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.

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.

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 preventsions.

• 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 “oligomers,” 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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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 Abeta 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

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.

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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...
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 pcmast@comcast.net or 973-896-9263.

Study Shows Sleep Loss Linked to Increase in Alzheimer’s 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.

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

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.

Jacqui Morby
### Financial Update

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These numbers as of December 1, 2009.

### Research Update

Research funded during the fourth quarter of 2009.

- **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**
  - **Distribution Amount:** $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**
  - **Distribution Amount:** $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**
  - **Distribution Amount:** $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](http://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.
Cure Alzheimer’s Fund received gifts in honor or in memory of the following in 2009:

Alda Lazaro’s mother
AngeloL, Richard
Armour, June
Armour, Wendy
Bailey, Veryl
Baldasare, Mary
Battiston, Giovanni
Bernot, Maureen
Blau, Molly
Boss, Diane
Boyle, Mary
Brongel, Alice
Brown, Mary
Buckley, Charley
Butchard, John F. Jr
Campo, Dorothy
Cantrell, Betty Anne
Carmichael, Donald S.
Chmiel, Pauline
Chuda, Scott
Cruz, Leslie
Daniel, Mrs. Ned
Demopoulos, Bess
Dotson, Milton
Dokania, Laxmi Narayan
Donahue, Bernard
Duke, Eugene
Engelberg, Elaine
Feinberg, Myron
Fetter, Julia
Fiegl, Frank
Fine, Barbara
Fisher, Lou
Gammom, Butch
Giff, Ben
Glenn, Blanche
Grandma Johnson
Greenstein, Seymour
Griggs, William
Hackworth, Cecil
Hale, Jane
Hans, Sarah
Harlington, Donald F.
Harold, Mark
Hauswirth, Fred
Hayashi, Merko
Helsley, Alma
Housing, Dorothy
Jackson, Gene
Johnson, Danielle and Alexander Schefer
Johnson, Lloyd
Jordan, Betty
Judge, John
Kaplan, Wendy
Karolinska, Henry
Kenny, John
Kincade, Geraldine
King, Florence Hills
Kirchhoffer, Reverend Robert
Klina, Seraphina
Kirz, Louis
Krebsbach, Elizabeth
Krumka, Frank
Kumaka, Lola
LaCourne, Dave and Jo
Laforce, Carol
Lindstrom, Victoria
Little, Hazel
Lizza, Wilbur
Lubrit, Harry
Malone, Sally
Marino, Fernando
Martinez, Cleofe
Masonov, John
Marchy, John
Maur, Mary
McCance, Allison Jennings
McCance, Ellen and Patrick Pinschmidt
McCance, Henry
McDonough, RoseMarie
McKernan, John F.
Megan, Christina
Melius, Beverly
Mendelsohn, Jay
Mera, Bill
Meyer, Arnette
Moniz, Robert
Monsson, Rosalyn
Monterosso, Julio
Morales, Virginia
Morby, Jacqui and Jeff
Mrs. Sokolowski
Mueller, Ann
Nieland-Fisher, Nancy
Noel, Caroline
Nymoen, Richard
O’Connor, Richard
O’Neal, Martha
Orr, Richard
Osborne, Barbara M.
Osborne, Eleanor
Patterson, Rose
Pheps, Robert
Porter, Cecil
Prince, Mary Jo
Pugliese, Maria
Rappaport, Phyllis
Reichert, John
Reinfeld, Hedy
Ritter, Walter
Rizu, Peter
Robinson, Helen
Rose Marie and Albert
Rubtianski, Josephine
Sanders, Helen
Schlepper, Dorothy
Schmidt, Janina
Schneider, Joan
Schultz, Ralph
Schumann, Alex
Scott, Joshua
Shelton, Eva
Shows, Rada
Shriner, Betty
Sims, Billie
Stewart, Neil P.
Stover, Helen
Team Paddlefish
Theodore Marolda’s Mother
Thornton, Ruby
Tragerthom, Amy
and Mark Riggs
Turpin, Mary
Van Ness, Julia
Vekich, Angela
Vicksburg, Edith
Vicksman, Edith
Voorhees, Betty Lou
Wada, Carol
Wagner, Dorothy
Williams, Michael
Wittmeyer, Doris
Wolff, Esther
Worthy, Lois
Yaw, William

Roberto Malinow Joins Research Consortium

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 Map and pursue research that will lead to a cure.
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 R01 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 R01 grants for major studies in this field. ■

Robert Moir

Guiseppina Tesco