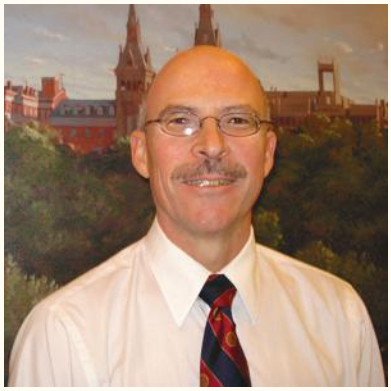
Resveratrol News

Winter 2013



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Resveratrol for Alzheimer's Disease

Newsletter for Participants and friends of the Resveratrol for Alzheimer's Disease Clinical Trial

Dear Participants and Friends of the RES Study,

I am delighted to write to you in my role as the Principal Investigator of the Resveratrol for Alzheimer's Disease clinical trial (otherwise known as the RES trial) and I am happy to report that the trial is enrolling participants at a rapid pace. In fact, we are fairly confident that we will meet our targeted number of participants and be in a position to officially close enrollment in the first quarter of 2013. This development is significantly ahead of schedule. You will hear more from me in the next newsletter regarding milestones in the RES trial.

Interesting Times

The phrase "may you live in interesting times" can be interpreted as both a blessing and a curse. I say, with confidence, that these are indeed "interesting times" in Alzheimer's disease (AD) research.

In 2012, AD research news was a rollercoaster of potential breakthroughs, apparent dead ends and calls for additional research on anti-amyloid and other therapies under consideration. It doesn't help that scores of news reports often appear contradictory – especially in the mainstream media. This will no doubt continue through 2013 as a number of high-profile trial results are disseminated through medical and mainstream media outlets.

This attention to AD will only increase in coming years. AD is now the sixth leading cause of death in the US and is the only leading cause of death with no strategy to prevent or arrest the disease. By 2050 the number of individuals with AD in the US is projected to triple – from the 5 million afflicted with AD today.

Moreover, despite the growth in AD research over the last 10 years, no new drugs have been FDA-approved for AD since 2003. Nor have researchers been able to definitively identify environmental modifications – such as exercise or diet – to significantly impact the inexorable progression of AD.

That doesn't mean that AD clinical research isn't working and there are reasons to remain hopeful about progress in finding ways to prevent and treat AD within the next few years. Perhaps I am too optimistic, but this is rooted in the process that enabled many major medical advancements over the recent decades. That is – breakthroughs in medical treatments and prevention of some major diseases are often identified only after we gain a clear understanding of the biology of the disease.

Understanding the Biology

For instance, through the 1970s, the diagnosis and treatment of heart disease relied on a patient's history of shortness of breath or chest pain. Today, through scans, biomarkers and other tools we are able to image a patient's heart, examine blood flow and monitor heart functions. Those new tools have enabled us to more accurately diagnose and effectively treat and prevent heart disease.

But progress in preventing and treating heart disease came only after we had the ability to directly observe heart function and establish uniform measurements of the biology and pathology of heart disease. The same can be said for lung and liver disease –we now have a better understanding of disease because we also have a better understanding of the basic biology.

To state the obvious, AD is an inherently complex disease because it involves the brain. In recent decades, we identified AD almost exclusively by progressive cognitive and functional decline in older people. However, the only way we could positively diagnose AD was by autopsy – the same way Dr. Alois Alzheimer originally identified microscopic plaques and tangles in brain tissue more than 100 years ago.

Why I am Optimistic

Today, we are developing distinct AD biomarkers earlier and earlier in the disease process. In clinical research settings, we are able to definitively diagnose AD using a combination of biomarkers, brain scans and cognitive testing. Add to the mix the startup of clinical trials (including the RES trial), and the future looks much brighter.

To participants and others or involved in the RES trial it may seem as though we are constantly scanning and testing our RES volunteers. Please remember we do so with good reason. The more we know about AD-related changes in the brain, the faster we will be able to find treatments and preventive strategies for the disease.

I look forward to reporting updates on the RES study in the Spring of 2013.

Sincerely,

R. Scott Turner, MD, PhD
Principal Investigator
Resveratrol for Alzheimer's Disease

Important Dates in the Resveratrol Trial

- October 2011 – Resveratrol for Alzheimer's Disease Clinical Trial, protocol approved by FDA
- May 2012 – First volunteer enrolled
- January 2013 – 82 percent of cohort is already enrolled
- Spring 2013 – Anticipated time frame to begin data analysis.

What AD Research Can Learn from Cancer Research

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Sidney Farber, MD is regarded as the father of modern cancer chemotherapy, and after whom the Dana-Farber Cancer Institute in Boston is named. He understood that to treat cancer, even to prevent it, early detection is essential. In the last 50 years, significant advances in cancer detection have been made in this regard.

Oncologists today will tell you that the treatment of early stage cancer is very different from the treatment of widely spread, metastatic cancers, even with the same type of cancer. It is also widely recognized that early treatment is much more successful than later treatment. The key to successful treatment of cancer is early detection.

