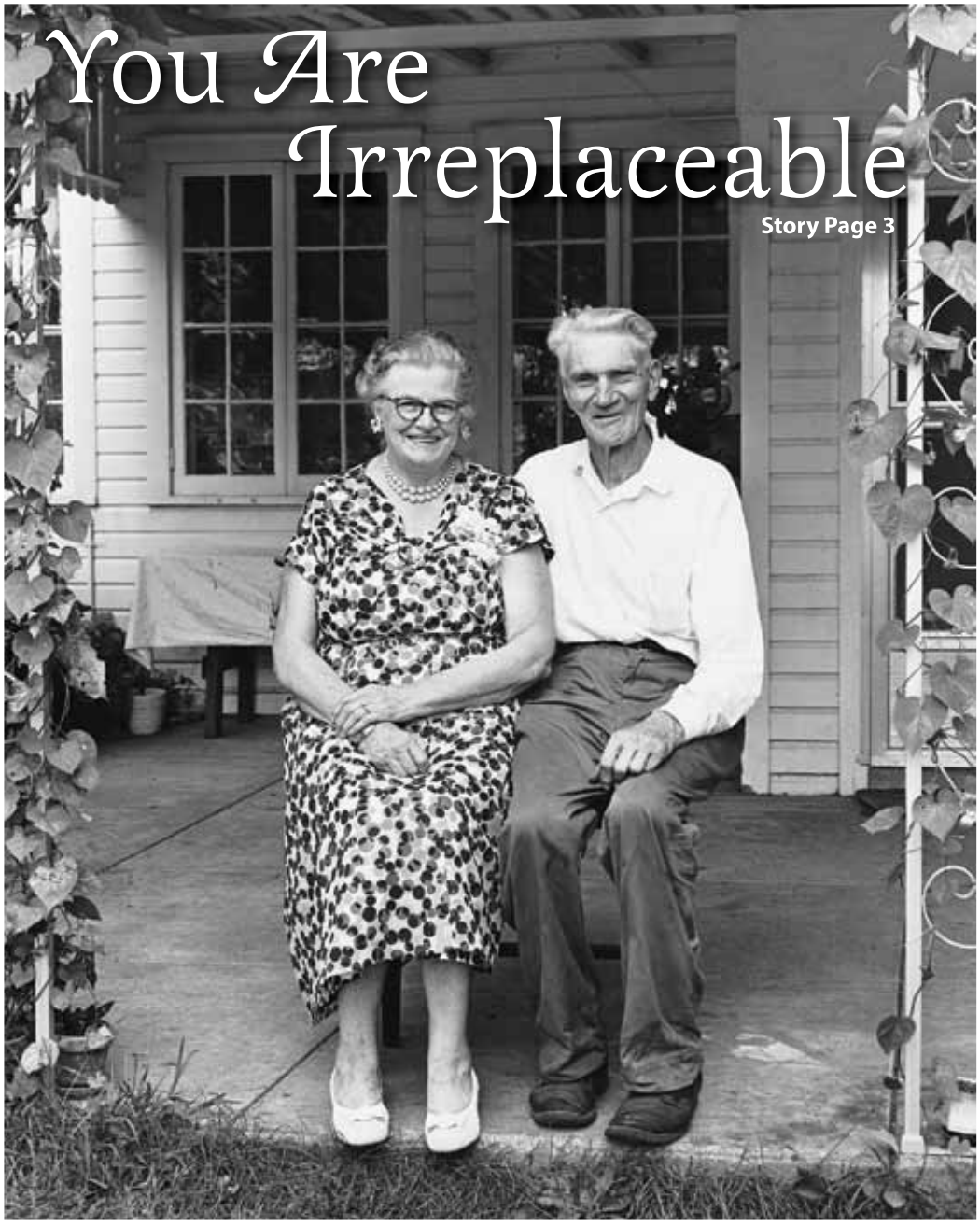
ALZHEIMER'S DISEASE COOPERATIVE STUDY

R.I. READER

THE JOURNAL FOR PARTICIPANTS IN THE R.A.G.E. INHIBITOR STUDY

FALL 2009



You Are Irreplaceable

Story Page 3

DIRECTOR'S

MESSAGE

Important News

REDUCING AMYLOID in ALZHEIMER'S DISEASE

We thank each and every one of you for your participation in this important Alzheimer's clinical trial. Congratulations to all of you for completing the initial enrollment. In this second issue of the RI Reader, once again we provide you with an update on recent AD research efforts. Another article addresses why you are irreplaceable. Finally, we offer you an interesting article on exercise and its possible relationship with cognition. As we began in our first issue, you will also find some simple recipes and a few creative brain teasers.

