

Why Should You Care About Alzheimer's Research?

An update from Cure Alzheimer's Fund Founders

Dear Friends,

Why should you care about Alzheimer's research?

Currently, for every dollar spent on Alzheimer's care, only a penny is spent working toward a cure. This is a bad equation for a disease estimated to cost well over \$100 billion in care (Medicare and Medicaid alone) in 2009.

Cure Alzheimer's Fund focuses on research that is speed-driven, results-oriented and innovative to stop a disease that will strike half of us older than age 85. More than 2,500 of you have joined us in making contributions to research that have a significant track record of success.

By addressing the problem at its root and finding major causes of the disease, we are accelerating the development of effective therapies.

We leverage contributions to research.

(see article on the last page)

Cure Alzheimer's Fund has invested relatively small amounts of high-risk seed money in innovative ideas to understand Alzheimer's pathology. These investments have paid off handsomely in "proof of concept" work that has provided data to win much larger federal grants for sustained investigations.

Our strategy and profile are unique.

- Our world-renowned researchers carefully developed a Research Roadmap that identifies the most expeditious route to a cure.
- All donated funds go directly to research. We have no endowment; our overhead costs are paid for by the founders.
- We insist that findings from our research be made available to other researchers as soon as possible. We take no intellectual property rights to our researchers' work.



"By targeting research now, we have a chance to stop this disease."

*Cure Alzheimer's Fund Co-Founders (l to r)
Jeff Morby, Jacqui Morby, Phyllis Rappaport, and Henry McCance*

Our funded research is cure-driven, based on the latest findings from Alzheimer's genetics and designed to collapse dramatically the time required to develop effective treatments and preventions.

- Cure Alzheimer's Fund supported 19 researchers at 14 organizations working on 28 projects.
- One set of investigators has focused on better understanding aggregates of Abeta or "oligimers," a key initial "actor" in Alzheimer's pathology that is thought to be toxic to the brain's neuronal synapses.
- Another is looking more closely at synaptic activity in particular.
- A third group is exploring certain enzymes that help produce Abeta to understand how to regulate that production for a more healthy brain.
- A fourth effort is under way to understand how Dimebon, a new drug in test trials, actually works in the face of contradictory early data.

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Update from the Founders

continued from front cover »

- And, our researchers are in the process of analyzing the more than 100 new Alzheimer's candidate genes identified in our Alzheimer's Genome Project™ to identify priorities for focused efforts to understand the deleterious actions of such genes and block those actions.

We have leading researchers following a Roadmap to a Cure.

- Cure Alzheimer's Fund is the only research organization with a real plan to end Alzheimer's disease—we call it our Roadmap to a Cure. By addressing the problem at its root and finding major causes of the disease, we are accelerating the development of effective therapies.
- Our research consortium recently held its annual meeting in Chicago, at which we laid out an aggressive strategy for the next year, exploring some of the more pressing questions that linger in Alzheimer's pathology. Funded projects in our future include: exploring the mechanism and structure of APOE4, the gene variant responsible for approximately 50 percent of late-onset Alzheimer's; understanding the crucial link between the Aβ peptide and the Tau protein that is a major component of tangles, the signature structural identifier of the disease; and creating a new mouse model for research that more closely approximates the natural biological context for AD pathology.

We hope you'll join with us to find the cure. Donations to Cure Alzheimer's Fund have paid off, and every new dollar leads us closer to understanding and eliminating Alzheimer's. If you have made a gift, we thank you for your continued support. If you haven't, please consider making a gift today to help end Alzheimer's in our lifetimes.

With best regards,

Henry McCance, Jeff and Jacqui Morby and Phyllis Rappaport

Study Shows Sleep Loss Leads to Increase in Alzheimer's

Chronic sleep deprivation in mice with Alzheimer's disease-type changes makes Alzheimer's brain plaques appear earlier and more often, researchers led by Cure Alzheimer's Fund's Dr. David M. Holtzman at Washington University School of Medicine in St. Louis reported in *Science Express*. The study was funded in part by Cure Alzheimer's Fund.

