated in programs at the St. Louis Zoo and Humane Society with his teachers. His passion for biology, anatomy and science, and his academic achievements, led him into the field of medicine, with a focus on neurology, where he has done groundbreaking work. Little did he know when he entered the field that his own family would suffer from the very disease he was dedicating himself to studying.

The oldest of three children, David Michael Holtzman was born to a nurse and an architectural engineer. Growing up, sports were always a big part of his life, especially basketball, which came to him naturally and which he played all through college and into his late 40s. He is now an avid tennis player. But baseball is the family passion. Holtzman watched his first cousin, Ken Holtzman, pitch for 15 years in the major leagues as an all-star for the Chicago Cubs, Oakland A's, Baltimore Orioles and New York Yankees.

Education

David Holtzman's parents also stressed the importance of education. "In the early 1950s, when my father was doing his Ph.D. at Washington University in St. Louis, he began teaching twice a week at the night school there, which he continued for over 50 years. I was always motivated scholastically, especially in math and science, and I knew I wanted to be a physician early on," he says. So after high school he attended a six-year medical program at Northwestern University, graduating in 1985 with an M.D. and a membership in Phi Beta Kappa. He was 23.

Research

Dr. Holtzman wanted to combine his interest in science with his medical training, so he decided to do his postgraduate work at the University of California, San Francisco (UCSF). "They had a great clinical and research program and I had the opportunity to work with people who were doing cutting-edge research in neurology. I had never lived anywhere outside of the Midwest and I was single," so he began his career there.

After a year as a medical intern, Dr. Holtzman did his residency in neurology at UCSF. "The logic of the anatomy of the nervous system was really compelling—it's the one field where there's still not a lot of understanding and not great treatments, yet has some of the most important diseases in human beings, including Alzheimer's," Holtzman says. After his residency he became a faculty member in neurology while he continued to treat patients and work as a postdoctoral researcher in the lab of William Mobley, M.D., Ph.D., at UCSF (Mobley is now a member of Cure Alzheimer's Fund Scientific Advisory Board). During that time, his research

focused on understanding neurotrophic factor signaling in the brain as well as trying to develop animal models of Alzheimer's disease using mouse models of Down syndrome. There, he was honored with a physician-scientist award by the National Institute on Aging (NIA).

In 1994, after almost a decade on the West Coast, Holtzman decided to return "home" to continue his research on Alzheimer's disease and teach at Washington University. "The opportunity was appealing because of Wash U's Alzheimer's disease research center, its Department of Neurology and its superb neuroscience community," he says. After moving to Washington University, his research began to focus on the neurobiology of APOE, an important genetic risk factor for Alzheimer's disease. At the same time, some of his family members began to develop the disease he was studying. "My great aunt had died of Alzheimer's and lived almost 20 years with it. My father's brother and sister, and finally my father, all became symptomatic—my dad at age 71. He died 10 years later."

Cure Alzheimer's Fund

In 2006, Dr. Holtzman's work on Alzheimer's disease had become so well known in the field that Dr. Rudy Tanzi, chairman of the Cure Alzheimer's Fund Research Consortium, approached him about joining the consortium. "Cure Alzheimer's Fund has some of the best researchers in the field," says Holtzman. "It's interesting to talk to other scientific leaders about what needs to be done. I often have ideas I want to test

immediately, and with funding from Cure Alzheimer's Fund I can get pilot data that can turn into a much bigger project. Having quick access to pursue an idea can make all the difference in the work."

After Dr. Holtzman's training in neurology, he started a memory clinic for patients with Alzheimer's disease. Even now, as chair of the Neurology Department at Washington University, he still sees patients once a month, focuses two weeks a year in the hospital seeing neurology patients, and does a morning report—where new admissions to the hospital are presented by the resident physicians to the professors to discuss diagnosis and therapy, once a week. "Experience with patients and with students and residents is both rewarding to me and is very helpful in deciding what questions are important to address in research," he adds.

