Cure Alzheimer's FUND
targeting breakthrough research

The Search for New Ways to Treat Alzheimer's Disease

With the help of Cure Alzheimer's Fund, our group initiated an ambitious project to discover new drugs that reduce Aß levels.

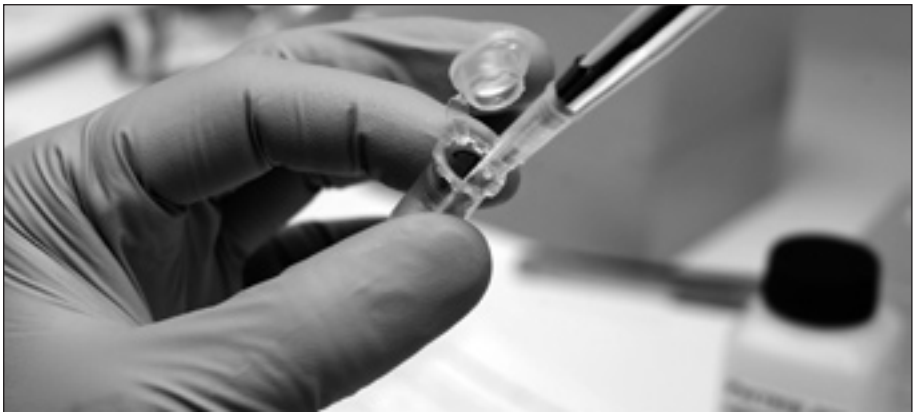
John R. Cirrito, Ph.D. and David M. Holtzman, M.D.
Microdialysis Core Facility, Department of Neurology
Hope Center for Neurological Diseases
Washington University—St. Louis, Missouri

A major contributing factor in Alzheimer's disease is the elevation of a protein called amyloid-ß or Aß(A-Beta). Since high levels of Aß play a role in the disease, many research groups around the world are developing therapies designed to lower the levels of this protein. With the help of Cure Alzheimer's Fund, our group initiated an ambitious project to discover new drugs that reduce Aß levels. Our approach is to test drugs in living animals (mice). While this process is time-consuming, it enables us to discover entirely new classes of compounds that traditional drug screening methods typically might overlook.

In Alzheimer's disease, Aß accumulates as amyloid plaques in the space between nerve cells. Several years ago, our group developed a technique called microdialysis to measure Aß within the space immediately adjacent to nerve cells in living mice. Microdialysis has been used in the study of the brain for more than 20 years to measure small molecules, however is rarely used for such large molecules as proteins and had never been used to detect Aß.

This procedure requires us to implant a small microdialysis probe in the brain of an anesthetized mouse. At the tip of this probe is a semi-permeable membrane that allows brain Aß to enter and be collected over time. We test the solution inside the probe every 60 minutes to determine what Aß levels were like inside the brain. Once the probe is implanted into the brain, the animal is allowed to wake up and is housed in a specialized cage that permits him to move around, eat and drink, all while Aß is being collected from the brain. Because the mouse is alive during our procedure, the changes in Aß levels are likely to be very relevant to both normal and diseased processes in the brain.

continued on page 2 »



The Search for New Ways to Treat Alzheimer's Disease

continued from front cover »

The microdialysis probe has several uses. The probe not only enables us to extract Aß from the brain, but also can be used to deliver drugs directly to the mouse brain in which Aß is being measured. By adding drugs to the inside of the probe we can both treat and assess the living brain. Each mouse receives several drugs over the course of a three to four day study. One drug is given to each mouse for several hours and then the drug is removed for several hours before the next drug is given. This enables us to test several drugs with each mouse, thus allowing us to use mice much more efficiently and to screen compounds more quickly.

Mice do not develop Alzheimer's disease exactly as humans do. Our mice however have been genetically engineered to contain the human type of Aß that accumulates in Alzheimer's disease. At young ages (up to four months old) these transgenic mice do not contain any signs of Alzheimer's-like changes. "Transgenic" just means that extra genes have been inserted into the mouse's DNA. At around six months of age however the transgenic mice develop amyloid plaques that are remarkably similar to plaques found in human Alzheimer's disease patients. While these types of mice are not perfect models of Alzheimer's disease, they have proven to be excellent models to study pathways that regulate levels of Aß in the brain over time.