They also found that orexin, a protein that helps regulate the sleep cycle, appears to be directly involved in the increase. Neurodegenerative disorders like Alzheimer's disease and Parkinson's disease often disrupt sleep. The new findings are some of the first indications that sleep loss could play a role in the genesis of such disorders.

"Orexin or compounds it interacts with may become new drug targets for treatment of Alzheimer's disease," says senior author Holtzman, the Andrew and Gretchen Jones Professor and chair of the Department of Neurology at the School of Medicine, and neurologist-in-chief at Barnes-Jewish Hospital. "The results also suggest that we may need to prioritize treating sleep disorders not only for their many acute effects, but also for potential long-term impacts on brain health."

Holtzman's laboratory uses a technique called *in vivo* microdialysis to monitor levels of amyloid beta in the brains of mice genetically engineered as a model

of Alzheimer's disease. Amyloid beta is a protein fragment that is the principal component of Alzheimer's plaques.

Jae-Eun Kang, Ph.D., a post-doctoral fellow in Holtzman's lab, noticed that brain amyloid beta levels in mice rose and fell in association with sleep and wakefulness, increasing in the night, when mice are mostly awake, and decreasing during the day, when they are mostly asleep.

A separate study of amyloid beta levels in human cerebrospinal fluid led by Randall Bateman, M.D., assistant professor of neurology and a neurologist at Barnes-Jewish Hospital, also showed that amyloid beta levels were generally higher when subjects were awake and lower when they slept.

To confirm the link, Kang learned to use electroencephalography (EEG) on the mice at the Sleep and Circadian Neurobiology Laboratory at Stanford University with researchers Seiji Nishino, M.D., Ph.D., and Nobuhiro Fujiki, M.D., Ph.D. The EEG readings let researchers more definitively determine when mice were asleep or awake and validated the connection: Mice that stayed awake longer had higher amyloid beta levels.

"This makes sense in light of an earlier study in our lab where John Cirrito, Ph.D., showed that increases in synaptic activity resulted in increased levels of amyloid beta," Holtzman notes. "The brain's synapses may generally be more active when we're awake."

Depriving the mice of sleep caused a 25 percent increase in amyloid beta levels. Levels were lower when mice were allowed to sleep. Blocking a hormone previously linked to stress and amyloid beta production

"The results also suggest that we may need to prioritize treating sleep disorders not only for their many acute effects, but also for potential long-term impacts on brain health."

inked Plaques



had no effect on these changes, suggesting they weren't caused by the stress of sleep deprivation, according to Holtzman.

Researchers elsewhere had linked mutations in orexin to narcolepsy, a disorder characterized by excessive daytime sleepiness. The brain has two kinds of receptors for orexin, which also is associated with regulation of feeding behavior.

When Holtzman's group injected orexin into the brains of the mice, mice stayed awake longer and amyloid beta levels increased. When researchers used a drug called almorexant to block both orexin receptors, amyloid beta levels were significantly lower and animals were awake less.

Miranda M. Lim, M.D., Ph.D., a neurology resident and post-doctoral researcher in Holtzman's lab, performed long-term behavioral experiments with the mice. She found that three weeks of chronic sleep deprivation accelerated amyloid plaque deposition in the brain. In contrast, when mice were given almorexant for two months, plaque deposition significantly decreased, dropping by more than 80 percent in some brain regions.

"This suggests the possibility that a treatment like this could be tested to see if it could delay the onset of Alzheimer's disease," says Holtzman.

Holtzman notes that not only does the risk of Alzheimer's increase with age, the sleep/wake cycle also starts to break down, with older adults progressively getting less and less sleep. Investigators are considering epidemiological studies of whether chronic sleep loss in young and middle-aged adults increases risk of Alzheimer's disease later in life.