Personal Life

Dr. Holtzman remains a fan of sports, especially baseball. When he's not working, he can be found playing tennis, hiking with his wife Tracy and rooting for his beloved St. Louis Cardinals. ■

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The Sleep- Alzheimer's Disease Connection

Wed., Dec. 16, 2015
Noon EST

Hear about the revolutionary work being done by Dr. Holtzman of Washington University on the connection between sleep and Alzheimer's disease, and sleep's possible role in managing the brain's Abeta and tau burdens.

No registration is required—
visit curealz.org/webinar on
Dec. 16 to join.

Alzheimer's: Focusing on the Big Picture

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and clearance rates of proteins in the brain. Holtzman also was involved in creating a biobank of CSF and plasma that he and such colleagues as Anne Fagan and John Morris utilized to carry out a series of fluid biomarker studies to demonstrate that measurements of certain proteins could be utilized to diagnose preclinical Alzheimer's disease as well as to predict who will convert from cognitively normal to impaired.

"Initially, this biobank was for my own research on apoE," he says, "but it burgeoned into a huge biomarker program." Holtzman joined Cure Alzheimer's Fund's Research Consortium in 2008 at the invitation of Consortium Chair Rudy Tanzi. His first CAF-funded study explored the relationship between synaptic activity and Abeta "plaques." Subsequently, Holtzman developed a new method to measure tau levels in the extracellular space of the brain in order to understand more about the connection between amyloid plaques and the tau "tangles" in Alzheimer's. Holtzman also has explored the role of certain vascular factors present in the disease such as "amyloid angiopathy," in which amyloid deposits form in the walls of blood vessels in the brain; and contributed greatly to our understanding of how anti-amyloid antibodies affect Alzheimer's pathology and how Abeta potentially can be cleared from the brain of Alzheimer's patients.

Holtzman also has played a vital role on the policy stage. For the past four years, he has served on the National Advisory Neurological Disorders and Stroke Council at the National Institutes of Health (NIH). "People look to David as a leader," says Tanzi. "He's a careful thinker, and he can bring many different strands together to make an important new observation or ask just the right question."

The levels of Abeta fluctuated during the day and night. During wakefulness, the levels of protein were higher than when sleeping, and if an animal was sleep-deprived, it caused a much earlier onset of Abeta deposition in the brain. This suggests that if you optimize non-REM (deep) sleep, it might delay the onset of Alzheimer's disease.

Some of Holtzman's latest work focuses on how sleep influences Abeta metabolism. "We found that, in the brains of animals and humans, Abeta is regulated by neuronal activity," he says. "The levels of Abeta fluctuated during the day and night. During wakefulness, the levels of protein were higher than when sleeping, and if an animal was sleep-deprived, it caused a much earlier onset of Abeta deposition in the brain. This suggests that if you optimize non-REM (deep) sleep, it might delay the onset of Alzheimer's disease. But once you get the pathology, it further disrupts your sleep."

Holtzman has found Cure Alzheimer's Fund energizing. "Certain institutions have a special collaborative spirit," he says. "But at Cure Alzheimer's Fund, we've gotten to know each other so well that we trust one another and share information all the time across many institutions. That stimulates what each of us is doing."

"The feeling is mutual," says Cure Alzheimer's CEO Tim Armour. "We're very fortunate to have such a deep and invigorating relationship with David." ■

Welcoming Four New Renowned Scientists to Our Team

As our research “bench” continues to grow, we’re thrilled to welcome two new Research Consortium and two new Scientific Advisory Board members to our team. Each member brings unique expertise to accelerate our progress toward a cure.

Bruce Lamb, Ph.D., of the Cleveland Clinic’s Department of Neurosciences, is the newest addition to our Research Consortium. Dr. Lamb has studied Alzheimer’s disease phenotypes with a focus on developing and characterizing genomic-based mouse models of the disease through the introduction of human AD genes into the germline of mice.



Li-Huei Tsai, Ph.D., director of The Picower Institute for Learning and Memory and Picower professor of neuroscience based at MIT, also joins our Research Consortium. Her research focuses on neuropsychiatric disorders, autism and Alzheimer’s disease.