The most important news relates to the discontinuation of one arm of the RI study.

As you already know, there are three groups of people taking part in this study: participants receive either a low-dose active study drug, a high-dose active study drug or a placebo (sugar pill). A previously planned six-month analysis of the safety data from all groups has just been completed. The findings show that more people in the high-dose group have had a faster rate of decline, on average, in their memory and thinking, than in the other two groups. There were also more side-effects reported in this high-dose group, namely falls which resulted in a need to seek medical attention, and psychiatric events such as agitation, confusion and anxiety.

An independent medical board of experts has reviewed the available safety data and recommended that the best course of action is to stop treatment in the high-dose group, and to continue the study with the low-dose group and placebo groups. They did not have any safety concerns about the low-dose or placebo groups. The ADCS and Pfizer, as co-sponsors of the study, agree with this recommendation and are working with all the study sites to make this change to the study. Procedures have been set up for sites to inform all subjects who are participating in the RI study about this safety review, and to inform subjects who were taking the high dose study drug to stop taking it.

For those who are discontinuing the high-dose active study drug we will continue to monitor them and we will repeat scrutinizing the safety data after all study participants reach the ninth month of taking the study drug or placebo. For those who are taking the low-dose or placebo, we would like to emphasize that no concerns have been raised to date about safety in subjects in either of these groups.

Please feel free to ask study staff any questions that you may have. We hope that you will continue to take part in this research study, but recognize that you have a choice, and may decide to stop at any time. If you do decide to stop, none of your current benefits or normal health care will be affected in any way. Thank you for the contribution that you have already made to this research.

The RI clinical trial remains an important study aimed at slowing the progression of Alzheimer's disease. Results from this study will have an impact on research efforts being made around the world to develop new and better treatments for Alzheimer's disease. We gratefully recognize your contributions as participants in this effort; without you, it would not be possible to gain ground in the fight against Alzheimer's disease.

Warmly,

Douglas Galasko, M.D.

RI Study Project Director,
Director – UCSD Shiley-Marcos Alzheimer's Disease Research Center

You Are Irreplaceable

As we approach the half way point in the RI study, we'd like to remind participants how important the RI study is and how valuable your contribution is to our research efforts. In short, YOU ARE IRREPLACEABLE, and we can't do this without you.

Previous research shows that we are on the right track towards finding out if RI will slow down or reverse Alzheimer's disease, provided that we do not have an excessive number of participants drop out. The ability to draw conclusions from this type of study is entirely dependent on having sufficient numbers of participants continue to the final visit.

We know that sometimes people decide to discontinue their participation because they do not sense any treatment benefits, and we'd like to address that issue. Since the goal of RI treatment is to slow down or halt the rate of progression, we do not expect the treatment effect to be self-evident to participants. A comparison can be made to the treatment of high blood pressure or high cholesterol—those are clearly valuable treatments but patients cannot "feel" or otherwise perceive the benefits while under treatment. We only know that they work because of controlled clinical trials. Similarly, we will only know if RI is effective for Alzheimer's disease and tolerable in participants by completing the RI study.

Others may discontinue because they want to participate in other clinical trials with experimental drugs which sound as though they may be more effective. We remind everyone that the RI study is based on strong evidence that the RAGE pathway is intimately associated with amyloid plaque formation, and RI appears to have anti-amyloid effects in previous basic and clinical trial research. Researchers have observed that sustained beta amyloid interaction with the receptor is an important element of amyloid plaque formation and chronic neuronal dysfunction. Therefore, we are very optimistic about this drug as a potential therapy for AD. Other studies are underway using other anti-amyloid effects, but RI has demonstrated very strong anti-amyloid effects as well.

Still others may simply find that the study visits are too burdensome. Should this be the case for you, we can work together to reduce the burden by accommodating your appointment at a different time, providing travel service, reimbursement for parking or providing a meal voucher to be used after fasting or lunchtime appointments. We don't want to lose you! However, if you truly cannot continue for reasons we cannot resolve, we can only respond by thanking you once again for your contributions to this important study. We cannot develop better treatments for Alzheimer's disease without your help, and we are grateful for your efforts. The next generation of patients will surely benefit from this.

