Cure Alzheimer's FUND
targeting breakthrough research

Relationship Between the APOE Genotype and Alzheimer's Disease

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A meeting of the minds. One of the most important, outstanding genetic questions about Alzheimer's disease is the relationship between the APOE genotype and the risk associated with the disease. To better understand this topic and speed progress, Cure Alzheimer's Fund (CAF) sponsored a meeting in February 2010 to explore this issue. The body of biological knowledge regarding how and why APOE likely is linked with AD was discussed in detail by members of the CAF Research Consortium and Cheryl Wellington, Ph.D., University of British Columbia; Michael Brown, M.D., University of Texas; Karl Weisgraber, Ph.D., Gladstone Institute; Alan Tall, Ph.D., Columbia University; and Joachim Herz, M.D., University of Texas, whose record of research includes valuable insights into this relationship. The meeting led to some important, newly funded research, including a project by David Holtzman, M.D., in his lab at Washington University in St. Louis.

Understanding the APOE linkage to AD. Although the genetic link has been known for 18 years, the critical links remain a puzzle. Other than age, the strongest risk factors for Alzheimer's disease (AD) are genetic. The most common form of AD is late-onset AD, which accounts for more than 95 percent of Alzheimer's cases and typically is defined by cognitive decline and dementia beginning after age 60. In this form of the disease, by far the strongest genetic risk factor for AD is one's APOE genotype. The APOE gene has several subtle differences, or "alleles," numbered APOE2 through APOE4. Although the APOE4 genetic variant is found in about a quarter of the population, not everyone with the variant will develop AD. Inheritance of the APOE4 form of APOE is associated with increased risk (three times the normal risk for those inheriting one copy of the variant; about 12 times the risk for those people inheriting two copies of the gene), and the APOE2 form is associated with decreased risk. How the APOE genotype is linked with altered risk to develop AD is the big question.

There is mounting evidence that one of the major reasons APOE is linked with AD is the ability of the APOE protein to influence when the amyloid-beta peptide (Abeta) begins to accumulate in the brain to instigate damage. Participants at the CAF-sponsored meeting discussed the relationship between APOE and Abeta and how APOE likely influences Abeta metabolism, as well as future experiments that can assist in nailing down the detailed mechanism of this effect. They also discussed other ways APOE may influence brain function in health and disease.

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New projects will provide better understanding and, potentially, therapeutic intervention. One of the co-chairs of the CAF conference on APOE, David M. Holtzman, M.D., the Andrew B. and Gretchen P. Jones Professor and chairman of the Department of Neurology at Washington University School of Medicine, was inspired by the meeting's discussion and initiated a CAF-funded study to learn more about this relationship and how it might be disrupted to provide a therapy for Alzheimer's disease.

Dr. Holtzman's work.

The specific hypothesis for Dr. Holtzman's project, inspired by the APOE meeting, is that anti-APOE antibodies that specifically target APOE in amyloid-beta containing plaques in the brain will result in less Abeta accumulation in the brain and decrease Abeta-related pathology, and that this treatment will have fewer side effects than the use of anti-Abeta antibodies.

Dr. Holtzman writes: *APOE is the most important genetic risk factor for Alzheimer's disease. A major reason it appears to act as an AD risk factor is via its effects on Abeta (Aß) metabolism. In vivo (cell) and in vitro (animal) data strongly suggest that APOE influences both soluble Abeta clearance as well as the probability of Abeta aggregation into clusters of the protein called "oligomers" and "fibrils," which have been determined to be toxic to neural synapses. These effects of APOE on Abeta buildup in the brain are APOE isoform-dependent. In addition, in the absence of APOE, Abeta can still aggregate in the brain; however, the conversion of Abeta into fibrils and probably oligomers is markedly inhibited. In the brain of a mouse genetically engineered to demonstrate Alzheimer's pathology (APP Tg mouse), and in humans, APOE strongly co-localizes with both amyloid plaques and the buildup of Abeta in certain blood vessels in the brain, a condition known as cerebral amyloid angiopathy (CAA). All of these facts argue that a treatment that could modify APOE/Aß interaction may provide a novel treatment strategy for AD.*