Vince Groppi, Ph.D., the director of the University of Michigan’s Center for the Discovery of New Medicines in Ann Arbor, joins our Scientific Advisory Board as a leader in pharmaceuticals and biotechnology. He has 30 years of technical and leadership experience in translational pharmacology and drug development.



Ron Petersen, M.D., Ph.D., joins our Scientific Advisory Board. He is director of the Mayo Clinic Alzheimer’s Disease Research Center and the Mayo Clinic Study of Aging in Rochester, Minnesota. Dr. Petersen investigates cognition in normal aging, mild cognitive impairment and dementia.



We anticipate great contributions by these remarkable scientists and look forward to sharing them in future publications. The fact that our organization continues to attract such high-caliber researchers is a testament to the breakthroughs we’re making in understanding what causes Alzheimer’s disease and how ultimately to stop it. ■

Research Funding Grows

It has long been acknowledged that Alzheimer’s is a big problem to solve. Our generous donors have enabled us to fund \$5.8 million in research projects so far this year, more than all of last year. As a result, we continue to deliver on our promise to you and to our researchers to support innovation and insight focused on a cure as efficiently and effectively as possible.

Thank you for supporting us on our journey—we couldn’t do this without you.

Help us fund research with the highest probability of preventing, slowing or reversing Alzheimer’s disease. Donations can be made through our website, 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 \(287-3259\)](tel:877-CURE-ALZ) for further information.

Raising Alzheimer's Awareness on Nantucket

In August, *Nantucket Magazine* featured one of Cure Alzheimer's Fund's co-founders, Phyllis Rappaport, and her contributions to the fight against Alzheimer's disease. A dinner was hosted at the Great Harbor Yacht Club by the sponsors of the Geschke Lecture Series, the Nantucket Atheneum. That evening, Dr. Rudy Tanzi, Cure Alzheimer's Fund Research Consortium chairman, was a guest speaker and gave a presentation titled, "Ending Alzheimer's Disease by 2025." More than 220 attended. ■



Co-founder Phyllis Rappaport

Gathering in Hyannis Port: A Decade Later

Sometimes history repeats itself. Ten years ago a group of avid supporters met at the home of Richard and Judy Brand in Hyannis Port to help fund Alzheimer's research. This past summer, many of these same individuals came together, again instigated by the Brands but hosted this time by Anthony K. and Alina Shriver, to hear Jeff Morby and Dr. Rudy Tanzi's perspective on the latest progress. More than 50 people attended this wonderful evening. ■

Alzheimer's Lecture in Chautauqua

For the third year in a row, Cure Alzheimer's Fund was invited to speak at the Chatauqua Institute in Chatauqua, New York. This past August, Dr. Sam Gandy, Cure Alzheimer's Fund Research Consortium member, spoke about the state of Alzheimer's research to a large and deeply engaged group of about 200 attendees. Through the years, interest in this event has remained very strong, with participants attending to find out the latest information on our progress and to raise awareness of the disease and its effects on patients and their families. ■

CURE ALZHEIMER'S FUND HEROES

3rd Annual Dick Hollander Open

For the third year in a row, brothers Josh and Jake Akman, ages 26 and 23, held the annual Dick Hollander Open™ at Blue Mash Golf Course in Laytonsville, Maryland, in honor of their beloved grandfather, who suffered from Alzheimer's disease. Cure Alzheimer's Fund President and CEO Tim Armour spoke to more than 175 participants at the event about the progress in the field to help people understand how their donations are being put to work. "We raised a lot of funds in honor of a great man for a great cause and we know our grandfather would be proud of the work we've done. Still, we would trade it all to have him back," said Josh. The Open was the most successful to date—raising more than \$77,000—bringing the three-year total to more than \$200,000. "I think that having a large and passionate family is part of our secret sauce. Dick also touched many people's lives, and they have generously supported our event because of their connection to him," added Josh. ■



Some of Dick Hollander's family members and Tim Armour.

