



Genes to Therapies: One Year Later



In just its first year of operation, Cure Alzheimer's Fund's ambitious new Genes to Therapies™ (G2T) research program has bloomed far beyond expectations. "We're firing on all cylinders now," says Research Consortium Chair Dr. Rudy Tanzi. "It's exactly where we need to be headed to stop this disease."

In 2015, Cure Alzheimer's Fund authorized nearly \$6.8 million for 22 gene variant investigations, along with the initiation of 21 transgenic mouse models. That accounts for more than half of its total research funding this year—and is far more than *all* of its research funding in 2014.

G2T is the next phase of Cure Alzheimer's Fund's long-term plan for attacking Alzheimer's disease from every possible angle. The key to defeating Alzheimer's, Tanzi proposed 11 years ago, is first to identify, and then closely examine, the relevant genetic variants impacting disease risk. The identification phase was accomplished through two methods—Genome-Wide Association Studies (GWAS) and Whole Genome Sequencing (WGS)—which together located nearly 100 gene variants that impact Alzheimer's risk.

By 2014, the Research Consortium and the Cure Alzheimer's board recognized that we were ready for the next phase: G2T, where researchers now would investigate the precise function of each gene, the consequence of each variant and precisely how to intervene to arrest the disease process. Tanzi explains that G2T establishes a highly efficient research plan. "We're not just studying genes at random anymore," he says. "We know to a certainty that these particular genes impact Alzheimer's. Now we can use our new mouse models to find the ones that are druggable. If we can find a switch that turns on a deleterious gene mutation, we want to turn that switch off."

Prioritizing these variants and recruiting the appropriate research talent to examine each one requires vision and coordination. To guide this process, Cure Alzheimer's Fund formed the G2T Steering Committee of leading Alzheimer's researchers David Holtzman, M.D. (Washington University, St. Louis), Sangram Sisodia, Ph.D. (University of Chicago), Rudy Tanzi, Ph.D. (Massachusetts General Hospital/Harvard University), Robert Vassar, Ph.D. (Northwestern University), and Steven Wagner, Ph.D. (University of California, San Diego). That group then set the priorities for gene investigations and implemented the time-saving idea of developing appropriate mouse models even before recruiting the appropriate researchers. Early G2T researchers include G2T Steering Committee members, as well as Berislav Zlokovic, M.D., Ph.D. (University of Southern California), and Li-Huei Tsai, Ph.D. (MIT).

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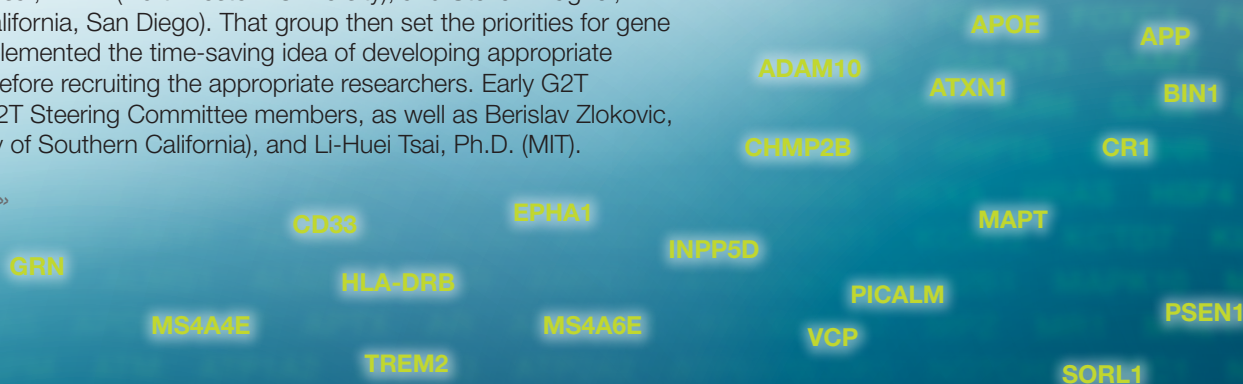
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Each gene to be studied may have several different mutations, each requiring its own strain of mice to study how that mutation affects Alzheimer's pathology. Originally, the first year of G2T was expected to involve just three to five new animal models and cost a few hundred thousand dollars. But the Research Consortium's strong support for the project quickly expanded it to 21 separate mouse models in 2015.

