



**Cure Alzheimer's FUND**  
targeting breakthrough research



## Alzheimer's and Diabetes: Finding the Common Origin

*Diabetes isn't  
causing Alzheimer's.  
Rather, they're both  
being caused by the  
same thing.*

Alzheimer's disease and Type II diabetes long have been observed to have a clinical connection, with patients with diabetes more than twice as likely as those without the disease to develop Alzheimer's. But the precise nature of this connection has been a mystery until recently.

Over the last few years, research projects funded by Cure Alzheimer's Fund and others have helped bring us much closer to an understanding of the molecular connection—and, potentially, to effective treatments for *both* diseases.

### The breakthrough

It began a few years ago with Rudy Tanzi's Alzheimer's Genome Project™ (AGP), which was able to identify more than 100 candidate genes previously unassociated with Alzheimer's. Researchers across the world were given access to this new list, to see what unexpected connections might be made.

Such a connection is exactly what happened when, in July 2006, Cure Alzheimer's Fund Research Consortium member Sam Gandy attended the prestigious, off-the-record Gordon Conference in New Hampshire to present some data on the Alzheimer's protein Abeta (also known as Amyloid  $\beta$  or A $\beta$ ). Gandy, who studied diabetes as a graduate student in the early 1980s, was curious about the state of diabetes genetics, and so went to a lecture by University of Wisconsin diabetes geneticist Alan Attie, who was focused on a sorting protein called SorCS1 (pronounced "sorx-one"). Sorting proteins act as a cell's "postal workers," reading every molecule's unique "zip code" and delivering proteins to their proper destinations inside the cell.

Tanzi's AGP had just discovered a possible Alzheimer's link to the gene controlling the same protein. Hearing Attie's presentation, Gandy wondered: Was this the missing Alzheimer's-diabetes connection?

"We had a hunch, but we hadn't done a single experiment and we had no data," recalls Gandy. Perhaps Alzheimer's and diabetes were both connected to this SorCS1 "postal worker" protein. Perhaps SorCS1 was responsible for reading the "zip code" on amyloid precursor protein (APP)? Gandy recruited post-doctoral fellow Rachel Lane to lead a very speculative high-risk study, in which Lane first used Attie's armamentarium of SorCS1 tools to study cell cultures and then examined SorCS1-deficient mice, also developed by Attie. Lane found that when SorCS1 was under-expressed, more Abeta was generated—particularly in female mice. This was significant, because Attie already had shown that SorCS1 was linked especially to Type II diabetes in women.

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## Eureka

Diabetes isn't *causing* Alzheimer's. Rather, they're both being caused by the same thing. "Until this link," explains Gandy, "it was hard to figure out what was *cause* and what was *effect*—what was the chicken and what was the egg? Identifying a gene that increased the risk for *both* diseases gave us a starting point. Now we know that both diseases can begin whenever the SorCS1 'postal worker' fails to read the 'zip code' on APP and then deliver it to its proper destination."

Alzheimer's is driven by the accumulation of A $\beta$  between and among brain cells. A $\beta$  is created by two aberrant cleavages in a larger protein called amyloid precursor protein (APP). In healthy cells, APP is sorted into the plasma membranes and the membranes of intracellular organelles, and assists the healthy functioning of cells.

What Gandy discovered is that, in both Alzheimer's and diabetes, there's something going wrong with that "postal" sorting process. The sorting protein SorCS1, when present at inadequate levels, interferes with the correct sorting of APP and therefore leads to the creation of the destructive A $\beta$ . This same malfunctioning sorting process also can start a cascade that leads to diabetes. Further, the mis-sorting by other proteins in this same family recently have been linked to other major metabolic and neurological illnesses, such as frontotemporal dementia and atherosclerosis. SorCS1, diabetes and Alzheimer's are just the tip of the iceberg—these "postal workers" hold the keys to major diseases affecting millions of people.

## The power of 'venture philanthropy'

In a recent interview, Gandy stressed that his initial study was exactly the sort of high-risk/high-payoff study that Cure Alzheimer's Fund has become known for.

"It took a while from my hunch to even get going, because this was so speculative. NIH usually requires extensive preliminary data. At the beginning, all we had was an intriguing idea. We went to the Cure Alzheimer's Scientific Advisory Board and said, 'Here's this idea we have...' Then we

had to find a postdoc—Rachel Lane—who would risk a few years of her early career on it." But it paid off.

Since Gandy's discovery, further progress has been made to flesh out the Alzheimer's-diabetes connection by Columbia University's Richard Mayeux and others. Tanzi also has made new links to other genes in the same gene family.

