The Resveratrol Trial Begins

Georgetown physician-researcher R. Scott Turner, MD, PhD, is leading the ADCS’ national study to test resveratrol in participants with mild dementia due to Alzheimer’s disease. But Turner says a bigger question is whether high doses of the red wine compound resveratrol can reduce the risk of many diseases of aging.

Human trials of resveratrol are now underway for a variety of aging maladies, including the new national study that Turner is leading. The Resveratrol for Alzheimer’s Disease trial is designed to test whether high doses of resveratrol are well tolerated and whether they can slow the progression of dementia in individuals with early Alzheimer’s disease.

The new Resveratrol for Alzheimer’s Disease clinical trial is recruiting 120 people to participate in the study at one of 26 academic medical centers across the U.S. Investigators will test daily doses of resveratrol equivalent to that found in about 1,000 bottles of red wine. He can’t wait to get started. That’s because he has worked to develop the study for more than seven years since he submitted his proposal to the National Institute on Aging (NIA), in collaboration with the ADCS.

Resveratrol for Alzheimer’s Disease: Observations from the Principal Investigator

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When Gulliver traveled to Luggnagg, he learned of rare individuals (called Struldbrugs) who were born with the mark of eternal life. While at first he thought this a gift, his interest abated when he discovered that such individuals were not also granted eternal health. Swift writes in Gulliver’s Travels (1726): “At 90 they lose their teeth and hair...they eat and drink without relish or appetite. In talking they forget the common appellation of things, and the names of persons, even of those who are their nearest friends and relations.” When Swift penned these words the average life expectancy in the U.K. was about 35.

The major risk factor for AD is aging – a so-called non-modifiable risk factor. Or is it? We have known for decades that caloric restriction (meaning consuming about 2/3 of one’s normal daily calories) can delay or prevent all diseases of aging,
including cancer, heart disease, and diabetes. However, this strict regimen is practically impossible for humans to maintain long-term.

Because careful studies of long-term caloric restriction have not been attempted in man, many questions remain unanswered. However, studies with several animal species including non-human primates have proven the manifold health benefits of caloric restriction. In fact, caloric restriction typically prolongs both life-span and health-span. So it is not surprising that studies with mouse models of AD demonstrate that caloric restriction prevents or delays AD. The question is, how? What is the mechanism? On the flip side of the coin, diabetes is a major risk factor for AD. Diabetes typically results from caloric excess and a sedentary lifestyle with weight gain and obesity. Again, questions of why and how diabetes increases AD risk remain unanswered.

So evidence is accumulating that AD is somehow linked to metabolism (energy balance), and that preventing diabetes by caloric restraint, by maintaining ideal body weight, and by exercising regularly in mid-life may prevent or delay AD in later life. These are modifiable risk factors that can be addressed and treated if needed by individuals and their healthcare providers. Some investigators speculate that diabetes is in fact a form of accelerated aging.

Meanwhile, scientists are probing molecular mechanisms linking metabolism to AD in animal models in the laboratory. Some findings are controversial, particularly those suggesting prolonged life-span from a drug that mimics caloric restriction. However, prolonged health-span is a more short-term, reliable, and consistent outcome of such studies. One gene (and protein) that is implicated in regulation of aging is SIRT1. A molecule that may activate SIRT1 is resveratrol. This compound is found in high levels in the skin of red grapes and thus in red grape juice, red wine, and other plant foods. Levels are higher if the plant is stressed (for example, by cold weather) suggesting that resveratrol is involved in a protective or restorative function. For the oenophiles in the audience, pinot noir wines from Oregon have a high resveratrol content. Retrospective human population studies often find health benefits associated with modest daily red wine consumption -- including a lower risk of dementia.

As predicted, resveratrol treatment delayed and prevented AD onset in mouse models in the laboratory. Resveratrol also improved metabolic profiles – lowered cholesterol levels, lowered fat stores in the liver, and improved muscle endurance. Likewise, a pilot study of obese men showed that resveratrol treatment improved lipid and glucose profiles in the blood. Human studies are underway to evaluate possible risks and benefits of resveratrol in the treatment or prevention of diabetes, heart disease, and cancer.

A larger and more definitive study was launched in May 2012 by the Alzheimer’s Disease Cooperative Study (ADCS) with funding from the NIA (National Institute on Aging). This Phase II study of individuals with mild to moderate dementia due to AD is primarily designed to evaluate the safety and tolerability of long-term treatment with high-dose resveratrol. We will also examine potential treatment benefits in tests of memory and cognition, in AD biomarkers (proteins in cerebrospinal fluid and brain volumes measured by MRI), and in metabolic profile (blood glucose and insulin).

