



*Our funded
research, supported
by people like you,
has a disciplined
and focused
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Letter from the President

Cure Alzheimer's Fund's mission is to support research that will slow, stop or even reverse the effects of Alzheimer's disease. We think this is accomplished most expeditiously by understanding the causes of the disease, which then will accelerate the development of drugs to intervene effectively and efficiently in those causes rather than to treat just the symptoms.

Our primary contribution to understanding the cause is through exclusive support of the Alzheimer's Genome Project™ (AGP)—the identification of all the genes that contribute to risk for Alzheimer's disease. With each newly identified gene, new pathways are opened for the development of drugs designed to arrest the pathology of the disease.

Meanwhile, drugs are being developed on the basis of current and imperfect knowledge of Alzheimer's disease. These drugs essentially are palliative and do not address the root causes. While not getting to the ultimate control or eradication of the disease, they represent laudable efforts to relieve suffering and, in some cases, slow the progress of the disease.

In keeping with our intent to share information about the science behind Alzheimer's disease and the research we are supporting to end it, we also provide a broader view from time to time on other aspects of the battle against the disease. The following report includes a brief background and overview of the drug discovery process and an inside perspective from the chair of our Research Consortium, Dr. Rudy Tanzi, on the current Alzheimer's drugs on the market and drugs in the immediate pipeline.

Our funded research, supported by people like you, has a disciplined and focused strategy to ensure our investments are dedicated to the highest potential research projects. We think that strategy is showing great promise and that our breakthrough findings in 2008 will accelerate significantly the timeline from discovery to drug development.

Sincerely,
Tim Armour



Tim Armour

The Basics of Drug Discovery

The path from research discovery to drug development can be a long one. Current estimates target the time for an Alzheimer's drug to get to market at around 12 years. However, with new technological advances in such areas as genetics, we are optimistic that scientific opportunities have never been greater to reduce this timeline significantly. In his article, Dr. Tanzi highlights some of the promising developments on the immediate horizon. We've compiled the following background information on the drug development process in the United States to explain the progress of a drug to market.

Preclinical Studies Before pharmaceutical companies start clinical trials on a drug, they conduct extensive preclinical studies, which involve in vitro (i.e., test tube or laboratory) studies and trials on animal populations (in vivo). Wide-ranging dosages of the study drug are given to the animal subjects or to an in-vitro substrate in order

A Perspective on Current Alzheimer's Drug Development

By Dr. Rudolph Tanzi, Massachusetts General Hospital

Recent developments regarding drugs aimed at treating and preventing AD

This article focuses on drugs that most researchers currently consider as having the most promise to retard disease progression by curbing the accumulation of Abeta, and particularly, Abeta42, in the brain. It is commonly accepted that the peptide (small protein) amyloid beta or Abeta plays a key role in Alzheimer's disease pathology. Understanding exactly *how* it affects risk for Alzheimer's is one of the primary objectives for basic Alzheimer's research, including that supported by Cure Alzheimer's Fund.

The four best-established AD genes (APP, presenilins 1 and 2 and APOE) have taught us there are two basic ways to achieve this desired reduction of accumulation: either turn down production of Abeta42 in the brain, or promote the clearance of Abeta42 from the brain.

Promoting Abeta42 Clearance

These drugs are aimed at blocking Abeta aggregation into toxic forms and clearing Abeta out of the brain. There are four major trials in this category:

1. The amyloid vaccine (Wyeth and 15 other pharmaceutical companies)

In the vaccine approach, antibodies targeted against Abeta are injected intravenously into the bloodstream. The antibodies then bind to Abeta peptides that have been exported from the brain and do not let them re-enter the brain. In this manner, Abeta levels in the brain are progressively reduced.

This is a promising strategy, which is being pursued by at least 15 companies and is currently in large phase III trials (Wyeth-Elan). However, this approach requires the production and IV injection of anti-amyloid antibodies, which makes it more expensive than oral medicines and more difficult to administer. When one considers the demographics of AD, it is not clear whether the health care system will be able to support the vaccine as a long-term solution for the greater population given its cost.