A recent pilot study at the University of Washington has reported promising results on the possibility of treating Alzheimer's with an insulin nasal spray, and NIH has followed up with funding for a full-blown drug trial. Meanwhile, there's much more to understand about the basic connection between Alzheimer's and diabetes; Rob Moir, at Massachusetts General Hospital, is pursuing this connection further, with the help of Cure Alzheimer's Fund dollars. And Gandy is now circling back to diabetes.

"Unraveling the Alzheimer's-diabetes story," he says, "has pointed to molecules and pathways that have never been linked to insulin sensitivity before. Here we have the tantalizing prospect that one gene, first studied on the basis of a hunch, might lead to a new understanding—and new drugs—for both Alzheimer's and diabetes. We hope to pick up the SorCS1-insulin sensitivity lead as a separate project." ■

## Want to Know More?

### Catch Our Next Webinar: Alzheimer's and Diabetes: Finding the Common Origin

Join Cure Alzheimer's Fund Consortium member Sam Gandy, M.D., Ph.D., and David Shenk, author of the national bestseller *The Forgetting, Alzheimer's: Portrait of an Epidemic*, for a discussion about the linkage between Alzheimer's disease and diabetes on Wednesday, April 4, at 2:30 p.m. Eastern Time. To register or for more information, visit [www.curealz.org/webinar](http://www.curealz.org/webinar). ■

## Toni Carbone Joins Cure Alzheimer's Fund Team



Toni Carbone joined Cure Alzheimer's Fund in January as office manager. As an integral part of the Cure Alzheimer's Fund team, Carbone manages the day-to-day operations of the office. She worked at Harvard Business School for more than 20 years in the External Relations office, serving as director of planning and administration and director of special events and travel; her efforts helped the school exceed its capital campaign goal by 20 percent. "It's important to me to work for an organization where I am fully committed to its mission," says Carbone. "I am so grateful to be here." ■

## Get the Facts

Visit [www.curealz.org](http://www.curealz.org) to order a copy of our latest publication, *Alzheimer's Disease: The Science*, written by Jeff Morby and Rudy Tanzi of Cure Alzheimer's Fund. This piece discusses the latest state-of-the-art findings on Alzheimer's research, including scientific breakthroughs, potential new therapies and a vision for going forward. Hard copies are available for a suggested contribution of \$25 or more each. ■



# Reaching New Heights in the Fight Against Alzheimer's

At age 28, Maria Pugliese may not be able to move mountains, but she certainly made an impact when she ran 60 miles across the Andes Mountains and raised more than \$1,300 for Cure Alzheimer's Fund.

On Feb. 3, Pugliese woke up in Chile, where she and her running partner, Laura Milsom, set out on a three-day adventure through the Andes to the finish line in Argentina. While Pugliese ran with 1,500 others in the *El Cruce de los Andes* race, her journey was a personal one.

## Alzheimer's family history

Pugliese's maternal grandmother, Dona, age 87, lives in a skilled nursing facility in San Diego. Dona was diagnosed with Alzheimer's disease seven years ago and sadly, no longer remembers her family. "She has her good days and her bad days," says Pugliese about her grandmother, "but she just isn't the woman she used to be. She has reverted to her childhood and goes by her maiden name." Having watched Dona and those around her suffer for the past several years, Pugliese is determined to help find a cure.

Pugliese not only worries about her grandmother, she also worries about her own mother and about herself. "My great grandmother died of Alzheimer's, as well as one of my great aunts. And I know that my family is at risk," says Pugliese. Not willing to take any chances, she is very active and particular about her diet and health regimen, which are all smart strategies for good brain health.

## Born to run

Pugliese has been a runner for most of her life. She ran cross-country at Troy High School in her home state of Texas, and she's been running ever since.

On the first day of *El Cruce de los Andes*, she ran almost a full marathon up a dormant volcano (Mocho-Choshuenco), past snow-draped peaks. "We ran a mile into the sky," says Pugliese. "When we got past the tree line, we had a 360-degree view and the scenery was absolutely gorgeous." She and Milsom camped in tents and ate different cuts of meat that were cooked over a bonfire as well as rice and stew and pasta.

Day two was much tougher, with lots of soreness from the day before and more than a full marathon ahead of them that day. Pugliese had to cross rivers and streams and run in wet shoes. When they arrived at Lake Pirehueico—their final destination for the day—they had to run around it, climbing under and over fallen trees only to be met by a race official who told them they couldn't finish.

