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# MISSION CRITICAL: Save the Synapses

At its core, Alzheimer's is a disease that disrupts communications between neurons (nerve cells) in the brain, and ultimately kills those neurons. Cure Alzheimer's Fund has committed to understanding this destructive process as a necessary component to stopping the disease. To that end, it has recruited four of the world's top experts in the field: University of California, San Diego's Roberto Malinow, Stanford's Robert Malenka and Thomas Südhof, and Rick Huganir at Johns Hopkins.

The human brain contains 100 billion neurons, exchanging electrochemical signals with one another via 100 trillion connections called "synapses." All human thought and action depends on the health of these synaptic connections. The destruction of synapses correlates very closely with the progressive symptoms of Alzheimer's.

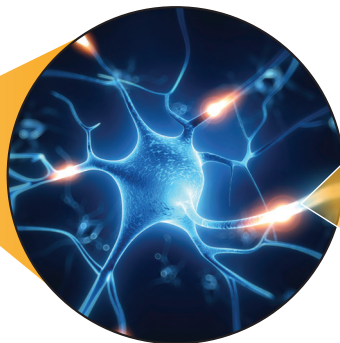
Growing evidence suggests that Abeta, one of the known culprits of Alzheimer's, affects synapses early in the disease. At the University of California, San Diego, Roberto Malinow is exploring precisely how Abeta disrupts the mechanism of synapses, and whether preventing this disruption would save neurons. He also is investigating whether some particular feature of neuronal activity spurs the production of Abeta to begin with. Malinow holds the Shiley-Marcos Endowed Chair in Alzheimer's Disease Research at UCSD.

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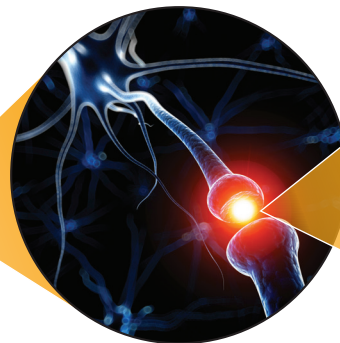
*This foundational work in understanding how synaptic signals affect—and are affected by—Abeta will no doubt bring us one step closer to our goal.*



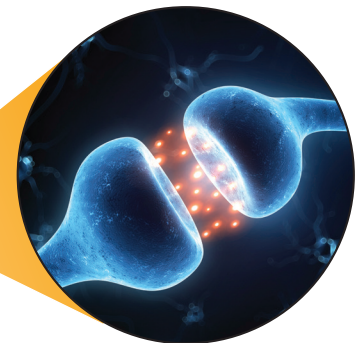
Brain



Neuron



Synapse



Normal electrochemical  
signal exchange

## FEATURED RESEARCHER

# Roberto Malinow, M.D., Ph.D.

*Professor, Section of Neurobiology, University of California, San Diego;  
Professor of Neurosciences; UCSD Shiley-Marcos Endowed Chair  
in Alzheimer's Disease Research in Honor of Dr. Leon Thal*



Roberto Malinow has always felt at home in a lab. He began his career as a summer research student and today has become a highly awarded and honored scientist and member of Cure Alzheimer's Fund's Research Consortium. He has lived in Milan, Zurich, Paris, London, Buenos Aires, Argentina, and all over the United States, bringing a truly global perspective to his work.

### Growing up

Dr. Malinow was born in Buenos Aires to a quiet, thoughtful physician-scientist and a loving homemaker. He grew up with an older sister and a younger brother with whom he is still close.

In 1963, Malinow's family moved to Portland, Ore., for his father's career. Malinow was 7 at the time and couldn't speak English. One of his earliest memories in America was at school. "An announcement was made over the loudspeaker and everyone started crying. I didn't know what was going on, but I cried, too." It was Nov. 22, 1963—the day John F. Kennedy was assassinated.

As a child, Malinow remembers his father always coming home being very excited about his work. "He would say things like, 'I'm thinking about this great experiment.' Then he would draw graphs and make predictions." That's how Malinow was introduced to the world of science.

### Education

After high school Malinow attended Reed College in Portland, Ore. "I studied math there. Even though I wasn't particularly good at it, I loved it—it was so clean and beautiful. I never got great grades nor did well on standardized exams. And I barely got into medical school at New York University." But that didn't dissuade him from pursuing his passions. While at medical school he attended a lecture by Rodolfo Llinas on synapses. After that, he was hooked on the topic.

Malinow earned his M.D. in 1984 and returned to the West Coast to attend graduate school at UC Berkeley. There he finished his Ph.D. in neurobiology in just two years. He served as a medical resident for a year and then received training as a post-doctorate fellow in the lab of Richard Tsien (at Yale and Stanford).

