



Untangling Tau

Seeking a Unified Understanding of Alzheimer's

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tau studies promise to

help create a more unified

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molecular disease process

characterizing Alzheimer's.

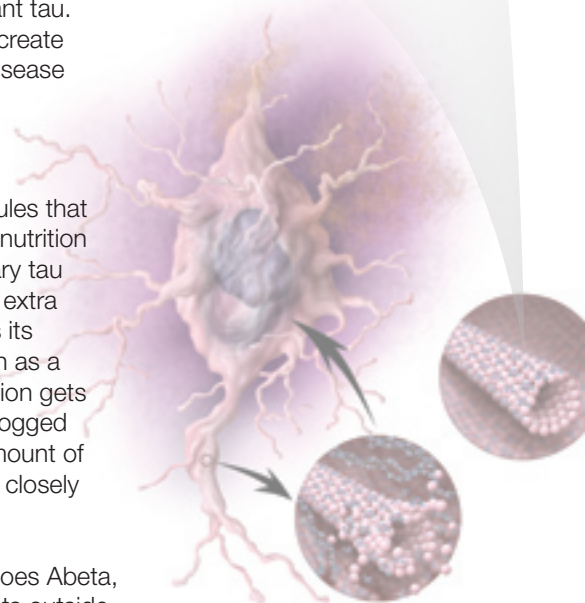
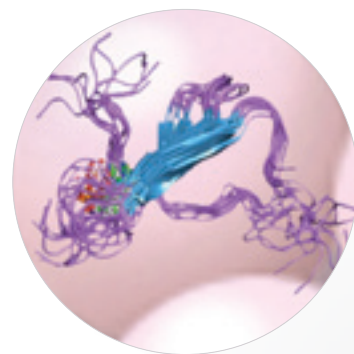
Alzheimer's research for many years has been dominated by a focus on Abeta "plaques," a focus that largely has overlooked the other infamous hallmark of the disease—the tau-based neurofibrillary "tangles." The research world recently has broadened its scope to include significant research into tau.

Cure Alzheimer's Fund is actively supporting this diversification by funding two tau-based projects: University of Pennsylvania researcher Virginia Lee's effort to identify antibodies that could neutralize aberrant tau, and a separate attempt by Brigham & Women's Hospital's Dennis Selkoe and Dominic Walsh to better understand how Abeta triggers the formation of aberrant tau. Together, these and other tau studies promise to help create a more unified understanding of the entire molecular disease process characterizing Alzheimer's.

Why tau matters

The tau protein is an essential component of microtubules that run through each neuron like train tracks, transporting nutrition and other vital materials. In Alzheimer's disease, ordinary tau becomes *hyperphosphorylated*—corrupted by several extra molecules of phosphorus. When that happens, it loses its structural integrity and folds into a twisted mess known as a neurofibrillary tangle. Subsequently, the transport function gets interrupted, and eventually the whole nerve cell gets clogged with unwelcome junk and dies. Studies indicate the amount of hyperphosphorylated tau in a patient's brain correlates closely to the severity of the disease.

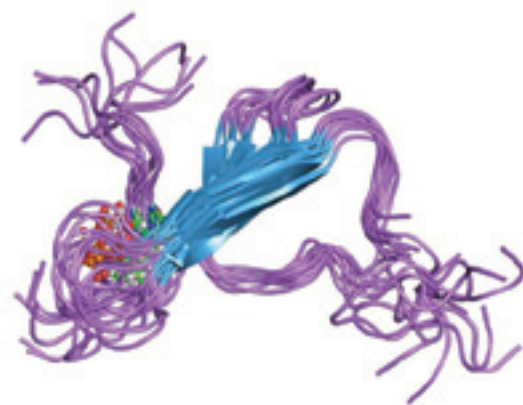
Two essential questions still vex researchers: 1. How does Abeta, which appears first in the Alzheimer's process and exists outside neurons, trigger the initial misfolding of tau proteins? 2. Once the first batch of aberrant tau is created, how does it spread from neuron to neuron? Answering these two questions may bring us much closer to treatment possibilities.



continued on page 2 »

“These interesting tau transmission studies will pave the way for passive immunotherapy for the treatment of Alzheimer’s disease.”