"No way," she said. "We've come this far, we're finishing." When they finally arrived the sun was down, the moon was up and they were wet, cold and exhausted. That's when they found out their bags had not yet arrived. But Pugliese didn't get discouraged.

Day three was mostly flat and a shorter run than the previous two days. It was also the day they got to cross the border. With passport in hand, Pugliese ran into Argentina and finished her long journey



*Pugliese and Milsom crossing the finish line.*

in the scenic Lanín National Park, where she received a stone medal that was handmade by local Chileans. "The entire race was an amazing experience," she says. "I could talk about it for days."

## Supporting Cure Alzheimer's Fund

Pugliese first learned about Cure Alzheimer's Fund through First Giving on the Web. The more she read about the organization, the more she was convinced that Cure Alzheimer's Fund was "going to get it done," so she chose to support them. "Alzheimer's disease has a daily impact on my family, and I want to see it cured as soon as possible," says Pugliese. Last fall, she ran a marathon along the streets of Buenos Aires and raised more than \$1,000 for Cure Alzheimer's Fund. "With more funds, I know a cure will be found soon," she says. "Please give whatever you can and we'll fight this disease together!"

What's next for Pugliese? "I will definitely do another race somewhere soon," she says. We thank her for her tremendous, unwavering support—and it's not too late to support her in her quest to raise funds for Cure Alzheimer's Fund. Please visit [www.firstgiving.com/fundraiser/maria-pugliese/cruce](http://www.firstgiving.com/fundraiser/maria-pugliese/cruce) to donate. ■



*Milsom and Pugliese at the tip of the Mocho-Choshuenco volcano.*

**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](http://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.**

## Financial Update

	This Quarter	YTD*	Inception to date
<b>Fundraising</b>	\$866,053	\$866,053	\$24,258,181
<b>Expenses paid for by the founders</b>	\$154,320	\$154,320	\$4,719,489
<b>Funded research</b>	\$1,125,000	\$1,125,000	\$15,846,141

\*These numbers as of March 1, 2012

## Research Update

Research funded during the first quarter of 2012

Project	Researcher	Distribution Amount
<b>Role of ADAM10 in the pathogenesis of Alzheimer's disease after head trauma*</b>	Giuseppina Tesco, Ph.D. Tufts University Medical School, Boston	\$100,000
<b>Metallomic Mapping of the Aging Brain in Trg2576 Transgenic Mouse Model*</b>	Lee Goldstein, M.D., Ph.D. Boston University, Boston	\$100,000
<b>General Anesthetics and Alzheimer's Disease</b>	Zhongcong Xie, M.D., Ph.D. Harvard Medical School, Massachusetts General Hospital, Boston	\$100,000
<b>Abeta Oligomers and the pathogenic spread of Tau aggregation: Implications for Alzheimer's Disease Mechanism and Treatment</b>	Dominic Walsh, Ph.D. Dennis Selkoe, M.D. Brigham and Women's Hospital, Boston	\$125,000
<b>Alzheimer's Genome Continuation:</b> 1. Elucidation of family-based genome-wide association study (GWAS) of Alzheimer's gene candidates 2. Re-sequencing of top family-based GWAS AD candidate genes 3. Functional studies of specific AD GWAS candidate genes	Rudolph Tanzi, Ph.D. Massachusetts General Hospital, Boston	\$600,000
<b>Development of UDP Analogs for the Treatment of Alzheimer's Disease</b>	Philip Haydon, Ph.D. Tufts University Medical School, Boston	\$100,000
<b>Total Distributed to Research for 1Q 2012</b>		<b>\$1,125,000</b>

\*Awarded on Dec. 29, 2011

## Cure Alzheimer's FUND

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### Mission

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

### Research Consortium

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Harvard Medical School/Massachusetts General Hospital  
**Sam Gandy**, M.D., Ph.D., Mount Sinai School of Medicine  
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### CHARITY DESIGNATION

Cure Alzheimer's Fund® is a "doing business as" name for the Alzheimer's Disease Research Foundation, a 501(c)(3) public charity with federal tax ID # 52-2396428.

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# The Case for Cure Alzheimer's Fund

## Through the eyes of a seasoned fundraiser diagnosed with Alzheimer's

As a nationally recognized expert in planned giving and family philanthropy, Charles Collier has worked with hundreds of individuals and families to help them shape their philanthropy, make tax-wise gift decisions and deal with family issues surrounding financial wealth. Formerly the senior philanthropic adviser at Harvard University for 25 years, Collier also has held development positions at Princeton, Brown, Andover and Dartmouth.