This study is currently recruiting volunteers and their study partners at 26 academic medical centers across the country. The initial dose will be 500 mg given by mouth once daily, with scheduled increases at three months intervals thereafter -- ending with a dose of 1000 mg twice daily. Half of the study participants will receive a placebo medication, and the treatment duration will be 12 months. Volunteers will be carefully monitored throughout the study to look for possible side-effects of high-dose resveratrol treatment.

The study of aging is maturing into a true science with the discovery of novel genes, proteins, and molecular pathways. These discoveries are revealing druggable targets perhaps involved in the regulation of aging. The resveratrol study may open a new chapter in AD prevention and treatment and has potential implications for treatment of diabetes and all diseases of aging. The goal of this research is improved health-span. Because of ever-advancing life-spans almost all of us are Struldbruggs now.

To learn more about the resveratrol study or other Alzheimer’s studies underway contact brainlink@ucsd.edu, or visit www.adcs.org and or the NIA.
The expression *in vino veritas* — “in wine there is truth” — is oft quoted.

But R. Scott Turner, MD, Principal investigator in the Resveratrol for Alzheimer’s clinical trial, is partial to *in vino vitalis* — “in wine there is life.”

That’s because Turner, Director of Georgetown University Medical Center’s Memory Disorders Program and ADCS Steering Committee Member, knows that resveratrol, (a compound found in red wine and red grapes), when used as a treatment of laboratory animals, lowers risk of diseases of aging — thus, prolonging their health and life spans.

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**A Look at the National Alzheimer’s Plan and the New Trials**

ADCS Associate Clinical Director Michael Rafii, MD, PhD answers some basic questions about the HHS/NIH/NIA May 2012 Alzheimer’s disease initiatives

**Q: The NAPA Plan sets a goal for finding a cure for Alzheimer’s by 2025. Could you characterize how challenging that is going to be? Do you think it is a realistic time frame?**

Yes, I believe there is a real opportunity to finally have a drug that essentially slows the progression of AD during the mildest stage (called Mild Cognitive Impairment), such that it does not reach the dementia stage. This will require AD to be diagnosed in patients who may have little or no visible symptoms of the disease. We are finally able to do this with the use of brain scans and cerebrospinal fluid.

One analogy to consider is high cholesterol. High cholesterol levels are associated with a higher incidence of heart attacks. However, a patient does not present to their doctor with any symptom associated with high cholesterol. In fact, up until 25 years ago when cholesterol levels started to be routinely checked, many patients would present with a heart attack as the first symptom of their long standing high cholesterol levels. The same is thought to be true about AD.

The symptoms of dementia are to the brain much like a heart attack is to the heart. By the time the symptoms of dementia have developed, there have been years of an underlying pathological process affecting the brain, namely the accumulation of beta-amyloid and the loss of synapses and neurons. And, much the same way, if a patient presents to the emergency with a heart attack, prescribing a cholesterol lowering medication for the first time may be too late. Specifically, 15-20 years too late. Now that we can check cholesterol levels earlier in life with a simple blood test, in the absence of any symptoms, we can start patients on cholesterol lowering medications to reduce their risk of have the heart attack in the first place. The same is believed to be true about treatment of Alzheimer’s disease dementia. By treating Alzheimer’s disease early, that is by lowering beta-amyloid levels, we may be able to prevent the dementia phase from ever developing.

**Q: As things are understood at this moment, what are the basic strengths and weaknesses of crenezumab and the trial announced in May by NIA?**

Crenezumab is an antibody that binds to beta amyloid. This drug removes beta-amyloid, the protein that is deposited into plaques found in the brains of patients with Alzheimer’s disease. Beta-amyloid is neurotoxic and believed to be the main cause of neuronal degeneration in AD. By virtue of binding beta-amyloid, early on in the course of the disease, it may prevent the widespread injury that occurs in the brain 10-15 years before patients with AD develop any memory symptoms.

**Q: The NIH also is funding a second trial involving nasal insulin – which was covered by mainstream media earlier this year when the initial results were reported. What can you tell us about the nasal insulin trial and what’s the difference between the two trials?**
A: It is a different approach. Insulin is critical for normal brain function, and abnormal insulin metabolism has been shown to contribute to the development of Alzheimer’s disease. Because patients with Alzheimer’s disease also exhibit decreased levels of insulin in the central nervous system, it has been hypothesized that raising these levels to normal might help maintain cognitive ability. Studies involving animals have suggested that insulin deficiency in the brain may possibly be a key factor in the progression of Alzheimer’s disease.