One example of this type of success in early detection of cancer is the Papanicolaou test or so called "pap smear." In 1952, 150,000 women had pap smears done as part of a clinical trial and were followed over time. About 500 of these women were discovered to have invasive cancer at that time, and were treated accordingly. Interestingly, another 500 women who were completely asymptomatic had precancerous lesions that were curable by a relatively simple surgical procedure. These women were on average, twenty years younger than the women with the invasive lesions. The pap smear, in effect, allowed for cancer detection, and treatment twenty years earlier than previously possible. Since then, the discovery of the human papillomavirus (HPV) as the cause of almost all cases of cervical cancer has led to development of a vaccine against HPV, which in turn, has led to prevention of cervical cancer.

> "The greatest need we have today in the human cancer problem, except for a universal cure, is a method of detecting the presence of cancer before there any clinical symptoms
>
> ~ Sidney Farber, November, 1962"

In primary prevention, a disease is prevented by stopping its cause, such as HPV vaccination that reduces the risk for cervical cancer. In secondary prevention, a disease is prevented by screening for its early, presymptomatic stage. In the case of the pap smear, detection of abnormal cervical cells allows for prevention of cervical cancer.

In Alzheimer's disease, the question is, are we detecting the disease early enough to make a difference? One way to answer this will be to look at the effect of the anti-amyloid drugs, including bapineuzemab and solaneuzemab, to see if they have any effect on biomarkers that demonstrate the presence of early AD. Even if the phase 3 studies of these drugs did not reach their clinical endpoints, a strong enough effect in reducing beta-amyloid will indicate that we are headed in the right direction and that perhaps with earlier detection and treatment could prevent the dementia stage of AD.

Sex and Gender Differences in AD

Neelum T. Aggarwal, MD
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Over the last year I have had the opportunity to attend conferences devoted to Sex and Gender Issues in Medicine and have been an active member of the Sex and Gender Women's Health Collaborative – Women's Health Working group. (http://sgwhc.org). Thus, I was pleased to see that the Society for Women's Health Research recently published an article that outlined the latest state of the science in sex and gender differences in Alzheimer's Disease (AD).

It comes as no surprise that most clinician researchers in the field of AD see predominantly more women than men in their offices and clinics. The question has always been, "Do women really develop AD more than men or is it a function of age – women live longer than men?"

The recent article by Carter and colleagues in the Journal of Women's Health, attempts to frame this issue by discussing the latest research and data in three themes: clinical, basic science, and psychosocial. The clinical research group, identified three areas that highlighted questions about potential differences among men and women:

- Are there sex linked risk factors for AD?
- Do sex and gender differences affect risk rate of progression or response to treatment?
- Does the timing (early stages of menopause vs. late stages of menopause) of hormonal replacement therapy affect cognitive status, and if so, would changing gynecologic practices contribute to preventing dementia and AD in women?

The basic science research group also identified three areas such as metabolism, physiology of hormonal regulation and AD genetics as areas of intense sex/gender research. It is known that brain

hypo-metabolism and loss of mitochondria (also known as the "powerhouse or energy center of the cell") function often occur before the development of AD. What is interesting is that in persons who have a maternal history of AD, greater reductions in brain glucose metabolism occur compared to persons without a maternal history of AD. This finding points to a basic biologic and genetic predisposition for AD, as mitochondrial inheritance is known to occur from the maternal line.

In addition, questions regarding differences inbioenergetics and aging between the sexes also are raised. Are there sex-specific modulators of aging that influence rate of decline in aging?

The final area of inquiry centered around Psychosocial themes and the sex and gender differences in service use, outcome measures and

societal expectations. Research in all of these areas is available, however more studies are needed that are specifically designed to include sex/gender interventions to provide effective services.

The roundtable experts suggested several action items for future sex/gender based research with the goal to further improve early diagnosis, quality of life and safer and more effective treatments. Briefly they included:

- Analyze sex-based differences systematically and comparativelyincorporate sex and gender into experimental designs, especially in clinical trials
- Determine how biomarkers relate to disease burden and risk for AD for sex and gender
- Integrate sex differences in AD drug discovery

Here are three articles you can read to learn about this particular report and the latest research in the area of Sex and Gender Medicine.

Carter CL, Resnick EM, Mallampalli M et al. Sex and Gender Differences in Alzheimer's Disease: Recommendations for Future Research. Journal of Women's Health Vol 21, Number 10, 2012.

Liu E, Sui X, Laditka JN, et al. Cardiorespiratory fitness as a predictor of dementia mortality in men and women. Med Sci Sports Exerc 2012; 44: 253-259

Mosconi L, Mistur R, Switalski R, et al. Declining brain glucose metabolism in normal invidviuals with a maternal history of Alzheimer's disease. Neurology 2009; 72: 513-520

Resveratrol for AD: Observations from the Principal Investigator

R. Scott Turner, MD, PhD
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When Gulliver traveled to Luggnagg, he learned of rare individuals (called Struldbruggs) 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 humans, 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.

Brain Teasers

Word Jumble

RETWEAH

ROSTM

NIRA

DANTOOR

HIAL

MDU

Word Jumble answers: weather, storm, rain, tornado, hail, mud

Final answer: summer

Mad Gabs (Hint: Sound out the sentence)

1. Abe An An Appeal
2. Abe Autumn Lisp Hit
3. Abe Ax Tree Tally
4. Abe Hair Heat Rash You're
5. Abe Hum Pen Thin Height

Mad Gabs answers:
1. A Banana Peel
2. A Bottomless Pit
3. A Back Street Alley
4. A Buried Treasure
5. A Bump in the Night