Outlook: Excellent, but with a small caveat for safety issues based on some reports that accumulation of Abeta-antibody complex on blood vessels can cause microhemorrhages. That said, so far, this does not seem to be a significant enough event to curtail the trials, and patients are closely monitored for such events by brain imaging.

2. IV-IgG

The alternative to the vaccine is the "IV-IgG" approach, which attempts to achieve the same goal as the vaccine, but instead of injecting purified antibodies to Abeta that have been carefully prepared and purified in the lab, they inject the whole set of antibodies from donors' plasma, hoping that some will be naturally targeted to Abeta.

Outlook: Poor. This approach is not very selective or "clean," and it may end up more expensive than making specific Abeta antibodies in the lab.



3. Alzhemed (Neurochem)

Alzhemed (Neurochem) is a drug designed to bind to Abeta peptides and prevent them from sticking together. In this way, the drug is intended to block Abeta aggregates, particularly oligomers, which are toxic to neurons and their synapses. This trial failed to prove efficacy. It failed most likely because the drug was not sufficiently powerful enough to block Abeta aggregation. Neurochem now is seeking supplement status for the drug.

Outlook: Poor. From experience in the trials, this drug is not a good prospect for primary therapeutic intervention.

4. PBT2 (Prana Biotechnology)

PBT2 is a "metal protein attenuation compound" (MPAC) that strips zinc and copper from Abeta and thereby prevents Abeta from aggregating and from forming oligomers.

PBT2 has been shown to dramatically reduce Abeta aggregation and accumulation in transgenic AD mice. It also is able to block the detrimental effects of Abeta on neuronal synapses and neurotransmission. In phase II trials, the results of which were announced in March 2008, the trial was largely successful; after only

12 weeks of oral administration, PBT2 dramatically lowered Abeta42 levels (by an unprecedented 60 percent) in the cerebrospinal fluid, which is representative of brain Abeta42 levels. Moreover, the drug significantly improved cognition in the treated AD patients based on their performance on two neuropsychiatric

tests. Finally, the drug had no side effects or adverse events and was entirely well tolerated.

Prana is seeking funds or a big pharma partner to move on to a larger phase IIb (or phase III depending on the partner) clinical trial of PBT2. »

The Basics of Drug Discovery

« *continued from page 1*

to obtain preliminary efficacy, toxicity and pharmacokinetic information (basically what a drug does to a body) and to assist in deciding whether it is worthwhile to go ahead with further testing.

Phase 0 (a very small number of human subjects: 10–15)

Phase 0 is a recent designation for exploratory, first-in-human trials conducted in accordance with new FDA guidelines. Phase 0 trials also are known as human microdosing studies and are designed to speed up the development of promising drugs by establishing very early on whether the drug behaves in human subjects as was anticipated from preclinical studies. They enable go/no go decisions to be based on relevant human models instead of relying on animal data, which can be unpredictable and can vary between species.

Phase I (a small group of human subjects: 20–80) Phase I trials are the first “official” stage of testing in human subjects. Normally, a small group of healthy volunteers will be selected. This phase includes trials designed to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of a drug. These trials often are conducted in an inpatient clinic, where the subject can be observed by full-time staff. The goal is to determine what the drug’s most frequent side effects are and, often, how the drug is metabolized and excreted.

Phase II (the number of subjects ranges from a few dozen to about 300) Phase II studies begin if Phase I studies don’t reveal unacceptable toxicity. While the emphasis in Phase I is on safety, the emphasis in Phase II is on effectiveness. This phase aims to obtain preliminary data on whether the drug works in people who have a certain disease or condition. For controlled trials, patients receiving the drug are compared with similar

patients receiving a different treatment—usually a placebo or a different drug. Safety continues to be evaluated, and short-term side effects are studied. Typically, at the end of Phase II the FDA and sponsors try to come to an agreement on how the large-scale studies in Phase III should be done.