Holtzman also plans to learn more of the molecular details of how orexin affects amyloid beta.

"We would like to know if there are ways to alter orexin signaling and its effects on amyloid beta without necessarily modifying sleep," he says.

Additional studies will address the questions of whether increased amyloid beta during wakefulness is connected to increased synaptic activity and whether some aspect of sleep lowers amyloid beta levels independent of synaptic activity. ■

Running 4 Answers to Raise Money for Cure Alzheimer's Fund

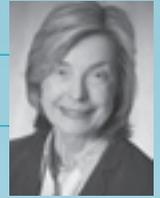
Join the Race on April 10, 2010!



"Running 4 Answers" is a 4-mile race planned for April 10, 2010 that will run through scenic Roseland and Essex Fells, NJ. All profits from this inaugural race will benefit Cure Alzheimer's Fund to support research into the causes of Alzheimer's Disease. The title symbolizes both a growing population's need for answers and the sadness that surrounds friends and family who are left without answers from loved ones who suffer from this devastating illness.

For one of the race organizers, Carolyn Mastrangelo, this cause is deeply personal. Carolyn's mother has suffered from early onset Alzheimer's for over 10 years. A personal trainer and a runner, Carolyn wanted to take her love of running and apply it to raising funds and awareness of the disease. If you would like to be a race sponsor, make a donation, become a volunteer or run in "Running 4 Answers" please contact Carolyn Mastrangelo at pcimast@comcast.net or **973-896-9263**.

Cure Alzheimer's Fund Founder Jacqui Morby Named Distinguished Daughter of Pennsylvania



Jacqui Morby

Gov. Edward G. Rendell and First Lady Judge Marjorie O. Rendell recognized the accomplishments of eight Distinguished Daughters of Pennsylvania and praised their contributions to a variety of fields. One of Cure Alzheimer's Fund's founders, Jacqui Morby, was among the eight honorees.

The Distinguished Daughters of Pennsylvania awards began in 1949 as a way to recognize influential women for their leadership, distinguished service and contributions to the commonwealth of Pennsylvania through their professional and/or volunteer service.

"This year's Distinguished Daughters have done extraordinary work in many different capacities," said Gov. Rendell. "It is a privilege to honor the dedication and commitment of these extraordinary women," said Judge Rendell.

Jacqui Morby was chosen because she is an innovator in the worlds of business and philanthropy. In 1988, Morby moved to Pittsburgh to open an office for TA Associates, a Boston-based private equity firm. In 2004, Morby co-founded Cure Alzheimer's Fund, which garnered *Time* magazine and CNN's designation in 2008 as one of the "Top 10 Medical Breakthroughs" in the world for its Alzheimer's Genome Project™. A world traveler, Jacqui chairs the board of Population Action International. ■

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

Rudolph E. Tanzi, Ph.D., Chairman, Research Consortium, Harvard Medical School/ Massachusetts General Hospital
Sam Gandy, M.D., Ph.D., Mount Sinai School of Medicine
Charles Glabe, Ph.D., University of California at Irvine
David Michael Holtzman, M.D., Washington University, St. Louis
M. Ilyas Kamboh, Ph.D., University of Pittsburgh
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Roberto Malinow, Ph.D., University of California, San Diego
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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.

Financial Update

| | This Quarter | This Year | Inception to date |
|--|--------------|-------------|-------------------|
| Fundraising | \$952,000 | \$1,266,000 | \$12,932,000 |
| Expenses Paid for by the Founders | \$118,000 | \$547,000 | \$2,411,000 |
| Funded Research | \$800,000 | \$2,388,000 | \$9,574,000 |

These numbers as of December 1, 2009.