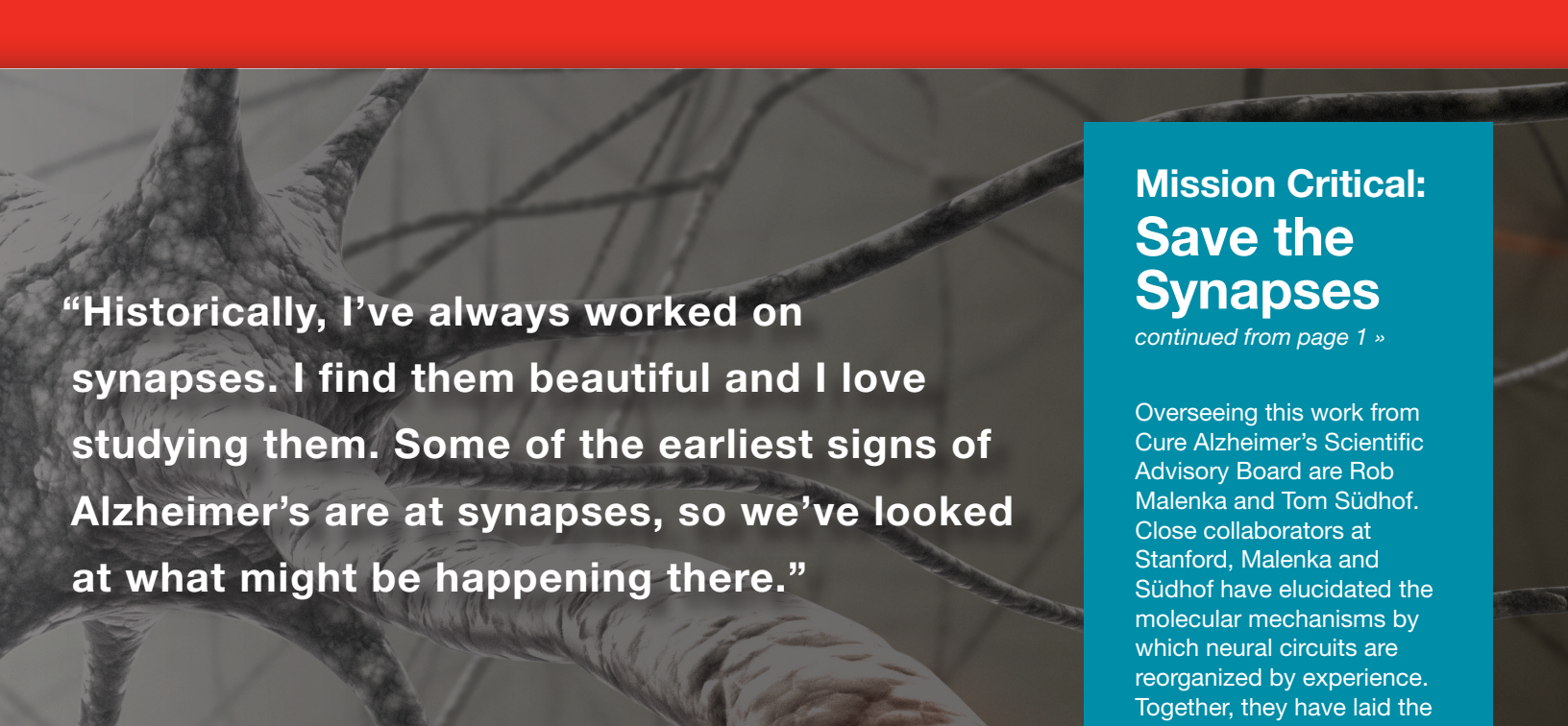
In 1994, Malinow started a lab at Cold Spring Harbor, Long Island, N.Y.

At CSHL he continued work he had started as a graduate student—trying to understand how synapses are modified during a model of learning called long-term potentiation (LTP), which refers to the persistent synaptic strengthening seen after a brief period of intense synaptic activity. "Through the visionary generosity of the institution, we were able to acquire and develop many new technologies," says Malinow.

"By combining electrophysiology, molecular biology and imaging, we contributed to the solution of a longstanding and hotly debated question: What changes at the synapse during LTP?," he says. "We identified an increase at the synapse of postsynaptic neurotransmitter receptors as a primary mechanism by which synapses are strengthened during LTP." Malinow and his colleagues found similar mechanisms underlying some forms of learning. Many of the tools and ideas they developed addressing this basic science question allowed them to start asking questions related to Alzheimer's disease.