To learn more about the NAPA plan, visit the new NIH AD website
To learn more about the new research initiatives visit the NIA

Brain Pacemaker Shows Promise in Fighting Alzheimer’s

By Janice Wood Associate News Editor

A pacemaker that sends continuous electrical impulses to specific regions of the brain appears to reverse the downturn in brain metabolism that typifies Alzheimer’s disease.

A pilot study on a handful of people suggests that deep brain stimulation, a therapy already used in some patients with Parkinson’s disease and depression, may offer hope for at least some with Alzheimer’s.

Alzheimer’s disease is a progressive and lethal dementia that mostly strikes the elderly, affecting memory, thinking and behavior. Experts estimate that as many as 5.1 million Americans may have Alzheimer’s — and that number is expected to skyrocket as baby boomers age.

The study was designed to establish the safety of the brain pacemaker and involved just six people, said the study’s first author, Gwenn Smith, Ph.D., a professor in the department of psychiatry and behavioral sciences at the Johns Hopkins University School of Medicine.

The research, published in the Archives of Neurology, was conducted while Smith was on the faculty at the University of Toronto, and will be continuing at Toronto, Hopkins and other U.S. sites in the future. The study was led by Andres M. Lozano, M.D., chairman of the department of neurosurgery at the University of Toronto.

Smith notes that while the study needs to be replicated on a larger scale, there is not another treatment for Alzheimer’s “that shows such promising effects on brain function.”

One month and one year after implanting a device that allows for continuous electrical impulses to the brain, Smith and her colleagues performed PET scans that detect changes in the metabolism of glucose in the brain’s cells. The scans showed that patients with mild forms of Alzheimer’s showed sustained increases in glucose metabolism, an indicator of neuronal activity. The increases were larger than those found in patients who have taken the drugs currently marketed to fight the progression of Alzheimer’s, the researchers note.

Other imaging studies have shown that a decrease in glucose metabolism over the course of a year is typical in the disease.

The researchers observed roughly 15 percent to 20 percent increases in glucose metabolism after one year of continuous stimulation. The increases were observed in patients with better outcomes in cognition, memory and quality of life. In addition, the stimulation increased connectivity in brain circuits associated with memory.

Deep brain stimulation (DBS) requires surgical implantation of a brain pacemaker, which sends electrical impulses to specific parts of the brain. For the study, surgeons implanted a tiny electrode able to deliver a low-grade electrical pulse close to the fornix, a key nerve tract in brain memory circuits.

The trial came about when Lozano used DBS on the fornix to treat an obese man. The procedure, designed to target the regions of the brain involved in appetite suppression, unexpectedly brought about significant increases in his memory, according to Smith.

Smith, who also is director of the Division of Geriatric Psychiatry and Neuropsychiatry at Johns Hopkins Bayview Medical Center, is an authority on mapping the brain’s glucose metabolism in aging and psychiatric disease. It was her earlier analysis of Alzheimer’s patients’ PET scans that revealed their pattern of lowered brain metabolism. She determined that specific parts of the temporal and parietal cerebral cortex — memory network areas of the brain where Alzheimer’s earliest pathology surfaces— became increasingly sluggish with time.
Resveratrol for Alzheimer’s is Recruiting

Resveratrol for Alzheimer’s Disease

http://www.adcs.org/Studies/RES.aspx

Nerve Growth Factor Study (NGF)

The NGF is a Phase II clinical study of Ceregene’s CERE-110, a gene therapy product designed to deliver nerve growth factor (NGF) to the brain for the treatment of Alzheimer’s disease (AD) is currently underway. This study is a randomized, double-blind, placebo-controlled trial and employs gene therapy to deliver nerve growth factor (NGF) directly into the brain.

http://adcs.org/Studies/NGF.aspx

ADNI II Study

The goal of the Alzheimer’s Disease Neuroimaging Initiative Study is to learn how to stop the progression of mild cognitive impairment (MCI) and Alzheimer’s disease in future generations. Information from the study might, in the future, lead to new treatments.

http://adcs.org/Studies/ImagineADNI2.aspx

Source: Johns Hopkins Medical Institutions

APA Reference

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