Research Update

Research funded during the fourth quarter of 2009.

| Project | Researcher | Distribution Amount |
|--|--|---------------------|
| Rescue of Synapses in Mouse Models Abeta has been shown to lead to a loss of synaptic receptors, synaptic depression and removal of dendrite spines — all leading to malfunction of the neuronal synapses so critical to communication within the brain. This research asks whether this loss can be prevented by blocking the toxic Abeta from contact with the synaptic receptors. | Dr. Roberto Malinow, University of California, San Diego | \$100,000 |
| Continuation of Alzheimer's Genome Project (AGP) This time last year, the AGP identified approximately 100 candidate genes that affect risk for Alzheimers. The next steps of the AGP involve prioritizing genes involved with biological pathways that are the most amenable to drug treatment. | Dr. Rudy Tanzi, Massachusetts General Hospital | \$600,000 |
| Tau Microdialysis This research involves the use of a novel microdialysis technique to study the Tau protein's role in Alzheimer's pathology. | Dr. David Holtzman, Washington University, St. Louis | \$100,000 |

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

Donations can be made through our website www.curealzfund.org 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.



Elaine Engleberg



John McKiernan



Robert Moniz



Bess Demopoulos



Fred Hauswirth

Cure Alzheimer's Fund received gifts in honor or in memory of the following in 2009:

- | | | | | | | |
|-----------------------|------------------------|---|---------------------------------------|------------------------|-------------------------------|---------------------|
| Alda Lazaro's mother | Dodson, Milton | Helsley, Alma | Lizza, Wilbur | Mrs. Sokolowski | Sanders, Helen | Voorhees, Betty Lou |
| Anderson, Nadine | Dokania, Laxmi Narayan | Housinger, Dorothy | Lubrit, Harry | Mueller, Ann | Schleppegrell, Dorothy | Wada, Carol |
| Angeloty, Richard | Donahue, Bernard | Jackson, Gene | Malone, Sally | Nieland-Fisher, Nancy | Schmidt, Juanita | Wagner, Dorothy |
| Armour, June | Duca, Eugene | Johnson, Danielle and Alexander Schefer | Marrujo, Fernando | Noel, Caroline | Schneider, Joan | Williams, Michael |
| Armour, Wendy | Duke, Paul | Johnson, Lloyd | Martinez, Cleotilde | Nymoen, Richard | Schultz, Ralph | Wittmeyer, Doris |
| Bailey, Veryl | Engelberg, Elaine | Jordan, Betty | Masonovich, John | O'Connor, Richard | Schumann, Alex | Wolff, Esther |
| Baldasare, Mary | Feinberg, Myron | Judge, John | Matty, John | O'Neal, Martha | Scott, Joshua | Worthy, Lois |
| Battistin, Giovanni | Fetters, Julia | Kaplan, Wendy | Mazur, Mary | Orr, Richard | Shelton, Eva | Yaw, William |
| Bernot, Maureen | Fiegl, Frank | Karolkiewicz, Henry | McCance, Allison Jennings | Osborne, Barbara M. | Shows, Rada | |
| Blau, Molly | Fine, Barbara | Kenny, John | McCance, Ellen and Patrick Pinschmidt | Osborne, Eleanor | Shriner, Betty | |
| Boss, Dianne | Fisher, Lou | Kincaid, Geraldine | McCance, Henry | Patty Johnson's mother | Sims, Billie | |
| Boyle, Mary | Gammon, Butch | King, Florence Hults | McDonough, RoseMarie | Pereira, Rose | Stewart, Neil P. | |
| Brongel, Alice | Gilfix, Ben | Kirchgeessner, Reverend Robert | McGeath, Christina | Phelps, Robert | Stover, Helen | |
| Brown, Mary | Glenn, Blanche | Klimas, Serafina | Mellus, Beverly | Porter, Cecil | Team Paddlefish | |
| Buckley, Charley | Grandma Johnson | Krantz, Louiss | Mendelsohn, Jay | Prince, Mary Jo | Theodore Marolda's Mother | |
| Butchard, John F. Jr | Greenstein, Seymour | Krebsbach, Elizabeth | Meraz, Bill | Pugliese, Maria | Thornton, Ruby | |
| Campo, Dorothy | Griggs, William | Kromka, Frank | Meyer, Annette | Rappaport, Phyllis | Tragethon, Amy and Mark Riggs | |
| Cantrell, Betty Anne | Hackworth, Cecil | Kromka, Lola | Moniz, Robert | Reichert, John | Turpin, Mary | |
| Carmichael, Donald S. | Hale, Jane | LaCourse, Dave and Jo | Monosson, Rosalyn | Reinfeld, Hedy | Van Ness, Julia | |
| Chmiel, Pauline | Hans, Sarah | Leinss, Carol | Monterroso, Julio | Ritter, Walter | Velcich, Angela | |
| Chuda, Scott | Harrington, Donald F. | Lindstrom, Victoria | Morales, Virginia | Rizza, Peter | Vicksburg, Edith | |
| Cruz, Leslie | Harrold, Mark | Little, Hazel | Morby, Jacqui and Jeff | Robinson, Helen | Vicksman, Edith | |
| Daniel, Mrs. Ned | Hauswirth, Fred | | | Rose Marie and Albert | | |
| Demopoulos, Bess | Hayashi, Meriko | | | Rudzianski, Josephine | | |