One way to modify the APOE/Abeta interaction once Abeta aggregates in the brain, or in CAA, is to use antibodies, which are proteins produced by the immune system to protect the organism. Numerous studies have injected anti-Abeta antibodies either systemically as well as intracerebrally into various types of APP Tg mice that develop Abeta accumulation in the brain. Via a variety of mechanisms, many of these antibodies are able to decrease Abeta accumulation when given in a prevention mode, and some of them are able to reduce existing Abeta oligomers and fibrils when given in a treatment mode (after plaques have begun to form). While this is potentially good news for treatment development, systemic treatment with certain anti-Abeta antibodies can also result in vasogenic edema (brain swelling) as well as cerebral hemorrhages in both animal models and in humans. Recent studies have attempted to utilize antibodies to reduce a minor component of Abeta plaques in the brain, such as pyro-glutamate-Abeta. These studies have shown a robust plaque-clearing effect, suggesting that if antibodies can bind to Abeta deposits, even if the component is only a fraction of the total material deposited, this can have a strong effect. To date, no one has published whether antibodies to other components of Abeta plaques, such as APOE, can have useful effects on the total amount of Abeta-deposited, Abeta-associated neuritic damage and inflammation, behavior or potentially any side effects.

Stay tuned for updates and progress on this critical work. ■

Goodbye Katie

We reluctantly say "farewell" to Katie Cutler as she moves to a new development position at the South Shore YMCA very near her home south of Boston.

Katie has been a key part of the establishment and growth of Cure Alzheimer's Fund (CAF). Doubling the staff when she joined in the fall of 2005, Katie quickly became an indispensible colleague in building CAF's capacity to contribute strategically focused funds to research. Katie developed our communications program, including the quarterly report and annual report, and led us in the use of the Internet and the Web for three generations of websites, our e-mail "blasts" that update all our friends on recent events, and the use of social media to help expand our reach and support.

Katie established our "In Memory" program to honor those lost to Alzheimer's disease. This has added additional revenue to our fundraising but—even more importantly—has added a warmth and empathy to CAF that is appreciated and highly valued by all involved. Katie also has worked extensively with each of the CAF founders in their outreach to friends and families for continued support of CAF—support that has grown over our five years and that is making a significant impact on the course of Alzheimer's research.

Katie moves to another post that will enable her to be closer to her and her husband Aaron's children, Libby, George and Bo, (all under 7!) and eliminate a very unproductive commute she's been battling for the last five years. She'll help us with the transition to new CAF staff and will be available for help with the projects she has helped to initiate here.

Katie's entrepreneurial spirit, her exceptional intelligence and commitment to this cause, her MBA skills and management, and most of all her unfailing cheerfulness and positive attitude for everything from stuffing envelopes to designing a new website will be greatly missed. She has been a wonderful colleague and will remain a good friend to all of us. ■

Bound for Everest!

Fresh off of summiting Aconcagua, the highest peak in South America, Alan Arnette is at it again. This spring, he will attempt to summit Everest—the highest peak on Earth at 29,035 feet. Everest is the third mountain in his *7 Summits Climb for Alzheimer's: Memories are Everything* campaign—his yearlong mission to scale the highest peak on each of the seven continents to raise money for the fight against Alzheimer's.

Inspiration. "I've always been someone who's tried to make a difference," says Arnette. "But before my mother showed signs of Alzheimer's a decade ago, I represented the typical person who didn't understand the disease, who didn't know what to look for, and who believed that losing your memory was just part of what happened when people got old."

Arnette's mother used to ask him the same questions over and over again, but he only realized there was something seriously wrong when she asked him over breakfast one day, "Now, who are you again?" Eventually, Arnette watched his mother and her two sisters pass away from Alzheimer's, but he couldn't just let them fade away. That's when he combined two of his passions—mountain climbing and fighting Alzheimer's—in an effort to get closer to a cure.

Support. The Alzheimer's Immunotherapy Program of Janssen Alzheimer Immunotherapy and Pfizer Inc. are completely funding Arnette's journey around the world. That means 100 percent of donations for his climbs will go directly to the Cure Alzheimer's Fund and now National Family Caregivers Association (NFCA). Arnette hopes to raise $1 million in donations this year.

"We welcome NFCA to the *7 Summits Climb for Alzheimer's* and look forward to ways we can work together and help promote this incredible campaign," says Tim Armour, president and CEO of Cure Alzheimer's Fund. "In order to fight Alzheimer's effectively, we need to fund more research to find a cure and we need to support the caregivers and families who are on the front lines dealing with the disease every day."