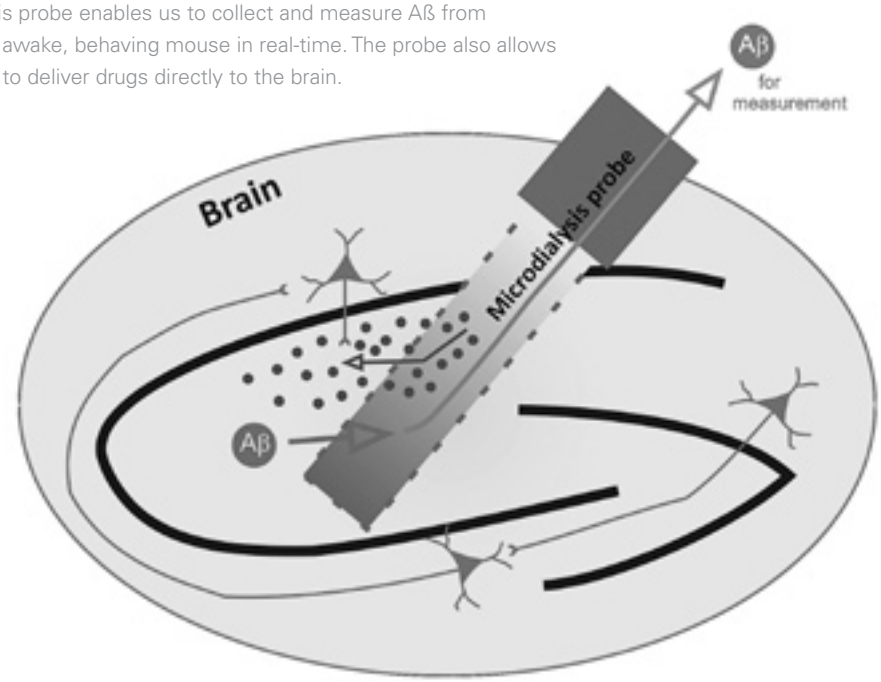
Because we can screen only a limited number of compounds within a several year period, we chose a library of compounds that are known to be "pharmacologically active." This means that each drug is known to affect a specific target in the body; however those targets are not necessarily related to Alzheimer's disease (as far as is known). By using this pharmacologically active library, we are testing pathways that in some cases have never been implicated in Alzheimer's disease.

Our group recently discovered that normal brain activity causes Aß to be produced. Over half of the drugs in this library affect brain activity which increases the likelihood of finding compounds that affect Aß levels. We are finding that some compounds have no effect on Aß levels while other compounds increase Aß levels. Most importantly, we already are finding compounds that lower Aß levels in mice. These compounds in particular have important therapeutic implications. This project is exciting for us because it discovers new ways to lower Aß which we hope will allow us to treat the disease in the future. We believe that this project is also giving us new insights into the fundamental processes that contribute to Alzheimer's disease.

There are few labs around the world performing this Aß microdialysis technique. Many groups however have expressed interest in using this technology to test their own set of compounds for their ability to reduce Aß. Consequently, we have opened our Microdialysis Core Facility to both academic and corporate groups that have novel compounds likely to influence Aß levels. We hope this service will help other groups develop drugs to combat Alzheimer's disease. We already have started working with several pharmaceutical companies as well as collaborating with academic labs.

One approach to drug discovery is to use a minimalistic experimental system to test many thousands of potential drugs that could affect a very specific therapeutic target. Many research groups are using these systems to target known pathways that produce or eliminate Aß, such as what are called secretase inhibitors or protease enhancers. In contrast, our approach uses the most complex system possible, an awake behaving mouse, in order to test a small number of diverse compounds that target pathways that have been largely untested in Alzheimer's disease. We believe our method offers an opportunity to identify entirely new targets for therapeutic intervention. Though the Microdialysis Core Facility is still young, we are already discovering new leads that we hope can be used to treat Alzheimer's disease in the future. ■

A microdialysis probe is implanted in the brain of a living mouse. This probe enables us to collect and measure Aß from an awake, behaving mouse in real-time. The probe also allows us to deliver drugs directly to the brain.



The Road Back to Everest: Memories are Everything

Alan Arnette wraps up his year long journey.

Dear Friends;
It is rare to have an opportunity to combine a personal passion with something critical to the future of your family. Over the past year, I was fortunate to combine my passion for mountain climbing with a global effort to raise awareness and money for Alzheimer's research.

The Road Back to Mount Everest: Memories are Everything was a year long journey that included climbing on five of the world's highest mountains plus a series of public events and mailings to raise money exclusively for the Cure Alzheimer's Fund.