—Dr. Virginia M.-Y. Lee, director of the Center for Neurodegenerative Disease Research at the University of Pennsylvania



A tau pioneer

Dr. Virginia M.-Y. Lee, director of the Center for Neurodegenerative Disease Research at the University of Pennsylvania, is one of the true pioneers of tau research. Her seminal 1991 *Science* article established tau’s essential role in tangles, and she has gone on to receive many prestigious awards for her work. Dr. Lee’s current project for Cure Alzheimer’s Fund builds on her previous research establishing how the destructive form of tau can spread by “seeding,” or converting, ordinary and harmless forms of tau into the dangerous form. In a process that has been described as “prion-like,” the benign, unfolded, water-soluble form of tau becomes insoluble and filament-like when coming into contact with other destructive tau. A chain reaction process apparently helps spread this destructive form of tau from neuron to neuron. Dr. Lee’s work is taking us deeper and deeper inside this malignant conversion process, and she hopes to identify opportunities to stop it. “These interesting tau transmission studies will pave the way for passive immunotherapy for the treatment of Alzheimer’s disease,” she says.

From amyloid to tau

On the other end of the research spectrum is Dominic Walsh, a relative newcomer to tau. Walsh, whose Dublin-based work on Abeta is well-known to the research community, recently returned to Brigham and Women’s Hospital and Harvard Medical School, and teamed up with Brigham/ Harvard’s Dennis Selkoe (a well-established contributor to both amyloid and tau research). “We need to know much more about how Abeta and tau interact,” explains Walsh, who sees this

project as a “natural extension” of his Abeta research. “There’s good evidence that Abeta triggers pathologic changes in tau, but it’s not understood how this happens.”

Working downstream

The dominant research focus on Abeta is, in part, attributable to its early role in the disease. “I’ve always worked on Abeta, because I want to understand the disease as close to its start as possible,” says Walsh. “Ideally, you want to treat Alzheimer’s with anti-amyloid therapy to stop it before it begins. This is why it is essential to develop biomarkers that will identify individuals at the earliest stages of the disease.”

“But,” Walsh continues, “if we ever hope to help individuals who already have Alzheimer’s, then we need to target processes downstream of Abeta—this is what is driving our new interest in tau.”

Prior work suggests the noxious effects of Abeta depend on tau, and that Abeta can induce formation of neurofibrillary

tangles. But since tau is not ordinarily secreted from the neuron, understanding how misfolded tau spreads from one neuron to another is of vital importance. Current Walsh-Selkoe experiments are exploring the possibility that Abeta triggers an unnatural release of tau. “We hope that by learning more about this secretion process, it may be possible to develop agents that can prevent the secretion and spread of tau pathology,” Walsh says.

Takes time

The Walsh-Selkoe work will use different types of cells in different stages, including neurons produced from the skin of human Alzheimer’s patients. This is slow work, cautions Walsh. It takes time to generate and validate appropriate models. The whole process will take five years and will require long-term NIH funding. Cure Alzheimer’s Fund’s crucial role here is, as in so many other areas, to kick-start the idea and give it room to gain its own momentum. “Cure Alzheimer’s is the springboard,” says Walsh, “and we are very grateful.” ■

UNTANGLING TAU

Find Out More!

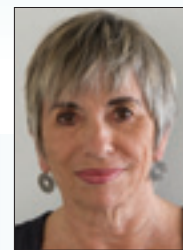
Don’t miss our next free webinar, Untangling Tau, on June 21.

Join special guest Brigham and Women’s Hospital’s Dominic Walsh and our host, *The Forgetting* author David Shenk, for an interactive discussion about the role of tau in Alzheimer’s on Thursday, June 21, at 2:30 p.m. EDT.

To register or for more information, visit www.curealz.org/webinar.

Looking at Alzheimer's Through a Different Lens

Dr. Cathy Greenblat hasn't always been a photographer, but she has always followed her heart. Before taking early retirement from Rutgers University, where she was a sociology professor for 35 years, she took a sabbatical in the spring of 2001 and made a decision that ultimately would change her life.



Dr. Cathy Greenblat

"I decided to work on a topic of social significance, and wanted to present my findings in a book that combined photographs and text in an equal partnership," explains Greenblat. "But focusing on Alzheimer's was the last thing on my mind." She had lost both her maternal grandparents to Alzheimer's and her mother was starting to show symptoms that were all too familiar. "I didn't understand the disease," says Greenblat. "I was frightened by it. And because I believed that my grandparents were no longer emotionally available, I stayed away from them more than I should have," explains Greenblat. "I responded with the kind of fear and ignorance that is so common with Alzheimer's."

