

Alzheimer's Disease Research Review

Better Health Through Research

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This Issue

P. 1 New Discovery May Lead to Prevention and Treatment
Researchers explore the APOE4 protein

P. 2 Oral Compound Protects Mice from Neurodegenerative Damage
ADR-funded researchers discover new drug

P. 2 Chairman's Corner
The last horizon

P. 3 Research Roundup

P. 4 Feel Good and Give Back
A planned gift can help fight Alzheimer's disease...and secure your own future



New Discovery May Lead to Prevention and Treatment

Researchers explore the APOE4 protein

In a recent issue of *Science Translational Medicine*, Alzheimer's Disease Research-supported scientists reported that brains with APOE4 versus other forms of APOE aren't as good in clearing the build-up of increased plaque deposits, a hallmark of Alzheimer's disease.

This groundbreaking discovery offers a new path for researchers to discover prevention and treatment approaches for Alzheimer's disease. The finding moves scientists closer to understanding a major risk factor for the disease and may point to pathways for clearing the plaque deposits.

"We knew that APOE was linked with amyloid-beta accumulation and suspected that APOE4 might slow amyloid-beta clearance," says David Holtzman, MD, the Andrew B. and Gretchen P. Jones Professor and head of the Department of Neurology at Washington University. "This study directly shows that this is particularly true for APOE4," he adds. "The next step is to find out how APOE affects amyloid-beta clearance and how APOE4 disrupts that process, with the eventual goal of developing ways to enhance clearance."

To begin the study, scientists analyzed the APOE genes in nearly 300 healthy human volunteers. Those with one or two copies of the E4 form of the APOE gene were much more likely to have plaque deposits compared to individuals with other versions of APOE. Although all volunteers were healthy, amyloid plaque deposition and other brain changes associated with Alzheimer's disease begin as much as 10 to 15 years before clinical symptoms become apparent.

Alzheimer's Disease Research contributed to this innovative research by awarding grants to the study's co-authors Drs. Jungsu Kim and David Holtzman (co-investigator on an award shared with Drs. Bradley Hyman and Benn Barres).

Oral Slow-Release Compound Protects Mice from Neurodegenerative Damage

ADR-funded researchers discover new drug that helps both Alzheimer's and Huntington's diseases

A breakthrough discovery that could bring hope to millions with Alzheimer's and Huntington's diseases was published recently in a special early online edition of the preeminent journal *Cell*.

A new slow-release oral drug given to mice engineered to show features of Alzheimer's disease prevents spatial memory deficits, anxiety-related behavior, and the loss of "synapses"—the nerve communication centers critical for brain cell survival, signaling, and memory. The study was supported by an Alzheimer's Disease Research fellowship grant to Dr. Daniel Zwilling.



The new drug, called JM6, helps to break down an amino acid called tryptophan. Problems with tryptophan processing have been linked to many serious diseases. More specifically, JM6 is converted by the gut to a form that, through a chain of reactions, increases the brain levels of a protective chemical called kynurenic acid. The effect of this new drug is exciting because people with Huntington's and Alzheimer's diseases have lower than normal amounts of kynurenic acid in their brains.

There is hope that since JM6 protects mice from neurodegenerative damage, it could be used as a treatment for humans. Drs. Muchowski, Zwilling, and collaborators are preparing for Phase I clinical trials. They may first test the safety and toxicity of JM6 in people with Huntington's disease as early as 2013.

Chairman's Corner

The last horizon

Sometimes the brain seems like the last uncharted horizon of the human body. We can replace our knees, hips, and hearts today, but a brain transplant seems unlikely. With the explosion of genetic research, though, the intricacies of how the brain works are beginning to unfold.

Groundbreaking discoveries, such as zeroing in on how a key Alzheimer's gene like APOE4 causes increased risk for Alzheimer's disease, only occur when innovative research is supported. We are proud that Alzheimer's Disease Research was instrumental in this and other truly valuable discoveries.

With more than five million Americans suffering from Alzheimer's disease today and the numbers increasing, the race is on to find effective treatments and a cure. Perhaps someday, with your support, we'll talk about Alzheimer's disease and its impact on the brain as a thing of the past. I truly hope so.

Thank you for your support in this effort.

Brian K. Regan, Ph.D.

Research Roundup

High blood pressure, diabetes, smoking, and obesity may shrink brain

A new study suggests smoking, high blood pressure, diabetes, and being overweight in middle age may cause brain shrinkage and lead to cognitive problems up to a decade later. The study is published in the August 2, 2011, print issue of *Neurology*[®], the medical journal of the American Academy of Neurology.