"This rapid expansion is a testament to both our researchers and our contributors," says Cure Alzheimer's Fund Chairman Jeffrey Morby. "The participating researchers have accelerated their work to a point where we can now take advantage of new techniques and breakthroughs. Meanwhile, our generous contributors have stepped up with dramatically larger donations, which has enabled us to fund more promising projects than ever before. It's a remarkable confluence."

The G2T Steering Committee recruited Wilma Wasco, Ph.D. (Massachusetts General Hospital), a geneticist and longtime colleague of Tanzi and other members of the Steering Committee, to manage the Genes to Therapies research core. Her expertise in Alzheimer's genetics-driven research and her science management experience make her an ideal fit. "This is an immensely difficult job with a mind-numbing amount of important details and many different strong personalities," explains Sisodia, a member of the Research Consortium and G2T Steering Committee. Tanzi concurs: "Wilma understands the science inside and out, and she also knows how to make the trains run on time. She's perfect."

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This is the first time a genes-to-therapies program of this scale has been attempted, and it already has drawn the attention of the National Institutes of Health (NIH). In fact, the NIH has indicated interest in modeling a mouse program of its own on Cure Alzheimer's G2T template.

of Health (NIH). In fact, the NIH has indicated interest in modeling a mouse program of its own on Cure Alzheimer's G2T template. "That's an incredible compliment," says Cure Alzheimer's CEO Tim Armour. "We're humbled. It's yet another way we continue to collaborate with NIH and take advantage of the scale they bring to the research effort."

Dr. Wasco also remarks how the G2T program dovetails very nicely with the recent "Alzheimer's in a Dish" technology developed by Tanzi and Doo Yeon Kim, Ph.D. "They're really complimentary," says Wasco. "Alzheimer's in a Dish is a great model and it will make things much faster for studying drugs. It's a way to quickly find therapies. But eventually, any drug that you find has to

be tested in animals for safety purposes and overall understanding of what's going on."

No treatment will emerge quickly, Wasco cautions. "It takes a lot of patience to be in science," she says. "As therapies become available, we'll be able to test them. G2T projects funded in 2015 are already producing new insights into the function of variants we know impact Alzheimer's risk, and that is a necessary step toward targeting their operation with a treatment someday."

"We have very high hopes for this project and are immensely proud of its ambitious scope," says Morby. "We're pressing forward with all the energy possible. Full steam ahead!"

Don't Miss Our Next Alzstream™ Webinar

Genes to Therapies—One Year Later

Mon., Feb. 29, 2016

Hear from Dr. Rudy Tanzi and Dr. Wilma Wasco about Cure Alzheimer's Fund's Genes to Therapies™ initiative one year later. This highly ambitious, multiyear, \$50 million project began in 2014. Visit curealz.org/webinar on or after Feb. 29 to watch. This webinar will be recorded in advance at the annual Scientific Advisory Board/Research Consortium meeting.

**Thank you for supporting Cure Alzheimer's Fund this year.
Every penny of your donation goes directly to research to get us closer
to finding a cure. We wouldn't be here without your support.**

FEATURED RESEARCHER

Wilma Wasco, Ph.D.