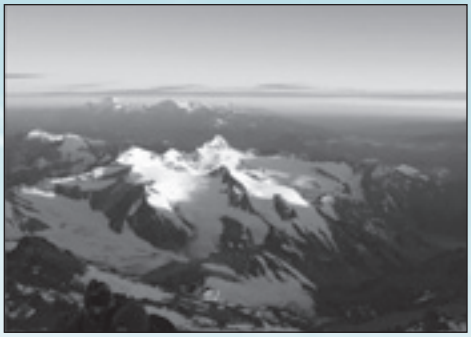
The climb. For 50 weeks a year, a jet stream with 100 to 150 mph winds hovers over Everest, making it impossible to climb. But in May, the jet stream moves to the north and creates a "weather window" for about two weeks, which attracts climbers from around the world. "But even in May," says Arnette, "Everest is a big, scary mountain and there's a process to climbing it."

It takes a week just to hike into base camp, and a month to go up and down the mountain. Arnette explains, "you have to go up to a certain altitude to let your body acclimate and then come back down and rest. Then you go up to the next altitude and come down again. It's sort of a zigzag process that allows your body to generate red blood cells so you can operate efficiently at each altitude."

Although he has attempted to summit Everest before, this time feels different for him. "There are so many people whom I've interacted with over the last few years who are so supportive of what I'm doing—including people from Cure Alzheimer's Fund, NFCA and researchers like Rudy Tanzi. When I think about Rudy toiling away in his lab, and all the other people working to fight Alzheimer's, I realize that what I'm doing has a much broader meaning than just trying to climb mountains. That's what keeps me going."

The commitment. A few years ago, when Arnette was climbing one of the Colorado 14ers, he met a woman whose mother had died of Alzheimer's. She told him she had tried to raise money to support research, but in the end never saw any progress and gave up. "Like climbing mountains," Arnette says, "there are thousands of reasons to turn around when you're tired and freezing to death, but there's only one reason to keep going. Not giving up is what this whole struggle against Alzheimer's is about."

You can track his journey or support him in his efforts by making a donation at www.curealzfund.org/7summits, www.alanarnette.com/ or www.climb4ad.com/campaign-overview. ■



Scenic view of Aconcagua

Alan Arnette on the summit of Aconcagua, January 2011

Financial Update

	This Quarter/ YTD*	Inception to date
Fundraising	$696,000	$18,057,000
Expenses paid for by the founders	$155,000	$3,304,000
Funded research	$500,000	$12,846,000

**These numbers as of April 1, 2011*

Research Update

Research funded during the first quarter of 2011

Project	Researcher	Distribution Amount
Selective Cell Vulnerability in Alzheimer's Disease	Paul Greengard, Ph.D. The Rockefeller University	$100,000
Structural and Functional Analysis of Novel Abeta and Tau Oligomers Using Conformation-specific Monoclonal Antibodies	George S. Bloom, Ph.D. University of Virginia	$100,000
Alzheimer's Disease Models Based on Human Neuronal Progenitor Cells	Doo Yeon Kim, Ph.D. Massachusetts General Hospital	$100,000
Cellular and Animal Models of Amyloid Pathology in Early Alzheimer's Disease	Charles Glabe, Ph.D. University of California, Irvine	$100,000
Exploring Adult Neurogenesis as a Therapeutic Target for Alzheimer's Disease	Se Hoon Choi, Ph.D. Massachusetts General Hospital	$100,000
Total Distributed to Research		**$500,000**

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Mission

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.

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Progress for Alzheimer's in Washington

In September, Cure Alzheimer's Fund representatives were invited by the White House to be panelists at a briefing on Alzheimer's disease. At the *White House Briefing on the Challenge of Alzheimer's Disease in the United States*, Tim Armour and Rudy Tanzi made presentations regarding the current state of Alzheimer's research to senior members of the White House, Department of Health and Human Services, National Institutes of Health and representatives of many Alzheimer's advocacy groups.

"It was an honor to accept the invitation from the White House Office of Health Reform and Domestic Policy Council to share the story of Cure Alzheimer's Fund and the state of research in America," Armour says. "I am glad Cure Alzheimer's Fund was able to meet the responsibility of being a leading voice on the need for additional government support for Alzheimer's disease research. We've met with White House staff in the past about the importance of investment in research and we look forward to continuing this dialogue."