Birthday Fundraiser

On July 27, Alan Arnette, avid mountain climber and tireless fundraiser for Alzheimer's research, turned 59. As someone who is always thinking about his own mother's struggle with the disease, Alan asked his friends and family to make a donation to Alzheimer's research this year instead of giving him a present. Last April, when Alan was climbing near Everest at 21,500 feet, a 7.8 magnitude earthquake struck Nepal. He was safe, but saw firsthand the devastation to this poor country. Alan's biggest challenge by far is on solid ground, trying to increase awareness for Alzheimer's disease, raise money for research and get people to sign up for clinical trials. He continues to use his climbing as a way to reach people and spread the word about the devastation of Alzheimer's disease. Over the next five years, he plans to tackle the 11 8,000-foot mountains he has yet to climb. ■

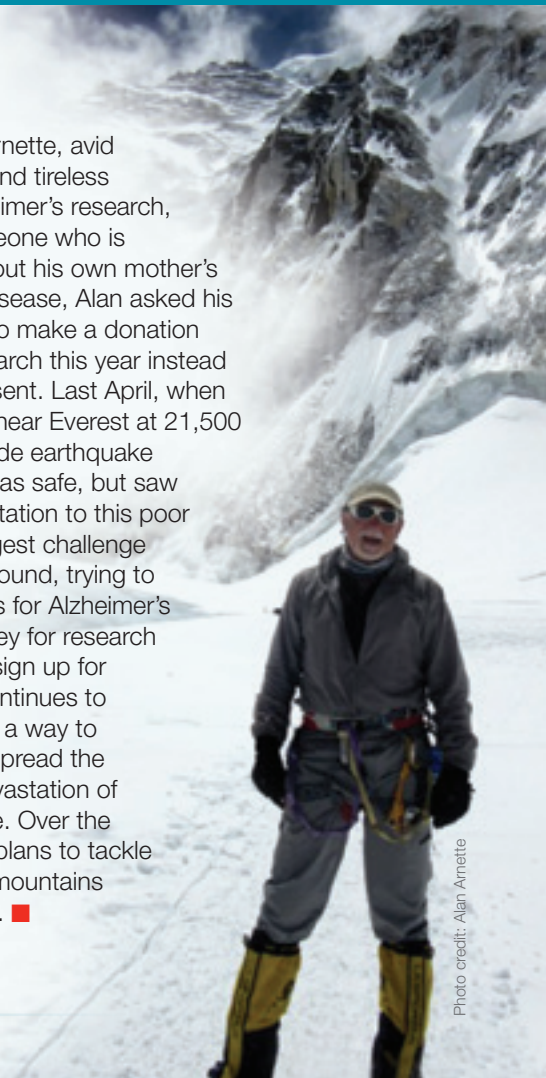


Photo credit: Alan Arnette

"Your donations make 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, president and CEO, Cure Alzheimer's Fund



Golfers gather to support three great causes.

15th Annual DKJ Foundation Golf Tournament

When their father was diagnosed with Alzheimer's disease at age 60, Gregg and Bruce Johnson, now in their 50s, founded the David K. Johnson Foundation in his honor. The goal? To raise awareness and funds to support a cure for Alzheimer's and help families affected by the disease. For 15 years, the annual August golf tournament at the Four Oaks Country Club in Dracut, Massachusetts, has been one of their largest fundraisers. This year they set out to raise more than \$50,000 for Sanborn Place Home Care & Day Services, the David and Susan Johnson Memorial Scholarship Fund and Cure Alzheimer's Fund. ■

Rotary Tournament

This past July, 60 players and guests gathered at Raven's Claw Golf Club in Pottstown, Pennsylvania, for the annual Bryn Mawr Rotary Club golf outing; Cure Alzheimer's Fund and two other organizations benefited from their day. Jeff Morby, co-founder of Cure Alzheimer's Fund and a Rotary member, spoke last June to the International Rotary Club about the urgent need to find a cure for Alzheimer's disease, and his message has caught on. "We lost my sister-in-law to Alzheimer's," said Dick Cuff, member and past president of the club. "We wanted to support Cure Alzheimer's Fund and we hope more Rotary Clubs will do so as well." They raised \$500 for research. ■