Associate Professor of Neurology at Harvard Medical School and the Massachusetts General Hospital Genetics and Aging Research Unit



Born and raised in Fairfield, Connecticut, Wilma Wasco was always a promising student. When she ended up in honors chemistry without taking the prerequisite course, she knew she had both an aptitude and passion for science. But when she accidentally cloned an amyloid precursor-like protein as a post-doctorate fellow, she began her lifelong career studying Alzheimer's disease. Today, Dr. Wasco is a renowned researcher at Massachusetts General Hospital and is spearheading the research core of Cure Alzheimer's Fund's Genes to Therapies™ (G2T) initiative.

Wilma Wasco was born the oldest of three to an attorney and a stay-at-home mom. As a child, Wasco was always looking under rocks in search of insects to play with. In high school, she enjoyed dissection and her science classes, but didn't develop an interest in disease research until later.

Education

In the late '70s, she attended the University of Connecticut (UConn) and thought at the time she might want to be a lawyer like her dad. When she tried to enroll in chemistry as a freshman, she wasn't able to get into the class, so the next year she tried again, without success. Instead, she decided to enroll in honors chemistry and loved it, ultimately declaring biochemistry as her major at the end of her sophomore year.

After graduating from UConn in 1981, Wasco went on to pursue a Ph.D. in molecular pharmacology at Albert Einstein College of Medicine in the Bronx. She loved New York, but after graduating in 1987, she wanted to try a new city—Boston—to carry out her post-doctoral studies, landing at the Massachusetts Institute of Technology (MIT) as a research fellow.

Alzheimer's Disease

While Wasco was at MIT, she accidentally cloned something that was similar to the amyloid precursor protein (APP). "At the time, almost 30 years ago, APP had just been discovered," says Wasco. "It was a precursor to amyloid and my post-doctoral adviser and I met with Dr. Rudy Tanzi to determine if my APP-like clone was worth characterizing."

After Wasco completed her post-doctoral work, Tanzi offered her a position at Massachusetts General Hospital (MGH) studying Alzheimer's disease genetics and cell biology, and she's been there ever since. "I was almost 30 years old at the time, and looking for an opportunity to focus my research on something that could have a direct impact." She most certainly has.

Dr. Wasco was part of an international effort that identified the familial Alzheimer's disease-associated presenilin 1 (PS1) and presenilin 2 (PS2) genes. In addition, her laboratory identified genes that encode the two amyloid precursor-like proteins (APLP1 and APLP2) and calsenilin, a calcium-binding protein that interacts with

the presenilin proteins. Her research has been focused on understanding the biological role that each of these AD-linked proteins plays in the normal, aging and diseased brain.

Cure Alzheimer's Fund

Most recently, Wasco has been at the helm of the research core of Cure Alzheimer's Fund Genes to Therapies project—an innovative and collaborative approach to studying genes and developing specific therapies. As a veteran in her field, Wasco has worked with many different investigators and has a very good understanding of the research.

"Working with Cure Alzheimer's Fund is unique," says Wasco. "As a scientist, I'm used to having to beg, borrow and steal funds for every project I work on. It's really wonderful to get up every morning and not have to worry about where we're going to get the money for this important research. I love Cure Alzheimer's Fund's single-minded drive to cure this disease, and their innovative approach."

Dr. Wasco is a Pew Biomedical Scholar and a member of the Genetics and Aging Research Unit at MassGeneral Institute for Neurodegenerative Disease. She has been honored with the National Research Service Award, the Becton-Dickson Research Fellowship Award and the MGH Women's Career Faculty Development Award.

When she's not in her lab working, she enjoys cooking, hiking with her dog and watching sports with her two teenage sons, neither of whom has an interest in science—yet.



New Head of Scientific Advisory Board

Dennis Choi, M.D., Ph.D., is now heading up Cure Alzheimer's Fund's Scientific Advisory Board. As professor and chair of the Department of Neurology and director of the Neurosciences Institute at the State University of New York at Stony Brook, Choi has a strong track record of research and a broad perspective on the Alzheimer's field.