Phase III (The number of subjects usually ranges from several hundred to about 3,000 people) Phase III studies begin if evidence of effectiveness is shown in Phase II. These studies gather more information about safety and effectiveness, studying different populations and different dosages and using the drug in combination with other drugs. While not required in all cases, it is typically expected that there will be at least two successful Phase III trials, demonstrating a drug’s safety and efficacy, in order to obtain approval from the FDA.

Phase IV A Phase IV trial also is known as a Post-Marketing Surveillance Trial. Phase IV trials involve the safety surveillance and ongoing technical support of a drug after it receives permission to be sold. The safety surveillance is designed to detect any rare or long-term adverse effects over a much larger patient population and longer time period than was possible during the Phase I-III clinical trials. Harmful effects discovered by Phase IV trials may result in a drug being no longer sold or restricted to certain uses; a recent example is the drug Vioxx (rofecoxib). ■

For more information on Alzheimer’s drug development, visit www.alzforum.org, which provides a thorough, more technical explanation of drug discovery, and www.clinicaltrials.gov, which provides information on becoming involved in clinical trials.

A Perspective on Current Alzheimer's Drug Development

« continued from page 3

Outlook: Excellent. PBT2 has the added benefit that it is a drug that can be taken orally, while the vaccine approach would require more expensive IV injections and has greater safety concerns.

Blocking Abeta Production

This therapeutic approach is aimed at curbing Abeta production in the brain.

There are three major trials:

1. Gamma secretase inhibitors (Lilly)

The first class of oral drugs developed for this purpose were called "gamma-secretase inhibitors" (GSI). These drugs completely block gamma-secretase (presenilin) activity, which is necessary to produce Abeta from its precursor, APP. Unfortunately, this approach leads to side effects because gamma-secretase is needed to process many other proteins beyond the APP. For example, gamma-secretase is required to process the essential protein called Notch. When this event is blocked, the result can be skin cancer. The first GSI was developed by Bristol-Myers Squibb with Sibia, but it was discontinued for safety concerns. Currently, only Lilly has a GSI in clinical trials.

Outlook: Poor. It is difficult to imagine that a GSI can be used at doses that are both effective at blocking Abeta production and well tolerated, although Lilly is proceeding with their trial.

2. Flurizan (Myriad)

Another alternative is to use "gamma-secretase modulators" (GSM). This class of drugs targets gamma-secretase, but instead of inhibiting overall gamma-secretase enzyme activity, GSMs "modulate" gamma-secretase enzyme activity.

This class of drugs allows gamma-secretase to carry out its normal functions, including the production of the benign Abeta40, while selectively blocking gamma-secretase's ability to produce the more toxic form of Abeta, Abeta42. About 90 percent of the Abeta made in the brain is Abeta40; roughly 10 percent is Abeta42. Abeta42 is the more dangerous form of Abeta, as it is able to oligomerize (aggregate) more readily into neurotoxic forms. All but a handful of the early-onset, familial AD gene mutations in APP and the presenilins (which are a part of the gamma-secretase enzyme complex), have the same pathogenic effect—they increase the ratio of Abeta42:Abeta40 in the brain.

Ibuprofen and other nonsteroidal anti-inflammatories (NSAIDs) were reported to have GSM properties; i.e., they lower the Abeta42:Abeta40 ratio.

Clinical trials were run for NSAIDs. Ibuprofen failed, but Myriad developed an NSAID called "flurizan." We currently await phase III clinical trials on flurizan. Thus far, flurizan has not been impressive in improving cognition in AD patients. However, given the huge size of the phase III flurizan trial, it is possible that significant endpoints might be reached, and flurizan may head toward approval.

Outlook: Fair to Poor. While GSMs hold great promise, it is unlikely that flurizan will be a very effective AD drug because of its relatively low potency as a GSM. Flurizan has a chance of hitting the market, but it is unlikely to be as effective or any more effective than currently available AD drugs (Aricept, Exelon, Reminyl, Namenda).