Barbara M. Osborne



Roberto Malinow Joins Research Consortium

Roberto Malinow, Ph.D.
Professor of Neurosciences, UCSD
Shiley Chair in Alzheimer's Disease Research in Honor of Dr. Leon Thal

Dr. Malinow's research is directed toward understanding how the brain forms and stores memories. His laboratory examines how neuronal activity controls the strength of communication between neurons, at sites called synapses. Synapses are key sites affected by diseases of cognition. Synaptic plasticity, or the ability of the connection between neurons to vary, is thought to underlie the formation and storage of memories. It is thought that a detailed understanding of synaptic plasticity will identify critical steps that may be the targets of diseases such as Alzheimer's disease. Such an understanding eventually may lead to treatments that prevent the disease.

Cure Alzheimer's Fund Research Consortium is made up of leading Alzheimer's researchers who serve on a voluntary basis. The Consortium helps guide the Cure Alzheimer's Fund Research Roadmap and pursue research that will lead to a cure. ■

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Leveraging Donations is Working

Rob Moir and Guiseppina Tesco Awarded Prestigious Research Project Grants as a result of Cure Alzheimer's Fund start-up funding

A big win by Cure Alzheimer's Fund has come by investing small amounts of money in what some deem as more risky research. These research ideas often are very innovative and therefore not appealing to traditional funding sources.

However, Cure Alzheimer's Fund's entrepreneurial approach and ability to nimbly provide funding in an efficient manner allow us to pursue this potentially groundbreaking work. And it's paying off. We fund early-stage research, giving researchers the opportunity to better understand their research hypotheses and to gather preliminary results, setting the stage for them to apply for much larger government grants.

Two Cure Alzheimer's Fund researchers, Rob Moir of Massachusetts General Hospital and Guiseppina Tesco of the Department of Neuroscience at Tufts University School of Medicine, have accomplished exactly this. Dr. Moir's work is focused on the concept that Abeta, a

peptide shown to be a primary initiator of Alzheimer's pathology, is an antimicrobial peptide and part of the innate immune system. His early work on this subject, funded by Cure Alzheimer's Fund, just resulted in a research project grant (R01).

An RO1 is the original and historically oldest grant mechanism used by the National Institutes of Health. The R01 provides support for health-related research and development.

Dr. Tesco has done pioneering work in the relationship between traumatic brain injury and Alzheimer's. After her initial paper on the topic in the journal *Neuron* in 2007, Cure Alzheimer's Fund supported her continued pilot studies, leading to her recent award of two RO1 grants for major studies in this field. ■



Robert Moir



Guiseppina Tesco