He received his M.D. from the Harvard-MIT Health Sciences and Technology Program, as well as a Ph.D. in pharmacology and neurology from Harvard. His own research has focused on cellular mechanisms of pathological neuronal death and the development of novel therapeutics and biomarkers. He has published more than 250 research papers and reviews, trained more than 50 graduate students and fellows in his laboratory, and is a co-inventor on seven U.S. patents.

Choi's long history of volunteer leadership and collaboration in the scientific community includes being a fellow of the American Association for the Advancement of Science, a member of the National Academy of Medicine, president of the Society for Neuroscience, vice president of the American Neurological Association and chairman of the U.S./Canada Regional Committee of the International Brain Research Organization, among other positions. The many thoughtful peer reviews he has provided to Cure Alzheimer's Fund in the past have improved already groundbreaking proposals from leading researchers. We welcome the insight and vision he will contribute to our research direction.

Fifth Annual Research Symposium Strikes a Chord



A cappella group Cartoon Johnny singing "Remember Me."

For the fifth year in a row, people gathered at our annual symposium to learn about the latest progress on Alzheimer's research. The event was funded by the Cure Alzheimer's Fund board and was open to the public in an effort to educate people about the research progress toward eradicating the disease. More than 200 people gathered at the Harvard Club in Boston in mid-October and 500-plus more tuned in online to hear the presentations. The event highlighted our growing understanding of the disease process from nine different areas of focus, and the research, collaboration and breakthroughs of the past year. In addition, Cartoon Johnny, an award-winning a cappella group, sang "Remember Me," an anthem for Alzheimer's that can be purchased on iTunes. A portion of all song proceeds will go directly to Cure Alzheimer's Fund. If you missed it, you can watch the symposium in its entirety at curealz.org/symposium.



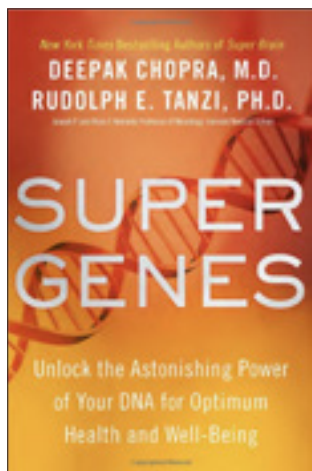
Rudy Tanzi, Ph.D., of Harvard Medical School/Massachusetts General Hospital and chairman of Cure Alzheimer's Fund Research Consortium



Symposium attendees view posters about the latest research breakthroughs.

'Super Genes'

After the huge success of their first book, "Super Brain," which helped readers tap into the power of their own brains, Dr. Rudy Tanzi, chairman of the Cure Alzheimer's Fund Research Consortium, and Deepak Chopra, M.D., author and spiritual leader, have once again collaborated on a new book, "Super Genes," released in November. The book serves as a guide to help readers lead a healthier life despite the genes they inherited. Their message? Rather than let fate take its course, Tanzi and Chopra urge people to take their well-being into their own hands. "This book will help to educate a broader audience about the important role of genetics in Alzheimer's disease and other illnesses, which will support our approach to finding effective therapies," says Tim Armour, president and CEO of Cure Alzheimer's Fund. "You cannot find a cure for a disease if you don't understand the cause, and you cannot understand the cause without understanding the genetics. This book is an extension of the rigorous science Dr. Tanzi pursues every day."



A Gang of Supporters

While Alzheimer's disease is far reaching, its impact is deeply personal for those who are directly touched by it. Stanley Gang of Venice, Florida, recently was diagnosed with Alzheimer's disease. He has two sons, Michael and David, a loving daughter-in-law and four grandchildren. "It is so sad to see a man who is so brilliant, accomplished and loving, impaired with this disease," says Michael Gang. After searching for potential cures, the family determined that "Cure Alzheimer's Fund has the best chance of eradicating this disease in the shortest time possible" — so the Gangs donated \$50,000 to Alzheimer's research. "The advances made by Cure Alzheimer's researchers have been amazing," adds Gang. "Their willingness to share their findings openly with the world scientific community should be applauded."