ALZHEIMER'S DISEASE RESEARCH ROUNDUP

by Michael Rafii, M.D., Ph.D,
ADCS Associate Medical Director

A number of promising new treatments for Alzheimer's disease (AD) have migrated from early development in the laboratory to being tested in humans. Research has provided a much more complete understanding of the processes that lead to the production and removal of Beta-amyloid protein (Aβ), the substance that forms sticky plaque deposits in the Alzheimer brain. Many scientists believe that Aβ is a molecule that initiates a cascade of damage in AD, and lowering Aβ levels in the brain is an important goal of treatment. Another approach is to target pathways related to tau, a protein that forms the other hallmark brain pathology of AD, the tangle. Basic research advances have provided methods to screen for new drugs that affect Aβ or tau and to test candidate drugs in animal models that express features of AD pathology. Recent areas of AD research interest include the following:

Eli Lilly, Inc. has performed research focused on **gamma-secretase**, an enzyme which cuts the parent protein of Aβ and many other proteins in the body. This enzyme may contribute to the abnormal cleaving and depositing of Aβ in persons with AD. Eli Lilly is working on a "gamma secretase inhibitor" (LY450139) that has shown promise in lowering Aβ production and decreasing plaque build-up in animal models. In a recently completed multi-center study in patients with mild-to-moderate AD, this drug appeared to be reasonably safe. It lowered the levels of Aβ in the blood for several hours after each dose. Some side effects were noted, but were not major, and a more comprehensive Phase III trial is currently underway.

Elan Pharmaceuticals, Inc. has pioneered approaches to reduce the build-up of Aβ in the brain by using **antibodies**. Initial studies showing that after mice had been genetically engineered to deposit Aβ in their brains were immunized with Aβ, they raised a strong immune response and made antibodies against Aβ that markedly reduced the build-up of brain amyloid and plaques. In 2002, Elan attempted an immunization study in humans using the Aβ peptide. This trial was stopped after approximately 6% of patients on active treatment developed brain inflammation. A long-term follow-up study on many of the study participants has been encouraging. Of those participants who were contacted, responders showed better performance on cognitive test scores and activities of daily living compared to placebo-treated patients. A series of studies is now underway in which patients are infused with anti-Aβ antibodies ('passive immunization'). To date, these infusions have been safe in patients with mild AD. A Phase II trial is currently recruiting.

Many other investigators are also studying approaches to active immunization, some of which may be safer than the methods in Elan's 2002 clinical trial. The ADCS is conducting a Phase III clinical trial of **Intravenous Immunoglobulin** (IgIV) infusions in AD, aimed at helping to remove Aβ and decreasing inflammation. Do you have a friend or family member who is interested in participating in an AD research study? If so, information on ADCS research sites conducting this study can be found at: **http://www.adcs.org/Studies/IGIV.aspx** Please encourage your friend of family member to consider enrolling in this study.

A small initial clinical trial in patients with AD was carried out by Dr. Mark Tuszynski at UCSD using **nerve growth factor**, or "gene therapy". Patients' skin cells were initially harvested and used to grow cells called fibroblasts in the laboratory. These were injected with the gene that makes nerve growth factor. The fibroblasts were then injected into the brains of patients with AD by a neurosurgeon. Initial data suggested that there may have been a slight improvement of symptoms in some of the study participants. This approach has been extended, using a type of virus with the nerve growth factor gene attached, to deliver the NGF gene to brain cells. Although this approach again requires injection into the brain, it is technically easier and may lead to longer lasting effects of the protein in the brain. The Phase II trial is now underway. Information on ADCS sites conducting

(Cont'd from Page 4)

this study can be found at: **http://www.adcs.org/Studies/NGF.aspx** Please refer any friends or family who may be interested in participating in a clinical trial.

Omega-3 fatty acids, typically deficient in the American diet, are essential for human health. Docosahexaenoic acid (DHA), in particular, is vital to proper brain function and is the most abundant fatty acid in the brain. In recent years, epidemiologists have tied fish-rich diets to a lower incidence of AD and homed in on DHA as the preventive factor. Having increased DHA levels in the blood and eating about three fish meals each week appears to be associated with a significant reduction in the risk of AD. The ADCS has now completed a Phase III clinical trial to study the effects of DHA in patients and results are forthcoming.