As we continue our efforts toward finding a cure for Alzheimer's, we also understand the importance of being active participants for change on Capitol Hill. Here's an update on some of our most recent activities.

A unified effort. Since CAF is not fighting the Alzheimer's battle alone, we recognize the importance of collaborating with the larger Alzheimer's community to make the case for a greater government investment in research. In September, we received a grant for $148,500, which CAF matched, to buy a piece of research equipment for genetic sequencing. This dramatically accelerated the process of confirmation and follow-up of genes identified through the Alzheimer's Genome project™.

The Alzheimer's Breakthrough Act. In the spirit of collaboration, we teamed up with other Alzheimer's organizations to support the Alzheimer's Breakthrough Act. This act has been proposed before and has not been passed because it calls for an incremental $2 billion a year for research. "If you're going to be serious about the Alzheimer's disaster that's going to break Medicare and Medicaid by the middle of this century, you're going to have to make a serious investment, and $2 billion is serious," says Tim Armour, president and CEO of Cure Alzheimer's Fund. Our efforts are not for naught, as they heighten awareness of the issues.

The largest legislative victory in years for the Alzheimer's cause. The National Alzheimer's Project Act (NAPA) was passed unanimously by Congress and signed into law by the president in January 2011. The purpose of NAPA is to create a national strategic plan to address the escalating Alzheimer's disease crisis, led by a group that reports directly to the secretary of health and human services. Under the guidance of Phil Cronin, a valued advocate with whom we work on governmental issues, CAF joined forces with other Alzheimer's organizations, including The Foundation of America, the Alzheimer's Association, Leaders Against Alzheimer's Disease and USAgainstAlzheimer's, on this push. "NAPA's success was a unified effort of the entire Alzheimer's community and a big step forward," says Armour.

The Next Frontier. Patrick Kennedy, son of the late Sen. Teddy Kennedy, did not stand for re-election in 2010 to represent Rhode Island in Congress. Instead, he is focusing on elevating brain disease research via a new organization called *The Next Frontier*. Rudy Tanzi, chairman of CAF's Research Consortium, has been selected to plan the Memory, Alzheimer's and Genetics portions of the Next Frontier scientific symposium to be held at Massachusetts General Hospital in May 2011.

We're pleased with our recent progress and will continue to keep you updated. ■

CAF Presented at Imagine Solutions Conference in March

In keeping with the "Inspiring Minds for Change" theme of this year's Imagine Solutions Conference, Henry McCance, co-founder of Cure Alzheimer's Fund, and Rudy Tanzi, chairman of CAF's Research Consortium, shared how CAF is changing the medical research game by taking a venture capital approach to finding a cure for Alzheimer's.

The March 21–22 conference gathered America's most knowledgeable and influential leaders to address critical issues and offer promising ideas to possible solutions. Being invited to Imagine Solutions is an honor and provided valuable exposure and insight from some of the most innovative minds in the country. ■

IMAGINE SOLUTIONS CONFERENCE & INITIATIVES

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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Local Heroes

Second Annual Running4Answers Road Race

On April 2, founders Carolyn Mastrangelo and Barbara Geiger held the second annual Running4Answers road race/fun run/fitness walk in Roseland and Essex Fells, N.J., to raise money toward finding a cure for Alzheimer's. The event was even more successful than last year and we thank Mastrangelo and Geiger for their tireless dedication to our cause. Check out www.curealzfund.org for more information.

Run for CAF

Brian Gray has chosen to run his first marathon—the Vermont City Marathon—alongside his dad as they honor the memory of his maternal grandmother, who suffered from Alzheimer's and passed away in 2003. We thank Brian for his commitment to our cause and wish him the best during his May 29 race.

'80s Night

For the second time, Robyn Kasper organized a "Back to the '80s Night" fundraiser in March to honor the memory of her mother, Rosemarie McDonough, her father, James Kelly, and her uncle, Albert Drinkwater—who all passed away last year from Alzheimer's disease. We greatly appreciate Robyn's dedication to Cure Alzheimer's Fund and thank her for her efforts.

Special Thank You

Last January Liza Gilhuly, a double chemistry/French major at Amherst College, interned in our Wellesley offices. We thank Liza for her help and her enthusiasm and we wish her all the best at Amherst.