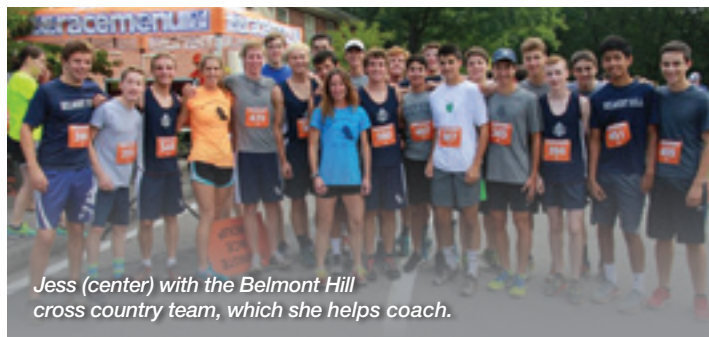


The Gang Family

CURE ALZHEIMER'S FUND HEROES

Jog Your Memory

After watching her mother suffer from early-onset Alzheimer's disease, Jess Rice and her husband, Bob, of Needham, Massachusetts, founded Jog Your Memory Inc., with the goal of raising money to eradicate Alzheimer's disease. Last September they held their second annual 5K road race and raised \$92,000, having donated \$14,000 the year before. "We are so inspired by all of the forward-thinking and proactive work that Cure Alzheimer's Fund does, and are proud to be aligned with such a philanthropic organization, where 100 percent of donations goes directly to research," says Jess. "Education, awareness and sharing of information is the lifeblood of Cure Alzheimer's Fund's structure, and we are driven to continue our annual race until a cure is found."



Jess (center) with the Belmont Hill cross country team, which she helps coach.

Philadelphia Golf Tournament

Last September 64 people came together at the Bidermann Golf Club in Wilmington, Delaware, to raise money for Alzheimer's research. Cathy Ingham of Philadelphia, who lost her father to the disease in 2012, coordinated the event along with friends and partners from Cure Alzheimer's Philadelphia—a nonprofit organization founded last year. Since 2012, Ingham has organized annual dinners in the area to raise awareness for the disease and support research. "This illness hit our family like a hurricane," she says. "I was frustrated by the ineffectiveness of the drugs my dad had been given. When I searched online for possible drugs that might be in the research pipeline, I stumbled upon Cure Alzheimer's Fund's website. The next day I was on the phone with Tim Armour, president and CEO of Cure Alzheimer's Fund, asking what I could do to help." The rest is history. The first golf outing raised \$30,000 for research. The next one will be held in September.



Cure Alzheimer's Philadelphia Committee (l to r): Cathy Ingham, Jim Beers, Bob DiFilippo, Tom Bond and John Coll.

Your donations make a big difference in our progress toward finding a cure for Alzheimer's disease.



Jeff Madden at the summit of Mont Blanc.

A Climb to Remember

Chicago native Jeff Madden started climbing at age 25. He was inspired to climb Mont Blanc, the highest peak in Western Europe, in memory of his grandmother, who suffered from Alzheimer's disease (since the Alps were one of her favorite places). As a portfolio manager at IronBridge Capital Management L.P., a company that "invests in firms that have a track record of making the world a better place," Jeff identified Cure Alzheimer's Fund as an organization he wanted to support. "I was very impressed by the backgrounds of the founders and Research Consortium, and their track record of delivering meaningful results by way of a repeatable, private equity approach to finding a cure for Alzheimer's," he adds. "I believe we all have an authentic self that is designed to do something bigger than ourselves by way of helping others less fortunate." He raised \$26,000 for research.