Refocusing

In 2001, Greenblat decided to photograph the elderly for her sabbatical project. She was living in Southern California for a few months and a geriatric psychiatrist acquaintance recommended she photograph residents at Silverado Senior Living, a residential care community for people with Alzheimer's and related disorders. "I was too ashamed to tell her that I didn't want to photograph Alzheimer's patients," admits Greenblat. "So I decided to visit for a few hours and then explain it wasn't the place I was seeking."

When Greenblat got to the facility, what she saw surprised her. Silverado was known for being the best Alzheimer's care around, and Greenblat had never seen care like this. "They provide a stimulating environment instead of planting their patients in front of TVs and expecting nothing of them," she says. "Silverado treats its patients with dignity and respect, and as a result I saw people here who

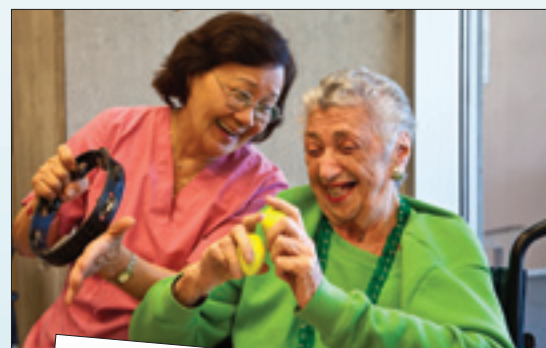
were very vibrant and alive, despite their illness. They sometimes had a "lost" look that many of us are familiar with in Alzheimer's patients, but the staff treated their patients like whole, valued people and re-engaged them with hugs, conversation, and a range of voluntary activities."

Greenblat spent the next seven weeks photographing there and by doing so, she felt she eventually could help change others' perceptions about what Alzheimer's patients are capable of. "We can't change the brains of people with Alzheimer's, but we can change our minds about their capacities, and then change how we treat them. Good care like that shown in my photos and discussed in my text improves mood, increases confidence, builds self-esteem, enhances interest in life, and contributes to declines in negativity and aggressiveness."

A different journey

When Greenblat's mother's symptoms started to get more severe, Greenblat had already faced her fears about Alzheimer's and knew what to do. "Although my mom passed away six years ago, she had much better care than she would have had because of what I learned through my experience photographing people with Alzheimer's."

Greenblat reached out for advice from professionals, the growing body of literature, and people who had dealt with or were dealing with the issues. She didn't try to go it alone. "Denial and fear often come from the fact that people think there is nothing you can do when a loved one is diagnosed, but that's not true. I constantly get messages



continued on page 4 »

FEATURED RESEARCHER

Sangram S. Sisodia, Ph.D.



Since the 12 members of Cure Alzheimer's Fund Research Consortium are the brains behind our organization's mission, we will be featuring one member in each issue of our quarterly report. These profiles will tell the story of each consortium member—their background, the research projects they're working on and why their research is important to finding a cure. First up is Dr. Sangram (Sam) Sisodia, director of the Department of Neurobiology at The University of Chicago and a leading expert on the cellular biology of proteins implicated in Alzheimer's disease.

The early years

Sangram Sisodia was born in India and came to the United States when he was 11 years old, after his father accepted a position teaching humanities and history at a small college in rural Colorado. "We basically moved to the middle of nowhere in the late '60s and were the darkest-skinned people around, except for the American Indians," explains Sisodia. He became "Sam" when the minister of his church asked if he could call him that since he couldn't pronounce Sangram. Sisodia has spoken English from day one and his parents have always been very Westernized, so the transition to life in the

United States wasn't as challenging as it might have been.

But when Sisodia's father changed jobs after a few years and moved the family to Newark, N.J., Sisodia had an eye-opening experience. "We moved into a racially diverse and tough inner-city neighborhood and I learned a lot of lessons quickly. I got mugged on a regular basis and learned how to fight my own battles," he says.

Educational path

After Sisodia graduated from high school, he attended the College of Wooster in Ohio, where he earned his B.S. in

chemistry. After that he attended the University of Denver, where he narrowed his focus to biochemistry. Next he did his doctoral work at the University of Georgia and then his post-doc work at Johns Hopkins University School of Medicine. There, he had an opportunity to join one of the premier clinical groups studying Alzheimer's disease, which he knew very little about at the time.

"I always wanted to learn about the brain because I believe it's the final frontier in science," says Sisodia. He collaborated with Don Price, a leading neurologist, who was a perfect match for Sisodia. Price's team didn't understand the mechanism of Alzheimer's disease beyond the pathology, and Sisodia understood the biological function of cells and how to test Price's hypotheses. "Don took me under his wing, and taught me about neuroscience and the brain and I taught him what I knew." Sisodia and Price worked together for many years, until 1998 when Sisodia went to The University of Chicago to chair the neurobiology department.