3. Novel, more potent gamma-secretase modulators (Eisai)

Novel, more potent GSMs are being developed at the clinical and preclinical levels. Neurogenetics (now TorreyPines



Dr. Rudolph Tanzi,
Massachusetts General
Hospital

The opinions expressed here are of Dr. Tanzi's alone and do not reflect the official position of Cure Alzheimer's Fund.

Evaluation of drug effectiveness, formal approval or their chances for success are speculative and for general information only.

Therapeutics, TPTX), designed and carried out a drug screen to identify such drugs. This program was partnered with Eisai (the Japanese pharma that invented Aricept). Eisai carried out the same screen in parallel with TPTX while also licensing first rights to TPTX's GSMs.

Eisai then advanced one of their drugs (interestingly, with the same core structure as TPTX's lead drug) into clinical trials. After entering phase I clinical trials for safety, Eisai's trial was put on hold because, while the phase I trial was proceeding, some side effects were observed in the eyes of dogs after long-term treatment. Eisai now is working to get the hold on their GSM phase I trial lifted.

Meanwhile, at TPTX, the screening for novel GSMs has continued, leading to other classes of even more powerful GSMs, based on preclinical testing. Unfortunately, Eisai chose in March 2008 not to renew

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the partnership on GSMs with TPTX, as the company thinks there is a good chance of getting the hold lifted on its GSM and proceeding with its clinical trial.

Outlook: Excellent. Based on preclinical studies in AD transgenic mice, GSMs appear to be as effective as the vaccine, PBT2 and the ACAT inhibitors. Moreover, safe and potent GSMs feasibly can be developed in the clinic in relatively short order.

Summary

In summary, perhaps our best chance for effectively treating and preventing AD based on what we have learned from the four established AD genes is to target Abeta with a cocktail of therapies that, on one hand, safely and specifically lower the production of Abeta (ACAT inhibitors) and/or selectively and safely lower the production of Abeta42 (GSM), and on the other hand, enhance the clearance of Abeta

while also preventing its aggregation into neurotoxic oligomers (vaccine, PBT2).

Cure Alzheimer's Fund's Alzheimer's Genome Project™ is on track for announcing results by this summer. Through this project, researchers are discovering new AD genes that suggest novel therapeutic strategies for treating and preventing AD. ■

Off to Everest!

Mountain climber Alan Arnette is on his way to Nepal to attempt a south-side summit of the world's highest peak. This is the last segment of his yearlong journey climbing mountains around the world to raise money in support of Alzheimer's research through Cure Alzheimer's Fund.

Alan sends dispatches from his climbs, reporting every few days on his progress and travel experiences. This is sure to be an interesting year on Everest as the Chinese are planning to carry the Olympic torch to the summit. You can follow Alan's adventures and sign up for his e-mail dispatches by visiting his website, www.alanarnette.com.



Alan Arnette crossing a crevasse in the Khumbu Icefall



Alan Arnette crossing a crevasse in the Khumbu Icefall

“The award honors extraordinary current achievement and outstanding potential for future discoveries,” said Tim Armour, President and CEO, Cure Alzheimer’s Fund. “It is a unique award in this field that we hope will both reward and inspire the most innovative researchers to continue their focus on Alzheimer’s research as a career path.”

Cure Alzheimer’s Fund and Two Other Alzheimer’s Organizations Announce Prize Winners

New Annual Awards Support Tomorrow’s Leaders in Alzheimer’s Disease Research and Honor Legacies of Drs. George Glenner and Leon Thal

Cure Alzheimer’s Fund, the Alzheimer’s Association and the Lou Ruvo Brain Institute announce the first three recipients of “Tomorrow’s Leaders in Alzheimer’s Disease Research” prizes, a new award to recognize promising investigators in Alzheimer’s and dementia research.

The three winners are:

Sterling C. Johnson, Ph.D.