Mom and Son Run for a Cure

For the second year in a row, Kim Chan and her son Ethan, 12, ran the Long Beach Half Marathon last October in honor of Kim's grandfather, who suffered from Alzheimer's disease. Last summer

Ethan wrote a paper about his experience. Kim explains: "Ethan chose to research and write about the disease, Cure Alzheimer's Fund and running, which



Ethan and Kim Chan

helped him think more about what he was running for." In his essay, Ethan wrote, "I am dedicated to raising awareness for this devastating disease that affects so many families, including my own." Ethan came in 3rd place in his age division, and he and his mom raised \$1,400 for research, bringing their cumulative donation total to more than \$7,000.



The Raw-Campbell family

NYC Marathon

Matt Raw of Brooklyn, New York, ran the New York City Marathon last November in honor of his mother, who has early-onset Alzheimer's disease. While he and his family had watched the marathon pass through their neighborhood every year, it was Matt's first time running. "My mom's diagnosis in 2012 motivated me to take up running seriously," he says. "It gave me some space to think about Mom and work through some of the emotions, providing me a kind of mental clarity." He raised more than \$1,600 for Alzheimer's research, a cause his wife, Maggie Campbell, has supported in the past through her hand-crafted calendars. If he had to do it all over again, though, he would change only one thing. "I might not have picked training for a marathon to coincide with having a newborn."

Juniper Boutique Gives Back

Jen Stamper and her business partner, Jennifer Lawrence, own a women's clothing and accessories boutique just north of Chicago. "We believe in using our store to help others—whether it's finding a perfect pair of jeans for a customer or giving back to causes that are important to us and our community." Juniper Boutique celebrated its two-year anniversary last October. "For our anniversary party, we chose to raise money for Cure Alzheimer's Fund, because just about everyone has been affected in some way by this atrocious disease," says Jen. "My husband's grandmother suffered from Alzheimer's, one of our employee's mothers was diagnosed with early-onset Alzheimer's, and too many of our clients are struggling to care for relatives with the disease. We all know research is the key to ending this horrible illness, and we're hopeful that there will be a cure in the near future." More than 100 women attended the event to shop and support Alzheimer's research, and the store offered a significant discount as a way to thank their clients. Together they raised \$500 for Cure Alzheimer's Fund.



Juniper Boutique

End Alzheimer's Fundraiser

As a hair stylist, make-up artist and esthetician at Lazuli Salon, Jen Syverson of Providence, Rhode Island, sees lots of people every day. She also sees the widespread impact Alzheimer's has on her clients and her own grandmother. One of Jen's customers, and the husband of another customer, currently are battling the disease and Jen wanted to raise money for the cause. Last November, she held a fundraising event to build awareness for the disease and funds for a cure. Customers and staff donated nearly \$700, and Jen already is planning another event for 2016.

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

Financial Update

	This Quarter*	YTD*	Inception to Date
Fundraising	\$7,799,000	\$11,753,000	\$60,015,000
Expenses paid for by the board	\$735,000	\$2,288,000	\$11,949,000
Funded research	\$3,782,000	\$10,022,000	\$38,042,000

*Numbers shown are preliminary for the period and are rounded to the nearest \$1,000.