Dick Cuff, past president, Bryn Mawr Rotary Club

9th Annual Hay Harbor Tennis Tournament

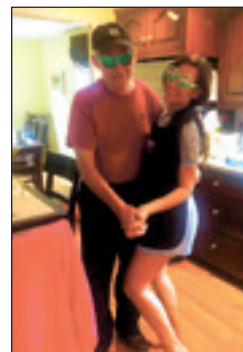
Once again, the ladies of Hay Harbor Tennis Club gathered to honor their friend Alison McCance, wife of Cure Alzheimer's Fund co-founder Henry McCance, and to raise money for Alzheimer's research. The annual round-robin tennis tournament took place on Fishers Island, New York, with club member Diana Fiske organizing and promoting the event, just as she has done for the last nine years. Together, they raised more than \$3,000 for research, bringing their nine-year total to more than \$34,000. ■



Hay Harbor tournament participants

\$30 for 30

Stefane Desmond of Boston usually goes away for her birthday. But this year, in honor of her 30th birthday, she decided to do something different. "I asked my family and friends to donate \$30, or whatever they could,



Stef and her dad

to fund Alzheimer's research. I wanted to raise awareness for the disease and raise money for such an important cause." Her father was diagnosed with early-onset Alzheimer's disease and Stef is committed to making a difference. She raised \$1,200 for research. ■

Springtime in the Cotswolds

Next spring, stopping to smell the roses not only will be relaxing and inspiring, it will help raise money for Alzheimer's research. Paul Coopersmith, landscape designer and entrepreneur, created Coopersmith's One-of-a-Kind Tours® more than 30 years ago to



Paul Coopersmith and his wife, Suzanne Parker

give travel buffs a unique way to see the British Isles (as well as Western Europe, Japan and New Zealand). For the past 10 years Paul has designated one of his tours to benefit a worthy cause; his 2016 selection is Cure Alzheimer's Fund. "I'm excited by all the research that CAF has funded and what it could mean for the treatment and prevention of Alzheimer's disease," said Paul. "At least three close relatives—my grandfather, aunt and father—suffered from the disease. Needless to say, I have a dog in this fight." For every person who signs up for the April 30–May 8 tour, which is limited to 20 participants, Paul will donate \$500 to Cure Alzheimer's Fund. For more information, visit coopersmiths.com. ■

For more information on our events, go to curealz.org/events.

Financial Update

	This Quarter*	YTD*	Inception to Date
Fundraising	\$418,000	\$3,706,000	\$51,848,000
Expenses paid for by the board	\$328,000	\$1,320,000	\$10,813,000
Funded research	\$4,347,000	\$5,994,000	\$34,015,000

*These numbers represent revenue and expenses for July and August only.
September financials will be included in the Q4 newsletter.