### Joining the Cure Alzheimer's Fund team

Two years ago, at age 61, Collier was diagnosed with Alzheimer's disease, which accelerated his retirement from Harvard last year. Collier first learned about Cure Alzheimer's Fund when he sent out his retirement notice to his clients, including Fund founders Phyllis and Jerry Rappaport. Says Collier, "Phyllis immediately called me and said, in her wonderful way, you've got to meet the people at Cure Alzheimer's Fund." He had known Henry McCance from Harvard already, but when Collier attended the Cure Alzheimer's Fund symposium in October, he decided he wanted to get involved with the organization.

"Henry and Phyllis are remarkable people who get things done," he says. "I knew then that I needed to understand more about how Cure Alzheimer's Fund supports important research that can make a difference to someone with

Alzheimer's, no matter what stage they are in, because that's me." Since then, Collier has focused his efforts on helping to support Cure Alzheimer's Fund's fundraising efforts.

### Collier's contribution

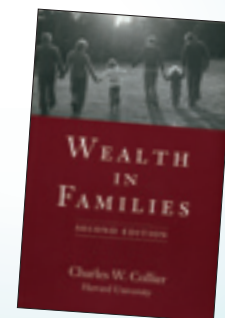
Each year Collier's functioning gets a bit worse, but he says, "I am a fighter and that's why I chose to contribute my time, expertise and my own money to this organization." Collier's father left him a donor-advised fund, and he told Collier, "when I die, you can have what's left of the IRA money yourself, but it will only be 35 percent of what's left over, or you can use 100 percent of it for philanthropy." So Collier made a significant donation to Cure Alzheimer's Fund.

"I believe it's critical to support the best researchers in order to find a cure for Alzheimer's, especially when 100 percent of donations go directly to research," says Collier. "Every minute a baby boomer is told that they have Alzheimer's. The country needs to wake up and understand the urgency of finding a cure."

### The future

When asked how he's doing, Collier says, "We're all dealt a hand of cards in life. Some are good, some not so good. What matters is how you react to those cards. I'm supporting Cure Alzheimer's Fund because it's a unique organization that's really trying to tackle the illness. And by volunteering, I hope I can make a difference." ■

Collier's book, *Wealth In Families*, addresses many of the questions of concern to families of wealth, including ways to teach values to your family through philanthropy.



Henry McCance, Phyllis Rappaport and Charlie Collier at Cure Alzheimer's Fund's Symposium last fall.



Collier and his father, Abram.



Collier and his family

**"As a thoughtful leader in his field, my father greatly values organizations that are founded on learning and innovation. Cure Alzheimer's Fund is one of those organizations."**

—Whit Collier, son of Charlie Collier

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## Our Heroes

### Third Annual Running 4 Answers Road Race

On Saturday, April 28, co-founders Carolyn Mastrangelo and Barbara Geiger will hold the third annual Running 4 Answers fundraiser run on the tree-lined streets of historic Roseland and Essex Fells, N.J. This four-mile race/two-mile fun run/walk brings families together to honor loved ones whom they have lost to Alzheimer's or those who suffer from the disease today, and helps raise money toward finding a cure.

David Cassidy, best known for his role as Keith Partridge of "The Partridge Family," is supporting the Running 4 Answers team. Like Mastrangelo's mother, Cassidy's mother has early-onset Alzheimer's, and Cassidy has agreed to post information about the race on his website and Facebook page.

"This year, we have allowed participants to create 'teams' so that they can race against each other physically or fiscally to heighten the competition," explains Mastrangelo. The race will be chip-timed to ensure accuracy for the runners.

Last year, Running 4 Answers raised \$30,000 for Cure Alzheimer's Fund.

This year, organizers hope to raise even more. We are extremely grateful to Mastrangelo and Geiger for their commitment to our cause. To register and/or donate, visit [www.running4answers.org/](http://www.running4answers.org/). ■

*running 4 answers*



### 26.2 Miles Toward a Cure

This spring, four runners will come together at an internationally acclaimed marathon for one reason—to raise money for Cure Alzheimer's Fund. While most of them have never met, they share a common bond—they all have been touched by someone who is/was afflicted with Alzheimer's disease, and they all share a driving passion to find a cure.

Anna Shepherd, Pam Girouard and Peter and Ann Bulson have set an aggressive goal—to raise \$5,000 each for Cure Alzheimer's Fund by the end of April. And best of all, 100 percent of the money raised will go directly toward Alzheimer's research, which will bring the organization one step closer to a cure.

We thank Anna, Pam and Peter and Ann for their drive and their commitment to our cause and wish them all the best on their marathon in Boston this April. ■