Research Update

Research funded during the fourth quarter of 2015

Project/Researcher	Distribution Amount
The Biological Impact of TREM Locus Mutations in Alzheimer's Disease Marco Colonna, M.D., and David Holtzman, M.D., Washington University	\$250,000
Investigation of sTREM2 in CSF as a Potential Biomarker for Neuronal Cell Death Christian Haass, Ph.D., DZNE, Munich	\$144,182
Systemic Inflammatory Networks in Alzheimer's Disease Filip Swirski, Ph.D., and Matthias Nahrendorf, M.D., Ph.D., Massachusetts General Hospital	\$200,000
Rejuvenation of Microglia in Brain Aging and Neurodegeneration Tony Wyss-Coray, Ph.D., Palo Alto Veterans Institute for Research/Stanford University	\$150,000
Role of the Gut Microbiome in AD Pathology and the Potential of Probiotic Therapeutic Strategies Deepak Kumar/Robert D. Moir, Ph.D., Massachusetts General Hospital	\$150,000
Targeting Beneficial Innate Immunity in Alzheimer's by IRAK-M Deletion Terrence Town, Ph.D., USC	\$150,000
Evaluation of AMX0035, a Neuroprotecting and M1-Deactivating Therapeutic, in an Immunological Model of AD (Part 2) Amylyx	\$150,000
Discovery of CK1 Activators for Inducing the Autophagic Degradation of APP Beta-CTF Paul Greengard, Ph.D., The Rockefeller University	\$450,000
Extracellular Vesicle-Based Targeting of CD33-Mediated Pathology for Alzheimer's Disease Therapy Casey Maguire, Ph.D., Massachusetts General Hospital	\$150,000
Genetic Targets to Block Tau Propagation Marc Diamond, M.D., University of Texas-Southwestern	\$150,000
The Role of PICALM Mutations in Alzheimer's Disease Berislav Zlokovic, M.D., Ph.D., and Zheng Zhao, Ph.D., USC	\$100,000
Studying the Functional Consequences of Alzheimer's Disease Risk Variants in the CLU and ABCA7 Genes Using Both Human and Mouse Models Li-Huei Tsai, Ph.D., MIT	\$250,000
G2T: Centralized Research Core Operations Management Wilma Wasco, Ph.D., Massachusetts General Hospital	\$185,350
Stem Cell Approach to Investigating the Phenomenon of Brain Insulin Resistance Sam Gandy, M.D., Ph.D., Icahn School of Medicine at Mount Sinai	\$100,000
Tau Missorting in AD—Causes and Consequences Eva-Maria Mandelkow, M.D., Ph.D., and Eckhard Mandelkow, Ph.D., DZNE, Bonn	\$150,000
Molecular and Cellular Mechanisms of ACE1 R1279Q in Alzheimer's Disease Robert Vassar, Ph.D., Northwestern	\$250,000
ABCA7 in Brain Homeostasis and Alzheimer's Disease Guojun Bu, Ph.D., Mayo Clinic Jacksonville	\$200,000
Abeta Expression Protects the Brain from Herpes Simplex Virus Robert D. Moir, Ph.D., Massachusetts General Hospital	\$325,000
G2T: Research Models and Materials Taconic Biosciences Inc.	\$305,069
Functional Characterization of GGA3 Mutations Associated with Alzheimer's Disease Giuseppina Tesco, M.D., Ph.D., Tufts University	\$150,000
Total Distributed to Research for Q4 2015	\$3,959,601

Cure Alzheimer's FUND

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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.

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American Ingenuity Award

Every year *Smithsonian* magazine gives out its prestigious American Ingenuity Awards to the people who have made the greatest revolutionary breakthroughs in the arts, sciences, education and social progress. This year the Natural Sciences award was bestowed upon Drs. Rudy Tanzi, chairman of Cure Alzheimer's Fund Research Consortium, and Doo Yeon Kim, fellow neurologist at Harvard Medical School. Their contribution? "Alzheimer's in a Dish," a Petri dish containing human brain cells that develop plaques and tangles—the hallmarks of Alzheimer's disease. Funded by a grant from Cure Alzheimer's Fund, Tanzi and Kim's innovation has been called a "game changer" by *The New York Times*. Wrote Natalie Angier, author of "The Two Brains at the Forefront of the Fight Against Alzheimer's" in *Smithsonian*, "[Alzheimer's in a Dish] offers researchers a chance to both track the course of Alzheimer's in unprecedented biochemical and genetic detail, and to quickly and cheaply test thousands of potential treatments that might block or at least slow its malign progress." While Tanzi and Kim are proud of this award, they are even prouder that their innovation is bringing us closer to a cure.



Doo Yeon Kim, left, and Rudolph Tanzi
(Photo illustration by Irvin Serrano)