Cure Alzheimer's Fund

Sisodia met Rudy Tanzi, Ph.D., the chairman of Cure Alzheimer's Fund Research Consortium, in 1990 at a conference in Berlin. "When I first met Rudy, I had already

continued from previous page »

from people who say, 'I'm so glad I saw your photos,' or 'I wish I had seen your book earlier because it showed me what's possible for patients with Alzheimer's. It's much more than I realized.'"



Cure Alzheimer's Fund

At one of her photography reviews, Greenblat met a physician who told her, "you need to get in touch with my husband's aunt, Phyllis Rappaport," one of the co-founders of Cure Alzheimer's Fund. So Greenblat did. "That's how I first learned about the organization and their mission."

Greenblat will be showcasing some photos from her collection at the Cure Alzheimer's Fund Symposium in Boston on Oct. 10, 2012. "One day, there will be a cure, and Cure Alzheimer's Fund is focused on finding one," says Greenblat. "In the meantime, there is a lot we can do for those patients and families who are living with Alzheimer's to reduce their burdens and improve their quality of life."

Love, Loss, and Laughter

Greenblat's first photography book, *Alive with Alzheimer's*, came out in 2004 and her most recent book, *Love, Loss, and Laughter: Seeing Alzheimer's Differently*, came out in March 2012. She is the author of 14 other books and more than 100 published journal articles. Since 2001, Greenblat has traveled the world to meet people living with Alzheimer's and document their stories.

"There are so many people out there today who feel the way I once did—like they haven't done enough for their loved ones. But hopefully, I've paid back some of my debt through my work and helped people learn how they can improve their connections and contributions to their loved ones who are living with Alzheimer's or a related disorder." ■

For more information on Greenblat and her work, visit www.LoveLossandLaughter.com.

heard of him,” says Sisodia. “He already had a prolific career in the field and I figured he was a 55-year-old professor from Harvard. He thought I was a 60-year-old Indian guy because he used my protocols as a grad student. In fact, we were both in our early 30s and we immediately became the best of friends.” Both Sisodia and Tanzi were into sports. They both loved jazz. And as scientists, they both spoke the same language. When Cure Alzheimer’s Fund was founded in 2004, Tanzi asked Sisodia to come aboard.

Today, Sisodia refers to Tanzi as one leg of their triumvirate. “Rudy finds the Alzheimer’s genes, I try to understand how they work, and Steve Wagner, another member of the consortium, develops the Alzheimer’s drugs. Cure Alzheimer’s Fund takes a unique approach to finding a cure. Instead of going through the traditional funding channels, its researchers are able to develop a proposal for a specific Alzheimer’s project and present it to the Scientific Advisory Board. If approved, they receive a one-year grant for the project and have to complete their work within that timeframe. “There’s a lot of accountability and efficiency with this model,” explains Sisodia. “We’re approaching research in an expedited way that you just don’t see anywhere else.”

Alzheimer’s research

One project Sisodia and his staff have been working on is trying to understand the types of cells that are important in amyloid deposition in the brain. “If we understand the biology of these particular cell types, we might understand how to control them.” In the past, Cure Alzheimer’s Fund has supported Sisodia on projects that allow him and his team to study the birth of new neurons in the hippocampus, the part of the brain that creates new memories. “While I am grateful to Cure Alzheimer’s Fund for the funding they have provided, this work requires a lot of people and resources,” explains Sisodia. “If we had more funds, we could test more hypotheses to get to a cure more quickly.”

The importance of exercise

One of Sisodia’s greatest scientific breakthroughs was the discovery that exercise has an amazing ability to mitigate the development of Alzheimer’s disease plaque pathology by favorably changing gene activity in the brain. While these studies were performed in mice, there is now unequivocal evidence from studies in aging humans and patients with mild cognitive dementia that exercise provides substantial cognitive benefits and an

increase in the size of the hippocampus. “What’s more, when you exercise, more neurons are born in the hippocampus, which keeps your ability to make new memories at a higher level,” explains Sisodia.

He has always been active. He played soccer his entire life, but when he went to Hopkins, the soccer field was inconveniently located, so he switched to squash. Today, Sisodia is a nationally ranked squash player. His son, Nicholas, a senior at Dartmouth, is also one of the top players in the country. Sisodia’s daughter, Anisha, is a freshman at UC Santa Barbara.