### Alzheimer's

When Malinow's father was 84 (and still working), he was diagnosed with Alzheimer's disease. "I had been trained as a doctor so I knew about the disease, but I hadn't ever experienced it firsthand," says Malinow. "My mother, who was very gregarious and loving, took care of my



**“Historically, I’ve always worked on synapses. I find them beautiful and I love studying them. Some of the earliest signs of Alzheimer’s are at synapses, so we’ve looked at what might be happening there.”**

dying father on her own at home for four years and then with full-time help until he died three years later. She was pretty heroic.”

Malinow joined the Cure Alzheimer’s Fund Research Consortium in 2008 after running into colleague Sam Sisodia (another consortium member) at a Society for Neuroscience meeting. “Since I was new to the Alzheimer’s field, I bounced a lot of ideas off of him and he told me which ones were ridiculous and which ones were good. Then I met Rudy Tanzi through Sam,” says Malinow. “Cure Alzheimer’s Fund is a very lean and agile foundation. They’ve identified the best neuroscientists and they’re willing to take chances on individuals who have a track record of doing good work. Their support has been instrumental in my ability to carry on high-risk, high-payoff projects.”

### **Current work**

“Historically, I’ve always worked on synapses. I find them beautiful and I love studying them. Some of the earliest signs of Alzheimer’s are at synapses, so we’ve looked at what might be happening there,” says Malinow. For instance, when you learn, it is thought that some synapses get stronger and some weaker. “We think that Alzheimer’s hijacks the normal process of synaptic weakening (which has been rigorously elucidated) and makes some of the

synapses too weak.” Overall, Malinow is trying to understand how some of these normal processes go into overdrive and contribute to the disease. “Science can be very hard, and often you just have to plug away and persevere.”

### **Personal life**

When Malinow is not working he likes to play tennis. He’s been playing since he was 8, although he took a 20-year hiatus when he started college, which he says gave him an extra 20 years on his knees. “Tennis clears my mind and I like occasionally beating guys half my age. The ultimate scientist would have the creative artistry of tennis pro Roger Federer and the dogged perseverance of pro Rafael Nadal.”

He also loves to travel with his girlfriend, a cancer biologist. Malinow has a 23-year-old daughter he thinks the world of; she graduated with a degree in bioengineering from Georgia Tech and currently works at Gilead Sciences, a biotech company in San Diego.

“We’ve had lots of doctor/scientists in our family—my father, my sister, my daughter and me. But my brother runs a pizza parlor and he’s the wealthiest of all of us,” he jokes. Still, Malinow wouldn’t trade his career for anything. ■

## **Mission Critical: Save the Synapses**

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Overseeing this work from Cure Alzheimer’s Scientific Advisory Board are Rob Malenka and Tom Südhof. Close collaborators at Stanford, Malenka and Südhof have elucidated the molecular mechanisms by which neural circuits are reorganized by experience. Together, they have laid the groundwork for a much more sophisticated understanding of the mechanisms by which neurons communicate and of the adaptations in synaptic communication, which underlie all forms of normal and pathological behavior. They currently are applying that breadth of expertise to the challenge of synaptic loss in Alzheimer’s.

“The guiding philosophy of Cure Alzheimer’s Fund is that we are unlikely to stop a disease that we don’t first truly understand,” said Chairman Jeff Morby. “This foundational work in understanding how synaptic signals affect—and are affected by—Aβeta will no doubt bring us one step closer to our goal.” ■

### **Learn more at our FREE webinar**

Our next Alzstream™ webinar, featuring Roberto Malinow, M.D., Ph.D., University of California, San Diego, will be held on Wednesday, May 28, at 3 p.m. EDT. The webinar is free, but registration is required. Please sign up at <http://curealz.org/webinar>.

## Financial Update

	This Quarter	YTD*	Inception to Date
<b>Fundraising</b>	\$1,871,000	\$1,871,000	\$39,353,000
<b>Expenses paid for by the founders</b>	\$363,000	\$363,000	\$8,038,000
<b>Funded research</b>	\$422,000	\$422,000	\$23,085,000

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

## Research Update

Research funded during the first quarter of 2014

Project	Researcher	Distribution Amount
<b>Molecular Mechanisms of Synaptic Plasticity in the Hippocampus: A Path to Novel Therapies</b>	Robert C. Malenka, M.D., Ph.D. Stanford University	\$100,000.00
<b>The Role of PICALM in Vascular Clearance of Amyloid-b – Year 2</b>	Berislav V. Zlokovic, M.D., Ph.D. University of Southern California	\$250,000.00
<b>High-Throughput Multiplex Real-Time PCR for CSF-Biomarker and MicroRNA Profiling in AD</b>	Lars Bertram, M.D. Max-Planck-Gesellschaft	\$72,354.77
<b>Total Distributed to Research for Q1 2014</b>		<b>\$422,354.77</b>