Associate professor of medicine at the University of Wisconsin School of Medicine and Public Health, Madison, Wis., and research scientist, GRECC, William S. Middleton Memorial Veterans Hospital, Madison. His research uses brain imaging in conjunction with neuropsychological measurement to study cognitive disorders of memory and self-awareness.

Dora Marta Kovacs, Ph.D.

Associate professor of neurology at Harvard Medical School, Boston, and associate neuroscientist, Neurology Services, Massachusetts General Hospital, Boston. Her research focuses on the molecular events underlying neurodegeneration in Alzheimer’s disease.

James J. Lah, M.D., Ph.D.

Associate professor in the Department of Neurology at Emory University School of Medicine, Atlanta, and staff neurologist, The Emory Clinic, Emory University Hospital, Wesley Woods Center, Grady Memorial Hospital, Atlanta. His research is driven by the goal of understanding basic, disease-causing mechanisms in neurodegenerative disorders.

Tomorrow’s Leaders in Alzheimer’s Disease Research awards, worth \$100,000 each, recognize and encourage promising new M.D. or Ph.D. Alzheimer’s disease investigators who have made pivotal contributions to early detection, treatment and prevention of Alzheimer’s. The new prizes honor the legacies of two pioneering Alzheimer’s disease researchers—George G. Glenner, M.D., and Leon J. Thal, M.D.

The awards will be presented May 14 at the Alzheimer’s Association National Gala in Washington, D.C. The prize funds may be used for any purpose at the discretion of each recipient. The sponsors expect to award prizes each year to recognize additional, well-qualified, promising investigators. More information about the Tomorrow’s Leaders in Alzheimer’s Disease Research awards, nomination procedures and deadlines is available on the Cure Alzheimer’s Fund website, www.curealzfund.org.

Financial Report

How much money have we raised this year and what have we done with it?

Current Year, January 1, 2008 to March 31, 2008 (to nearest \$1,000)

Funds raised from donors and founders: \$ x,xxx,xxx

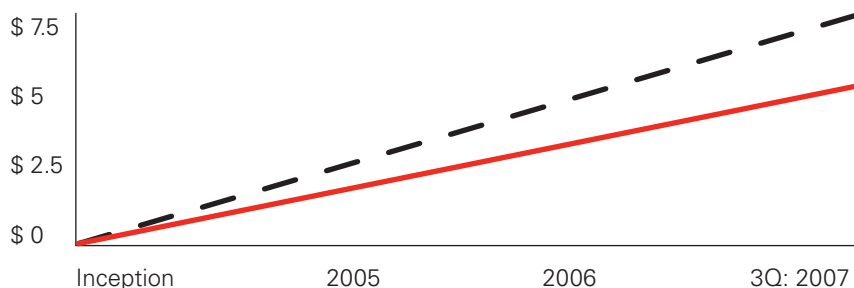
Funds distributed to Research: \$ x,xxx,xxx

- See www.curealzfund.org/research for research detail.
- 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: \$ x,xxx,xxx

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

How much money have we raised this year and what have we done with it? (in Millions)



Please 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.

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Mission Statement

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

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Join us for a sail!

A few spots remain on Cure Alzheimer's Fund's yacht as part of Massachusetts General Hospital's America's Cup Experience on June 24, 2008.

Please join us for a unique day of sailing off Newport, R.I., on an America's Cup yacht. The day's events include lunch on the New York Yacht Club veranda, an afternoon of racing with 10 of America's Cup's most famous yachts and then an evening at the Club featuring cocktails, a clam bake and a brief, silent auction of premium items. Crew members will be asked for a \$2,500 donation to Cure Alzheimer's Fund to support cutting-edge research at Massachusetts General Hospital.

More information about the America's Cup Experience and Cure Alzheimer's Fund is available at their respective websites; www.mghamericascup.org and www.curealzfund.org.

To sign up or for more information, please contact tarmour@curealzfund.org or 781-237-3800.



*Columbia
America's Cup
Boat*



The 12 Meter Intrepid, two-time Defender of the America's Cup, is one of the most famous racing yachts of all time.