These days, Sisodia can’t wait to go to work every day. “I know I’m going to learn something new each time. That’s what drives me—studying the science of the brain in order to stop this devastating disease.” Fortunately for Sisodia, none of his friends or family has been afflicted with Alzheimer’s.

Dr. Sisodia will be joining his “triumvirate” colleagues, Rudy Tanzi and Steve Wagner, at Cure Alzheimer’s Fund’s fall symposium on Oct. 10 in Boston. Please join us for what we know will be an enlightening and fascinating discussion. ■

CURE ALZHEIMER’S FUND HEROES

An Incredible Journey

22-year-old Bobby Zerwick from Bowers, Pa., set off to hike the Appalachian Trail on March 10 from Springer Mountain in northern Georgia. An avid hiker, Zerwick is aiming to complete his trek on Mount Katahdin in northern Maine this fall. He is hiking in honor of his grandmother and his girlfriend’s grandmother, who both died a few years ago from complications due to Alzheimer’s disease. To date, he has raised \$3,400 for Cure Alzheimer’s Fund.

“Alzheimer’s disease has affected my entire family. I was in 10th grade when my grandmother passed away,” says Zerwick. “It was sad because she couldn’t even remember who I was or who anybody was for that matter. I can only imagine what it would be like not recognizing the people I love.”

The Appalachian Trail runs through 14 states over more than 2,000 miles. It is not only physically grueling, it can be psychologically tortuous as well, and only 10 to 15 percent of people who set out on the trail complete it. While it took some convincing to get Zerwick’s parents to support him on his journey, in the end, his entire family was behind him. His biggest supporter is his girlfriend, Ashley Bragner. “She and my family will be driving to certain locations along the trail to meet me, and a few family members and friends will be hiking with me on parts of the trail as well.

“Hiking has always been a passion of mine and to complete the entire Appalachian Trail would be a dream come true. I have yet to realize what I am hoping to accomplish, but I’m doing what I can to help fight Alzheimer’s,” he says.

We receive regular updates from Zerwick, and last we heard he was in the Blue Ridge Mountains of Virginia. Cure Alzheimer’s Fund staff members hope to climb along with him when he reaches New England this summer. We wish him the best on his trek and thank him for dedication. To donate, please visit www.firstgiving.com/fundraiser/bobbyzerwick/hikingforacureontheappalachiantrail?fge=ask. ■

Bobby on the Blue Ridge Trail

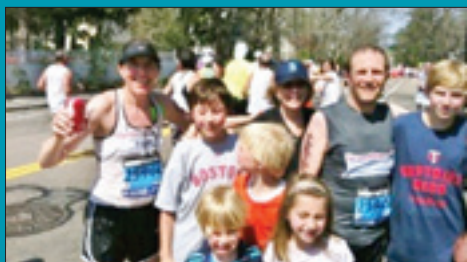


Beating the Heat

On one of the hottest marathon days on record, three committed individuals ran 26.2 miles for Cure Alzheimer's Fund—Peter and Ann Bulson of Wellesley, Mass., and Anna Shepard of Cape Cod, Mass. While they all had trained hard, nothing could prepare them for the blistering temperatures on Patriot's Day.

Still, these avid runners persevered, sticking together throughout the race and finishing within eight minutes of each other. "Basically, the only reason I finished," says Peter Bulson, "was because I was running for Cure Alzheimer's Fund. I couldn't let them down."

Together, along with the support of Pam Girouard of the Boston area who assisted in coordinating the group, they raised more than \$15,000 toward finding a cure. "We are so appreciative of their commitment and passion to make a difference," says Tim Armour, president and CEO, Cure Alzheimer's Fund. ■



Ann and Peter Bulson and their family on marathon day.



Running 4 Answers

On Saturday, April 28, co-founders Carolyn Mastrangelo and Barbara Geiger held the third annual Running 4 Answers fundraiser in Roseland and Essex Fells, N.J.—their most successful race to date. Each year, this fun run/walk not only brings people together to honor the memories of loved ones who have been afflicted with Alzheimer's disease, but it also raises money toward finding a cure.

This year, Cure Alzheimer's senior vice president, Mike Curren, attended the event along with 145 registered runners and 125 walkers. Together, they raised \$40,000 for Cure Alzheimer's Fund, bringing Running 4 Answers' three-year total to \$95,000.

"We are so appreciative of Mastrangelo and Geiger's commitment to our cause," says Tim Armour, president and CEO of Cure Alzheimer's Fund. "Each year, they continue to raise more and more money and reach more and more people. It's amazing what they've been able to accomplish."