**Help us fund research with the highest probability of preventing, slowing 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 \(287-3259\)](tel:877-CURE-ALZ) for further information.**

### 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.

## Cure Alzheimer's FUND

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[www.curealz.org](http://www.curealz.org)

Centre City Tower  
650 Smithfield St., Suite 2015  
Pittsburgh, PA 15222  
Telephone: 412-261-2785

### 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*  
*Sam Gandy, M.D., Ph.D., Icahn School of Medicine at Mount Sinai*  
*Charles Glabe, Ph.D., University of California, Irvine*  
*David Michael Holtzman, M.D., Washington University, St. Louis*  
*Richard L. Huganir, Ph.D., The Johns Hopkins University*  
*Virginia M.-Y. Lee, Ph.D., M.B.A., University of Pennsylvania*  
*Roberto Malinow, M.D., Ph.D., University of California, San Diego*  
*Eric E. Schadt, Ph.D., Icahn School of Medicine at Mount Sinai*  
*Sangram S. Sisodia, Ph.D., University of Chicago*  
*Robert Vassar, Ph.D., Northwestern University*  
*Steven L. Wagner, Ph.D., University of California, San Diego*  
*Berislav Zlokovic, M.D., Ph.D., University of Southern California*

### Scientific Advisory Board

Reviews individual grant proposals for science integrity and roadmap objectives. Provides advice and counsel to Cure Alzheimer's Fund regarding scientific soundness of the roadmap.

*John C. Mazziotta, M.D., Ph.D., Chairman, Scientific Advisory Board; UCLA*  
*Dennis Choi, M.D., Ph.D., Stony Brook University*  
*Caleb Finch, Ph.D., University of Southern California*  
*Paul Greengard, Ph.D., The Rockefeller University*  
*John S. Lazo, Ph.D., University of Virginia*  
*Robert C. Malenka, M.D., Ph.D., Stanford University*  
*William Mobley, M.D., Ph.D., University of California, San Diego*  
*Thomas C. Südhof, M.D., Stanford University*  
*Marc Tessier-Lavigne, Ph.D., The Rockefeller University*

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*“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



### ‘My Mother Has 4 Noses’

Three-and-a-half years ago, Jonatha Brooke, 46, moved her mother to New York City to live with her. “My mother was in the mid-stages of Alzheimer’s. I had no idea what I was getting into,” Jonatha admits. In her blog she wrote, “My mom had always been dramatic, but in her dementia she elevated her own particular brand of theater to a whole new level. Almost daily she would say, ‘BOOLIE! [Jonatha’s nickname] Are you getting this down? This is GOOD. We should make a PLAY out of it!’ ” So Jonatha did. She wrote a musical and an album called “My Mother Has 4 Noses,” which opened at The Duke on 42nd Street in February to rave reviews. Jonatha already has raised \$5,000 for Cure Alzheimer’s Fund with her Pledge Music campaign—a fan-funding project that also paid for her album and early workshops of the play. She continues to raise awareness for Cure Alzheimer’s Fund, which she calls “a no-nonsense organization that spends every penny they make on finding a cure.” Jonatha’s mother passed away in 2012, but thanks to “4 Noses,” her memory will live on forever. To find out more, visit <http://4noses.org/home>. ■



### Lifting for a Cure

On April 19, Greg Hodlin from Waltham, Mass., competed in the Revolution Powerlifting Syndicate (RPS) Vermont & New Hampshire Powerlifting State Championships.



Greg Hodlin

He wanted to do something to honor his grandpa, affectionately known as

“Crazy Legs,” who passed away from Alzheimer’s in 2010. “My grandpa struggled at the end of his life, so all the money raised will go towards fighting that disease,”



Pearl and “Crazy Legs” Hodlin.

says Greg, 24, who got into powerlifting about five years ago. While searching for an organization devoted to finding a cure, he discovered Cure Alzheimer’s Fund. “All donations go toward research, which is the most effective way to fight Alzheimer’s,” he says. So far, he’s raised more than \$550. To support Greg, visit <http://curealz.org/heroes/greg-hodlin>. ■

### Double Half-Marathon

In April, Rachel, 29, and Alastair Lawson, 27, ran their first half-marathon in Fort Collins, Colo., for a cause close to their hearts. “Both our families have been affected by Alzheimer’s,” says Alastair. “Our grandmas [Myrtle and Janet] and my Aunt Betty were all diagnosed within the last few years. But Cure Alzheimer’s Fund has a great chance to beat this horrible disease, since they hire the best scientists in the field to find a cure. It’s really hard to see a loved one not only lose their memories, but have their personalities gradually stolen away,” says Alastair. Their fundraising goal was \$400. ■



Alastair and Rachel Lawson.

