



Alzheimer's Disease Research Grant Takes Research in Promising New Direction

Targeting multiple proteins may be key to success

With the help of a \$1 million grant from Alzheimer's Disease Research, an independent team of scientists is leading an international, multidisciplinary effort to design a drug that might one day prevent the onset of this devastating disease.

In Alzheimer's disease, an accumulation of beta amyloid protein "plaques" around the brain's nerve cells and tau protein "tangles" within these cells is connected to a breakdown in cell communication and eventual cell death. Evidence suggests that both beta amyloid and tau play a role, but the research community has been split on the relative significance of each protein.

"If we could control both proteins in the same patient, we might get a synergistic benefit," says Donald F. Weaver, M.D., Ph.D., of Dalhousie University in Halifax, Nova Scotia. Rather than seeking multiple drugs to accomplish this task, Dr. Weaver's team is looking for single molecules that will bind to both proteins and possibly other Alzheimer's-related

proteins before they begin to "misfold" and start their toxic buildup.

"Right now, we're treating the symptoms of this disease – only slowing cognitive decline and memory loss in patients," says Dr. Weaver. "My colleagues and I are using this grant to design drugs that may one day prevent or even reverse progression of Alzheimer's disease."

Dr. Weaver's team is creating unique new drug compounds

and testing each drug's ability to bind to both proteins and prevent shape changes. To date, the team has produced more than 240 variations of the most effective compound. Once identified, these compounds are sent for further analysis to researchers at the University of Liege in Belgium. Compounds that pass this second step are sent for animal testing to Ottavio Arancio, M.D., Ph.D., at Columbia University Medical Center in New York.

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Since the Alzheimer's Disease Research grant was awarded last year, the team has already made impressive progress. "Our lead compound is very effective in mice with conditions similar to Alzheimer's," says Dr. Weaver. "It can be delivered orally, inhibits aggregation of these proteins, protects brain cells from beta amyloid damage, restores normal memory

functioning and shows no toxicity at high doses."

Adds Guy Eakin, Ph.D., Director of Research Grants for Alzheimer's Disease Research: "This work is particularly important because Alzheimer's disease patients are often taking several medications for other health conditions. Rather than give them a 'cocktail' of drugs that might produce harmful

interactions, Dr. Weaver's research shows it may be possible to limit these concerns by designing a single drug that tackles several factors."

The program has been substantially funded by a very special \$1 million Centennial Award from Alzheimer's Disease Research.

President's Corner

Working together to beat a common enemy

Solving the riddle of Alzheimer's demands more than "business as usual." It means breaking down the boundaries that have long existed in the scientific community and forging innovative new collaborations.

To help foster those partnerships, Alzheimer's Disease Research created its \$1 million Centennial Awards, which are granted exclusively to scientists working with interdisciplinary colleagues at multiple institutions.

You can read the fruits of that approach in this issue of *Alzheimer's Research Review*. With the help of Alzheimer's Disease Research, an international chain of researchers has made startling progress in developing compounds that will, for the first time, reduce both the beta amyloid plaque that builds up around brain tissue and the tau tangles that materialize within neurons.

This work holds out the possibility of one day designing a single drug that can comprehensively stop Alzheimer's on many fronts.

Advances like these are a useful reminder of what can happen when we all work together against a common enemy.

Brian K. Regan, Ph.D.



Please share this newsletter with someone you know who might be interested in learning about some of the latest advancements in research to prevent, treat and cure Alzheimer's disease. The *Alzheimer's Research Review* is published by Alzheimer's Disease Research, a program of the American Health Assistance Foundation, a nonprofit organization located at 22512 Gateway Center Drive, Clarksburg, Maryland 20871, 301-948-3244, 800-437-2423, www.ahaf.org.

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Simply click through the site to learn more about what's new in the world of research, as well as important information about risk factors for Alzheimer's disease.

High-fat Diet Could Speed Alzheimer's Progression

Findings underscore downside of Western diets

The classic Western diet—high in saturated animal fat and low in omega-3 acids—exacerbates Alzheimer's disease in the brains of laboratory mice, according to a study at Université Laval in Quebec City, Canada.

The study, published in *Neurobiology of Aging*, tracked the impacts of different diets on mice over a nine-month period. Mice with a high-fat diet (i.e., where fat accounted for 60 percent of consumed calories) showed concentrations of beta amyloid and tau that

were 8.7 and 1.5 times higher than mice on low-fat diets. Researchers theorize that high fat consumption could affect the brain's inflammatory response.