The study found that people with high blood pressure developed white matter hyperintensities, or small areas of vascular brain damage, at a faster rate than those with normal blood pressure readings. They also had a more rapid worsening of scores on tests of executive functioning, or planning and decision making, corresponding to five and eight years of chronological aging than those in the normal range.

People with diabetes in middle age lost brain volume in the hippocampus (measured indirectly using a surrogate marker) at a faster rate than those without diabetes. Smokers lost brain volume overall and in the hippocampus at a faster rate than nonsmokers and were also more likely to have a rapid increase in white matter hyperintensities.

People who were obese at middle age were more likely to be in the top 25 percent of those with the faster rate of decline in scores on tests of executive function. People with a high waist-to-hip ratio were more likely to be in the top 25 percent of those with faster decrease in their brain volume.

Adapted from the American Academy of Neurology

Cancer drug holds promise

A drug already approved for people with cancer shows early potential as a therapy for a common form of dementia, according to researchers from University of Texas Southwestern Medical Center.

“Suberoylanilide hydroxamic acid (SAHA) holds promise as a first-generation drug for the prevention and treatment of familial frontotemporal dementia (FTD), a progressive, inherited neurodegenerative disease for which there is no treatment,” says Dr. Joachim Herz, director of the Center for Alzheimer’s and Neurodegenerative Diseases and the study’s senior author.

Up to 25 percent of patients with FTD have reduced production of cell-signaling protein progranulin (GRN). In an attempt to move as quickly as possible from basic science to clinical trials, the team screened 1,200 drugs that already had Food and Drug Administration approval. SAHA emerged as the most active of the chemicals they screened.

“SAHA is already approved for clinical use in an unrelated condition, which should make it easier to move quickly to human trials,” adds Dr. Herz. The study, published in the *Journal of Biological Chemistry*, showed that SAHA increased the GRN levels in cultured mouse cells and also demonstrated that it restored near-normal GRN production in cells from human subjects with FTD.

Dr. Joachim Herz and Dr. Gang Yu are grantees of Alzheimer’s Disease Research.

Stress and brain disease

Scientists at the University of Southern California recently published a study with tremendous implications for understanding and treating Alzheimer’s disease.

The study, published in the *Journal of the Federation of American Societies for Experimental Biology*, examined the brains of rats that had experienced psychological stresses and found high levels of the RCAN1 gene. The scientists suggest that chronic stress—physical or mental—causes over-expression of RCAN1, in turn leading to neurodegenerative disease.

In a healthy person, the RCAN1 gene helps cells cope with stress. Overproduction, however, can eventually damage neurons, preventing the brain’s signals from traveling and thus causing disease.

Chronic overproduction of RCAN1 causes too much phosphate to be added to tau proteins in the brain. Previous research has shown that when the tau protein is tagged with too much phosphate, it forms snarls that prevent the brain’s signals from effectively traveling.

These tangles eventually choke the life out of neurons, killing off brain function a tiny piece at a time, resulting in degenerative brain disease.

Feel Good and Give Back

A planned gift can help fight Alzheimer's disease... and secure your own future



Through thoughtful planned giving, you can help the world's most innovative research and leading scientists search for a cure for Alzheimer's disease while also passing along the values that have guided your life.

Whether you send a check, donate stock, or include Alzheimer's Disease Research in your will, your gifts will put you front and center in the fight to discover prevention methods and treatments that will benefit millions. You may

also be able to reduce your estate taxes and leave a larger inheritance for your loved ones.

For additional information, or if you want to discuss the many giving options available, please contact June Marlin Falb, Director of Leadership Gifts, at 800-437-2423.

Thank you for thinking of Alzheimer's Disease Research!

Become an advocate for change

The screenshot shows the AHAF website interface. At the top, there are navigation links for 'Español', 'Contact Us', 'Sitemap', 'Logout', and 'Edit Profile'. Below that is a search bar and the AHAF logo with the tagline 'Compassion for Today - A Cure for Tomorrow.' There are buttons for 'DONATE NOW' and 'GET INVOLVED'. A navigation menu includes 'Alzheimer's Disease Research', 'Macular Degeneration Research', and 'National Glaucoma Research'. The main content area is titled 'Advocate for Change: Speak Out on Alzheimer's Disease'. It contains text about the importance of education and advocacy, and a list of ways to advocate for change, including 'First Steps to Take', 'Share Information with Your Friends and Community', 'Advocate for Policy Changes: Let Your Federal and State Legislators Hear Your Voice', and 'Speak Out During This Election Cycle'.

The more we educate others about Alzheimer's disease, the closer we get to stopping a disorder that takes a horrible toll on patients and their families. To find out some ways to advocate for change, call 800-437-2423 or visit www.ahaf.org/advocateAD.

You can also easily join us on Twitter, Facebook, and YouTube by going to www.ahaf.org/connect.

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 Disease 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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