For a list of winners and photos from the event, visit

www.running4answers.org/. ■



Friends and supporters on race day.



Carolyn Mastrangelo and Barbara Geiger, founders of Running 4 Answers.

Moving On

Rachel Weinstein joined Cure Alzheimer's Fund as a summer intern last year. When she returned to Brandeis University last fall for her senior year, Weinstein decided to stay with Cure Alzheimer's Fund as a part-time coordinator for social media marketing. As such, she has helped Cure Alzheimer's Fund reach out to audiences on Facebook, Twitter and YouTube. She also assisted on a variety of projects including marketing, fundraising, event planning and writing and editing content for the website. She graduated from Brandeis this spring with a B.A. in public health and plans to pursue a career in health care marketing and administration. We thank Rachel for all her help and wish her our very best. ■



Rachel Weinstein

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.**

Financial Update

	This Quarter	YTD*	Inception to date
Fundraising	\$120,963	\$1,043,732	\$24,435,791
Expenses paid for by the founders	\$207,037	\$487,145	\$5,036,978
Funded research	\$0	\$1,425,000	\$15,946,141

*These numbers as of May 24, 2012

Research Update

Research funded during the first quarter of 2012

Project	Researcher	Distribution Amount
The amyloid protein of diabetes and the Abeta protein of Alzheimer's are antimicrobial peptides*	Robert Moir and Rudolph Tanzi	\$300,000

*Awarded in 1st Quarter, 2012

A Very Special Thank You

This spring a few of our major donors hosted fundraising events in their local areas across the country to raise awareness for Cure Alzheimer's Fund by bringing key researchers and supporters together:

Cathy Ingham held an event in Philadelphia on March 22 where 65 people joined David Shenk, author of the national bestseller *The Forgetting*, *Alzheimer's: Portrait of an Epidemic*, and Cure Alzheimer's Fund Research Consortium member Virginia M.-Y. Lee, Ph.D., M.B.A., to hear about the latest breakthroughs in Alzheimer's research. Ingham attended the Cure Alzheimer's Fund Symposium last fall and offered to host this event. Sadly, she lost her father to Alzheimer's disease in January.

Paul and Ann Bridges held a reception on April 9 in Naples, Fla., with approximately 60 attendees who heard presentations from Rudy Tanzi, Ph.D., Harvard Medical School/Massachusetts General Hospital and chairman of Cure Alzheimer's Fund Research Consortium, and Jeff Morby, co-founder of Cure Alzheimer's Fund.

Steve and Allyson Cook hosted an event in Houston on April 18, as 80 friends, family members and colleagues gathered for a presentation by David Shenk and Cure Alzheimer's Fund Consortium member Steve Wagner, Ph.D., from UC, San Diego.

Jeff and Jacqui Morby, two of the co-founders of Cure Alzheimer's Fund, hosted an event at Ocean Reef in Key Largo, Fla., on April 10. Both Jeff Morby and Rudy Tanzi presented.

"We are very grateful to all our hosts for their incredible effort and generosity," says Tim Armour, president and CEO, Cure Alzheimer's Fund. "We wouldn't be where we are today without their support." ■

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

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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
Virginia M.-Y. Lee, Ph.D., MBA, University of Pennsylvania
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Roberto Malinow, M.D., Ph.D., University of California, San Diego
Sangram S. Sisodia, Ph.D., University of Chicago
Thomas C. Südhof, M.D., Stanford University
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Steven L. Wagner, Ph.D., University of California, San Diego
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Get the Facts

Visit www.curealz.org/the-science 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. ■



Save the Date for Our Fall Symposium – Wednesday, Oct. 10

Taking Control of Alzheimer's Through Research – The Road Map to Therapies

On Wednesday, Oct. 10, from 4–5:30 p.m. at the Mandarin Oriental Hotel in Boston, leading researchers from the Cure Alzheimer's Fund Research Consortium, including Steve Wagner, Ph.D., Sangram S. Sisodia, Ph.D., and Chairman Rudy Tanzi, Ph.D., will gather to discuss the road map to therapies. David Shenk, author of the national bestseller *The Forgetting, Alzheimer's: Portrait of an Epidemic*, will moderate the event and questions will be encouraged from the audience. While the symposium is free, registration is required, so please go to <http://curealz.org/symposium> to sign up.

ON DISPLAY: *Love, Loss, and Laughter: Seeing Alzheimer's Differently*,
by Cathy Greenblat, Ph.D.