Research Update

Research funded during the third quarter of 2015

Project/Researcher	Distribution Amount
Development of Novel APP Dimerization Inhibitors That Lower Abeta Levels Carmela R. Abraham, Ph.D., Boston University	\$100,000
3DDS: A 3-D Human Neural Cell Culture System for Studying Neuron-Microglia Interaction in Alzheimer's Disease Hansang Cho, Ph.D., University of North Carolina at Charlotte	\$150,000
Role of Blood-Brain Barrier Function in Alzheimer's Disease Pathogenesis Investigated Using a 3-D Microfluidic Platform Se Hoon Choi, Ph.D., Massachusetts General Hospital Roger D. Kamm, Ph.D., Massachusetts Institute of Technology	\$291,056
Uncovering Determinants of Neuronal Vulnerability in Alzheimer's Disease Paul Greengard, Ph.D., The Rockefeller University	\$250,000
3DDS: Microglial Core/CD33 and Alzheimer's Disease: From Biology to Therapy Ana Griuciu, Ph.D., Massachusetts General Hospital Rudy Tanzi, Ph.D., Massachusetts General Hospital	\$400,000
3DDS:3-D Neural Core/High-throughput Drug Screening for Alzheimer's Disease Using 3-D Human Neural Culture Systems Doo Yeon Kim, Ph.D., Massachusetts General Hospital	\$400,000
Cell Cycle Re-entry and Tau Tangle Formulation John S. Lazo, Ph.D., University of Virginia George Bloom, Ph.D., University of Virginia	\$100,000
The Putative Role of Red Blood Cell CR1 Levels in Amyloid-β Clearance and Alzheimer's Disease Pathogenesis Cynthia A. Lemere, Ph.D., Brigham and Women's Hospital: Boston Hospital and Medical Center	\$150,000
Alzheimer's Genome Project™ Rudy Tanzi, Ph.D., Massachusetts General Hospital	\$1,500,000
Regulation of Tau Oligomerization by Interaction with TIA-1 Benjamin Wolozin, M.D., Ph.D., Boston University	\$100,000
3DDS: High-content Drug Screen Using a Novel 3-D Cell Model of Alzheimer's Disease Stephen Wong, Ph.D., Houston Methodist	\$150,000
3DDS: Alzheimer's Disease Drug Discovery in 3-D Weiming Xia, Ph.D., Boston University	\$150,000
PICALM Gene Therapy and Drug Screening for Abeta Clearance Berislav Zlokovic, M.D., Ph.D., University of Southern California Beverly L. Davidson, Ph.D., Perelman School of Medicine, University of Pennsylvania	\$375,170
Identification of Reactive Astrocyte-Secreted Neurotoxic Protein Responsible for Neuronal Apoptosis Ben Barres, Ph.D., Stanford University School of Medicine	\$150,000
BIN1 in Alzheimer's Disease Neuropathology Gopal Thinakaran, Ph.D., The University of Chicago	\$150,000
Total Distributed to Research for Q3 2015	\$4,416,226

Cure Alzheimer's FUND

34 Washington St., Suite 200
Wellesley Hills, MA 02481
Phone: 877-CURE-ALZ (287-3259)
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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 preventing, slowing 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*

P. Murali Doraiswamy, M.D., Duke University

Karen Duff, Ph.D., Columbia University

Sam Gandy, M.D., Ph.D., Icahn School of Medicine at Mount Sinai

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

Christian Haass, Ph.D., Ludwig-Maximilians-Universität München

David Michael Holtzman, M.D., Washington University, St. Louis

Richard L. Huganir, Ph.D., The Johns Hopkins University

Bruce Lamb, Ph.D., Cleveland Clinic

Christoph Lange, Ph.D., Harvard T.H. Chan School of Public Health

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34 Washington St., Suite 200
Wellesley Hills, MA 02481

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6th ANNUAL RESEARCH SYMPOSIUM **From Genes to Therapies** CONVERGING ON A CURE

With each year dedicated to Alzheimer's research we continue to get closer to finding a cure. By selecting and supporting the best scientists in the world, funneling all donations into research and developing a systematic roadmap for getting to a cure, we have made powerful progress toward ending this disease.

Our Scientific Advisory Board and Research Consortium have identified nine research areas of focus. They are: Genes to Therapies™/Drug Screening; Identification; Innate Immunity; Microbiome; Individual Projects; Pathological Pathways and Systems; Stem Cell Models; Therapeutic Strategies; and Whole Genome Sequencing/Epigenetics.

At this year's symposium, we'll share how this approach is helping the field converge on a cure. Hear directly from Rudy Tanzi, Ph.D., chair of the CAF Research Consortium. The symposium will be held at the **Harvard Club on Commonwealth Avenue in Boston on Wednesday, Oct. 14, at 4 p.m. EDT**. Attendance is free, but registration is required and opens at 3:30 p.m. Sign up now at **curealz.org/symposium**. ■