Amyloid is known to bind to **Receptors for Advanced Glycated Endproducts** (or RAGE, for short) on the surface of cells (e.g. the brain's nerve cells and microglial cells) and at the blood brain barrier. This binding may trigger inflammation and damage to nerve cells. However, by blocking Amyloid-RAGE binding, researchers have found that plaque formation was reduced in animal models. PF-04494700 is an orally bioavailable small molecule antagonist of the RAGE. The drug has been tested in animals, in small Phase I safety studies in healthy volunteers, and in a preliminary short safety study in AD patients. This is the study in which you are enrolled and is now being investigated in a larger Phase II clinical study to determine its efficacy.

Although much is known about the **tau protein**, it is still not clear exactly how tangles form. Adding phosphate groups to tau is an important regulatory pathway that may influence tangle formation. There are several currently available drugs that can alter tau phosphorylation. One of these, valproic acid, is being studied in a clinical trial run by the ADCS. Another drug, with a stronger effect on these pathways, is Lithium, which has been used for many years to treat bipolar disorder. Treatment with lithium has been shown to decrease tau deposits in an animal model.

Dimebon, another oral agent, is an interesting molecule whose mechanisms of action remain under study. It first came to attention as a drug with specific action on brain receptors because it had been used in a pilot study for AD patients in Russia. Later, additional, possibly neuroprotective actions have been discovered, such as a protective effect on mitochondria under conditions of stress. Dimebon has been used in a recently completed Phase II study conducted in Russia and showed benefits compared to placebo on multiple outcomes including cognition, global abilities, functional abilities, and behavior at six months. In a blinded six-month extension of the study, the benefits persisted for a year and in many cases the difference between drug-treated patients and placebo-treated patients widened over time. A global Phase III study of oral Dimebon in patients with mild-to-moderate AD is currently underway.

Neuroglobin is a protein that was first identified in 2000. It is a member of the globin family, similar to hemoglobin (which carries oxygen inside red blood cells) and myoglobin (which carries oxygen inside muscle cells). It is a highly conserved protein, meaning that it is a very important protein in all species ranging from mice to humans. It is known to be activated by cerebral ischemia (decreased brain oxygen) and is known to protect neurons from such injury.

Despite its ability to bind to oxygen, like hemoglobin and myoglobin, neuroglobin is unlikely to function as an oxygen delivery system. Instead, it seems to be involved in scavenging reactive oxygen molecules (oxidants) generated in response to brain ischemia and injury. Many researchers believe antioxidants are beneficial in various neurodegenerative diseases.

Recent work had shown that neuroglobin decreases beta amyloid neurotoxicity in animal models of AD. Now, a paper from a group at The Johns Hopkins University (Szymanski et al, Neurobiology of Aging, 2009) shows that variations in the gene for the neuroglobin protein may in fact increase one's risk of developing AD by producing inefficient neuroglobin. This inefficient protein is unable to defend against the toxicity of beta amyloid.

More work will be needed to determine if neuroglobin can be affected in a positive way to reduce beta amyloid toxicity in AD patients and if it may be helpful in making a diagnosis of AD.

Exercise and Brain Health in Older Adults

By Amy Jak, PhD

Exercise is a general recommendation for maintaining health across the lifespan. There is increasing evidence that physical exercise is not only good for the body but is good for the brain. Evidence comes from animal models as well as research with humans. For example, rodents housed in enriched environments with access to a running wheel and other interesting objects to play and interact with have been shown to have enhanced brain systems involved in learning and memory. In humans, evidence suggests that older adults who participate in physical exercise have improved thinking skills compared to more sedentary individuals. Exercise appears to be particularly beneficial to "higher order" or more complex thinking skills such as planning and multi-tasking. Physical activity may also prevent cognitive decline and may delay the onset of dementia. There is also emerging evidence that physical activity may contribute to maintenance of brain volume over time. These positive changes in the brain have been noted most prominently in the frontal lobes of the brain, a region generally associated with higher order mental skills.

Even in individuals with MCI, physical activity may extend periods of normal cognition and slow brain volume changes over time.

Nonetheless, many questions remain regarding the link between exercise, brain volume, and thinking. How is exercise actually exerting its positive impact? What specific brain structures might be most positively impacted by physical activity? How much exercise is enough to reap the positive benefits? At what point in life does one need to begin physical activity to gain cognitive benefits? These are just some of the questions that I am interested in answering in my studies of the effects of physical exercise on cognition and brain health in older adults.