### A Special Birthday

When Charline Kim of Los Angeles turned 27 on Feb. 28, 2014, she asked



Charline and her grandma.

her friends to make a donation to Cure Alzheimer’s Fund to support her grandma, who has the disease. Charline even donated \$100 as a birthday present to herself. “I love my grandma and she is one of the sweetest souls I’ve known,” Charline wrote on her fundraising page. “Alzheimer’s is a scary disease. I wish someone would find a cure so that other families wouldn’t have to go what we’re going through.” Charline asked her friends for \$10 or even \$5. “That’s like a Starbucks drink you can spare,” she says. “And every dollar is a step closer to a cure.” She raised \$1,565. ■

### 13.1 Miles for a Cure

Last year, in her early forties, Kim Chan ran her first half-marathon for her grandfather, whom she lost to Alzheimer’s



Kim Chan with her medal.

disease in 1991. This year she ran again, for the very same reason. “The disease affects so many people’s lives,” she says, “So I ran to find a cure. Hopefully I’ll be able to keep it up for many years.” Kim raised \$1,500 for the second half-marathon, in her hometown of Huntington Beach, Calif. ■

To find out more, visit [curealz.org/heroes](http://curealz.org/heroes).



Check out our Facebook page for our most recent posts, photos, videos and more!  
Go to [www.facebook.com/CureAlzheimers](http://www.facebook.com/CureAlzheimers).

## Florida Events Raise Awareness for Alzheimer's

Despite the progress being made on the Alzheimer's disease front, awareness continues to be a huge issue—not only of the disease itself, but of what causes it and how it progresses.

In January, Cure Alzheimer's Fund sponsored two events for the public to help provide a better understanding of the disease. The Lyric Theatre in Stuart, Fla., presented two free screenings of "The Genius of Marian," an intimate portrayal of a family's experience with Alzheimer's, which was featured at the 2013 Tribeca Film Festival. Each time, the movie was followed by a Q&A session with Phyllis

Rappaport, co-founder of CAF, and David Shenk, author of *The Forgetting: Alzheimer's: Portrait of an Epidemic*.

The second event was also in January and was held at Willoughby Golf Club. CAF Research Consortium Chairman Rudy Tanzi, Ph.D., spoke about the disease at a luncheon, which was followed by a lively Q&A. It was a full house with 120 attendees and the questions continued long after the event was over.

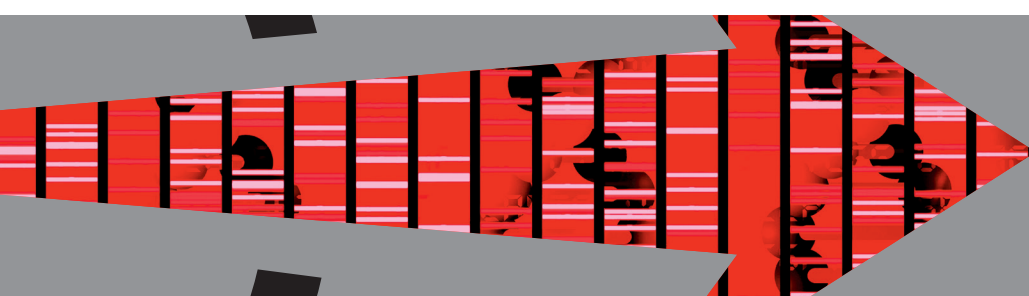
Rappaport is a resident of Stuart, member of Willoughby Golf Club and friend of the Lyric. She played a key role in organizing both events. ■



*L to R: Phyllis Rappaport, John Loesser, executive director of The Lyric Theatre, David Shenk and Kia Fontaine Hamill, assistant executive director of the theatre.*



*L to R: Jerry and Phyllis Rappaport, Allan Mostoff, co-chair of Willoughby Wellness Luncheon, Dr. Rudy Tanzi, Sally Rosenfield and Neil Fitzgerald, chair of Willoughby Wellness Day.*



**Save the Date**  
**4th Annual Symposium**  
**Boston • Oct. 15, 2014**