It was an amazing year. I love the mountains and enjoyed each climb but it will always be the thoughtfulness and caring of so many people that touched me deeply. Students from four grade schools across the U.S. held fund raisers and donated almost $8,000 altogether. More simply gave from their hearts. I was contacted by hundreds of people telling me of their special stories of parents, grandparents or friends who have been touched by this horrible disease. A survey on my website showed almost 70% of the respondents had contact with Alzheimer's. The epidemic is real and the impact is staggering.

My journey spanned 12 months, five huge climbs, hundreds of emails, hundreds of calls, and almost 20 million hits on my website. I raised enough money to fund serious research at Cure Alzheimer's Fund. And I established more awareness of what this devastating disease does to caregivers, family members and the Alzheimer's patients themselves. What it is doing to my mom, Ida.

In terms of my adventures, I sometimes laugh that I have had three serious talks with myself standing at 27,300 feet on the side of a mountain. Should I go up? Should I go down? Some water? Go faster? Go slower? If only...

No I didn't summit Everest—for the third time. Yes I got to about the same spot. Yes it was tough to turn around. Yes, it is hard.

And it was wonderful.

What a ride. What a gift. What a life.

Thanks to all my supporters and the staff, board and researchers at Cure Alzheimer's Fund. Together we are making a difference.

Climb on!

Alan

Financial Report

How much money have we raised this year and what have we done with it?
Current Year, January 1, 2008 to June 30, 2008 (to nearest $1,000)

Funds raised from donors and founders: $1,176,000

- No funds from Cure Alzheimer's Fund may be used for overhead or indirect costs by receiving researchers or institutions.

Funds contributed by Founders for Operations: $ 284,000

- Founders contribute funds for all expenses of Cure Alzheimer's Fund; all non-founder contributions go directly to research.

Research Update

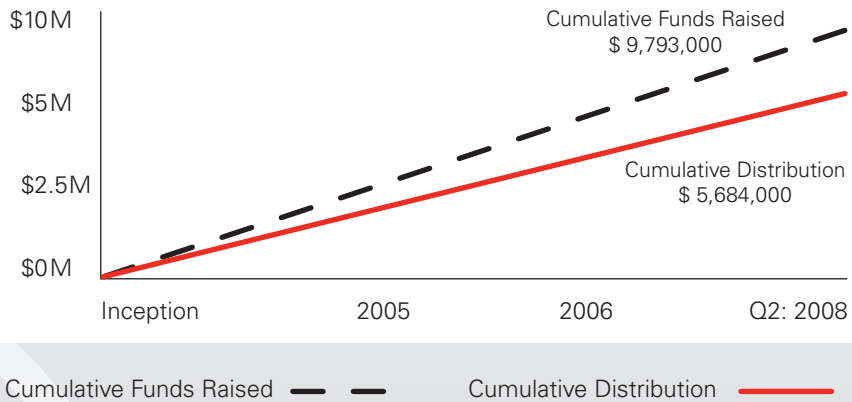
Funds distributed to research for 2008: $886,000

- See www.curealzfund.org/research for research detail.

Total research funded since inception - **$5,684,000** funding 18 projects at 8 major research labs

$2,598,000 in reserve for follow up projects based on results of the Alzheimer's Genome Project and some reserve for plausible "wild-card" paradigm changing discovery emerging from recent findings.

How much money have we raised and distributed since our inception?



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.

Cure Alzheimer's FUND

34 Washington Street, Suite 300
Wellesley Hills, Massachusetts 02481
Telephone: 877-CURE-ALZ (287-3259)
Fax: 781-658-2399
www.curealzfund.org

Mission Statement

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

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.

Newsletter Design by Winking Fish

BREAKING NEWS . . . BREAKING NEWS . . . BREAKING NEWS

Dr. Rudy Tanzi
to appear on
PBS
Sunday, August 3
9:00 PM ET

Dr. Rudy Tanzi Honored with the Kennedy Family Chair at Harvard, To Appear in Award Winning Documentary on PBS TV

Harvard Medical School and Massachusetts General Hospital have honored Dr. Rudy Tanzi, Professor of Neurology at Harvard Medical School and Director of the Genetic and Aging Research Unit at Massachusetts General Hospital, with the Kennedy Family Endowed Chair in Neurology.