Preliminary work from my research shows that older adults without dementia who self-reported higher levels of physical activity had significantly better visuospatial skills (i.e., visual perception and spatial relationships among objects), memory, and executive functioning (i.e., higher level cognitive skills like problem solving and planning). Exercise also aided cognition and brain maintenance in individuals with Mild Cognitive Impairment (MCI). Individuals with MCI are at increased risk for developing Alzheimer's or a related dementia. My preliminary work in this area suggests that persons with MCI who are more physically active appear to have slower hippocampal volume loss in the brain (the hippocampus is a brain structure essential to forming memories) and better maintenance of overall thinking abilities and executive functioning than those who are more sedentary.

In summary, regular physical exercise holds promise as an important non-pharmacologic strategy to delay onset or slow the rate of cognitive decline in older adults; however, the exact amount and duration of exercise needed to reap these cognitive benefits is still not clear. It is also particularly encouraging that even in individuals with MCI, physical activity may extend periods of normal cognition and slow brain volume changes over time. As such, physical exercise may be particularly important for those who have already evidenced some mild cognitive decline.

Easy Recipes

Hawaiian Chicken Salad

Serves 4

- 12 ounces frozen cooked grilled chicken breast strips, thawed
- 1 mango, peeled and diced
- 1 papaya, peeled, seeded and diced
- 1/2 sweet onion, diced
- 1 red bell pepper, seeded and chopped
- 1 cup berries
- 3/4 cup raspberry vinaigrette salad dressing
- 10 oz. pkg. mixed baby greens
- 1/2 cup chopped macadamia nuts or cashews, toasted

Combine all ingredients except the last two in a large bowl and toss gently to coat. Divide salad greens among four plates. Top with fruit and vegetable mixture and sprinkle with nuts.

Barbecued Shrimp with Pineapple

Serves 4

- 12 large raw shrimp, peeled and deveined, leave on tails
- 12 chunks or fresh or canned pineapple
- 1 red bell pepper, seeded and cut into same size chunks as pineapple
- 4 green onions, trimmed of green
- ½ cup of teriyaki or barbecue sauce

Alternately thread three shrimp, three pineapple chunks, three bell pepper chunks and one green onion on each skewer. Brush with sauce and place on the grill. Cook until shrimp turns pink and remove from grill. Brush with sauce again and serve with rice or couscous.

Chocolate Orange Frozen Pie

Serves 6

- 1 chocolate graham cracker pie crust
- ½ cup chocolate fudge ice cream topping
- 3 cups orange sherbet or sorbet
- 2-1/2 cups vanilla ice cream or frozen yogurt
- 1 cup mini chocolate chips

Spoon half of the chocolate fudge topping into the bottom of the pie crust and put in the freezer while you prepare the next step.
In a bowl beat together the orange sherbet and vanilla ice cream. Try not to mix completely, let there be streaks of orange and white throughout. Spoon mixture into the pie shell. Smooth with a spatula and top with remaining fudge sauce. Sprinkle with mini chocolate chips. Freeze until very firm. Remove from freezer 8-10 minutes before serving.

BRAIN EXERCISE

Mind Games are a really fun way to exercise the mind. Check out the mind games on the AARP website — good for both caregivers who want to stay sharp and study participants with mild dementia.

http://www.aarpmagazine.org/games/printandplay_brain_teasers.html

Time to Rhyme – Find a pair of rhyming words to describe the defintion:

1. SAD MARSUPIAL
2. COMICAL RABBIT
3. CLUELESS BOYFRIEND
4. TROJAN HORSE
5. OPERA SOLOIST
6. LOATHING
7. CENTRAL GERMAN BLONDE
8. GENUINE ENTHUSIASM
9. CITY HALLS
10. CERTAIN REMEDY
11. FAKE DIAMOND
12. ODD TRANSFORMATION
13. ASTRONAUT
14. CROP

ANSWERS

1. *Blue Kangaroo* 2. *Funny Bunny* 3. *Slow Bean* 4. *Phony Pony* 5. *Lone Baritone*
6. *Great Hate* 7. *Flaxen Saxon* 8. *Real Zeal* 9. *Mayors' Lairs* 10. *Sure Cure*
11. *Mock Rock* 12. *Strange Change* 13. *Space Ace* 14. *Field Yield*

R.I. READER

A Publication of the Alzheimer's Disease Cooperative Study

University of California, San Diego
9500 Gilman Drive
La Jolla, CA 92093-0948
(858) 622-5800
http://www.adcs.org

ADCS Director:
Paul Aisen, MD

Program Director:
Joseph Quinn, MD

Editor:
Jeffree Itrich

Contributing Editor:
Ronelyn Chavez

Layout and Graphics:
Larry Janus

ALZHEIMER'S DISEASE ADCS COOPERATIVE STUDY