“Our findings lead us to believe that a diet containing more omega-3s and less saturated fat could prevent the development of Alzheimer's, at the very least among people genetically predisposed to the disease,” says study leader Frédéric Calon.

Epilepsy Medication Could Benefit Alzheimer's Patients

Human clinical trials to follow

A commonly prescribed epilepsy drug can reverse memory loss in early-stage Alzheimer's patients, according to a study by the University of British Columbia. Published in the *Journal of Experimental Medicine*, the study found that a drug called valproic acid (VPA) inhibits the enzyme that produces beta amyloid plaque.

“We found that if we used VPA in the early stage of Alzheimer's disease, in model mice, it reduced plaque formation and further prevented brain cell death and axon death,” says Professor Weihong Song. “The drug also improved performance in memory tests.”

Researchers now plan to test their findings through small-scale human clinical trials. Preliminary results could be available within the next year.

Statins May Prevent Development of Alzheimer's

Study indicates potential avenue for future cures

People at high risk of Alzheimer's disease are half as likely to develop dementia if they take cholesterol-reducing statins, says a continuing study partially funded by Alzheimer's Disease Research.

The study, conducted by the University of Michigan School of Public Health, tracked older Mexican-Americans who were metabolically at risk for Alzheimer's and other forms of dementia. “The bottom line is that if a person takes statins over a course of about five to seven years, it reduces the risk of dementia by half, and that's a really big change,” says lead author Mary Haan.

Haan pointed out that her team's study measured only the ability of statins to prevent

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Thank you for thinking of Alzheimer's Disease Research!

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Alzheimer's disease, not to treat it. She added that many people currently taking statins have unknowingly benefited from the drugs' anti-dementia properties.

Statins are specifically designed to reduce "bad," or lower-LDL cholesterol. "We aren't suggesting that people should take statins for purposes other than what they are indicated for," says Haan, "but hopefully this study and others will open the door to statin testing for dementia and other types of cognitive impairment."

A Gift That Benefits You ... and the Fight Against Alzheimer's Disease

Charitable gift annuities benefit givers and receivers alike

If you want to advance the work of Alzheimer's Disease Research *and* ensure a steady stream of income for yourself or others, then consider a charitable gift annuity.

A charitable gift annuity is essentially an irrevocable contract under which you transfer cash or other assets, such as stocks or bonds, to Alzheimer's Disease Research. In exchange, you receive a fixed sum of money, paid out over your lifetime.

An annuity can be made for a single party or for two parties – for example, a husband and wife, an aunt and niece, or a father and daughter. Many times a married couple will choose an annuity to ensure that both parties enjoy an income for life.

A charitable gift annuity is considered a particularly good investment for people 55 years of age or older. Annuitants receive:

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- The option of receiving payments annually, semi-annually, quarterly or monthly;
- Income tax benefits; and
- Competitive annuity payment rates.

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Research Roundup

Combination therapies really work, study finds

Existing treatments can significantly slow the progression of Alzheimer's disease in human patients, and combination therapy with two different classes of drugs can be even more effective at helping people continue their daily functioning, according to a study by Massachusetts General Hospital. The study, published in *Alzheimer Disease and Associated Disorders*, is the first long-term assessment of the real-world impact of Alzheimer's medicines.

"There has been the impression that these drugs only work for some patients and for a limited amount of time," says lead author Alireza Atri, M.D., Ph.D. "One of the problems in judging these drugs has been that patients naturally continue to decline, which can make them think the drugs have stopped working. But our study, which as some unique strengths, indicates that treatment does have long-term benefit."

Scientists examine role of calcium in Alzheimer's

Researchers with the University of Pennsylvania School of Medicine have found that mutations in two proteins commonly associated with Alzheimer's disease can disrupt the calcium signaling pathway. This in turn could boost the production of beta amyloid protein, a characteristic feature of the Alzheimer's brain.

The findings suggest the importance of targeting the flow of calcium ions within neurons. "The significance of identifying the molecular mechanism and pathway of disrupted calcium signaling is that a number of novel treatment targets can now be developed and tested," says lead author J. Kevin Foskett, Ph.D., professor of physiology. This research has been funded by Alzheimer's Disease Research.

Metal-bearing compound reverses Alzheimer's in mice models

A compound that carries metal ions through cell membranes has been shown to produce a rapid and marked improvement in mice subjects with Alzheimer's disease, reversing symptoms within a few days, according to a study by the Mental Health Research Institute of Victoria, Australia.

The study builds on recent evidence that the impaired functioning of metal ions like copper and zinc in the brain may play a key role in the aggregation of beta amyloid proteins and the development of Alzheimer's disease.