Tanzi, Chair of Cure Alzheimer's Fund Research Consortium, will also appear on an expert panel in a newly produced 30-minute follow-up of a rebroadcast of *The Forgetting*, a 2004 Emmy award winning documentary about Alzheimer's disease. Dr. Tanzi and colleagues will provide up to the minute perspectives on current Alzheimer's research, emerging drug therapies and caregiving. Air time is scheduled for **9:00 PM Eastern Time** on **Sunday, August 3**. Check your local listings for details, consult *The Forgetting* website at **www.pbs.org/theforgetting**, or call us at Cure Alzheimer's Fund toll free at 877-CURE-ALZ (287-3259) for more details.

UNDERSTANDING ALZHEIMER'S

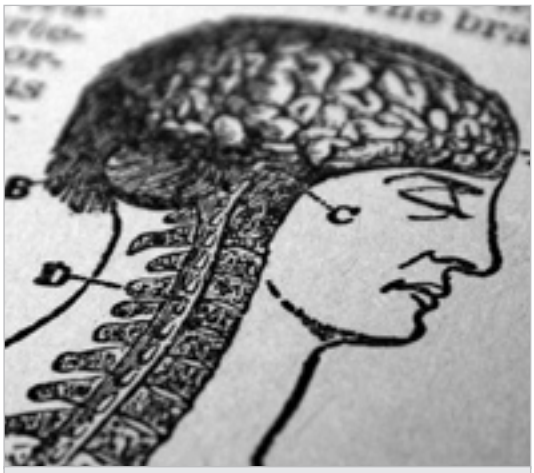
Get the Facts

Q Isn't Alzheimer 's disease just a part of getting old?

A No, Alzheimer's is not a normal part of the aging process.

All parts of our bodies change as we age and this includes the brain. As people get older, they notice slowed thinking and changes in memory. However the changes in memory associated with Alzheimer's are not part of normal aging. Alzheimer's disease is a progressive, irreversible and fatal brain disease. Overtime it causes nerve cells in the brain to shrink and die. The disease is divided into three stages: mild, moderate and severe. Early symptoms involve memory loss and cognitive deficits and the disease progresses to major personality changes and eventual loss of bodily functions. It is the seventh-leading cause of death in the United States.

Alzheimer's disease is a type of dementia and in fact is the most common cause of dementia but not all dementia is Alzheimer's. Dementia is not a disease itself, but a group of symptoms that characterize diseases and conditions. It is commonly defined as a decline in intellectual functioning that is severe enough to interfere with the ability to perform routine activities and social functioning. In addition to Alzheimer's, other types of dementia include Mild Cognitive Impairment (MCI), Vascular Dementia, Dementia with Lewy Bodies, Parkinson's disease, Creutzfeldt-Jakob disease and Huntington's disease.



Do you have questions about Alzheimer's disease?

Send them our way! Every quarter, we'll choose one question to answer and include in our Quarterly Report. Email questions to **kcutler@curealzfund.org**.

Resources for more information:

Watch a quick video: What is Alzheimer's Disease? www.aboutalz.org

Interesting articles:
Perform Google or internet search of the phrase "Alzheimer's vs. Normal Aging"

Patient and caregiver information and services: National Institute on Aging's Alzheimer's Disease Centers at major medical institutions across the country. www.nia.nih.gov/Alzheimer's/caregiving

Cure Alzheimer's FUND
34 Washington Street, Suite 300
Wellesley Hills, Massachusetts 02481

Presorted
First-Class Mail
U.S. Postage
PAID
Washington, DC
Permit No. 13

877-CURE-ALZ (287-3259) • www.curealzfund.org

Cure Alzheimer's Fund takes a *Sail!*

Phyllis Rappaport and Dr. Rudy Tanzi hosted the Cure Alzheimer's Fund yacht in Massachusett's General Hospital (MGH) America's Cup Experience. Seven other guests and a number of professional sailors joined Phyllis and Rudy for an afternoon of racing off Newport, RI. Cure Alzheimer's Fund participated in this unique event raising just under $50,000 for Cure Alzheimer's Fund research and as part of approximately $300,000 total for MGH.

The Onawa Crew supporting Cure Alzheimer's Fund at the MGH America's Cup Event in Newport, RI. ***From left to right:*** *Susan Zises Green, Bridget Baratta, Rudy Tanzi, Katherine Kirk, Phyllis Rappaport, Lois Watson, John Dragat, Mary Campbell, and Charles Nolfi*