NOBLE

A New Study for People with Mild to Moderate Alzheimer's Disease

A special newsletter for particpants in the Noble Research Study

Spring 2015

Letter from the Director

Dear Noble Study participants,

Allow me to take this opportunity to thank you for participating in the Noble Study for People with mild to moderate Alzheimer's disease. As you may recall, this clinical trial is evaluating a study drug, T-817, a possible neuroprotectant, designed to protect the brain from neuron loss. A neuroprotectant is used for many central nervous system disorders. It may work by protecting brain cells, which in turn may result in improved memory. That is our objective and what we are hoping to find out over the course of the study. It is our greatest desire to find a way to stop Alzheimer's and improve the lives of millions of sufferers worldwide. We could not do this without you.

As of this writing the Noble study has enrolled 40% of the people necessary in order to be able to determine if the experimental study drug is working. We hope that by the time you receive this newsletter that we will be closer to 50% enrollment. If you know of anyone with mild to moderate AD who is not taking part in this or another AD study we would be grateful if you would let them about the Noble Study and encourage them to take part.

You'll be pleased to hear that we have extended the study for those who wish to stay in longer. Participants who remain in the study through Week 52 may participate in the extension period and receive treatment until Week 80. All participants in the extension period will receive active study drug.

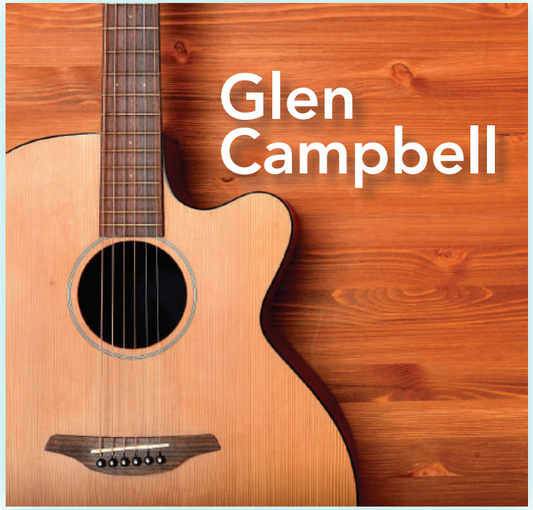
Finally, you may be interested to learn more about the experimental drug's mode of action. T-817, has both neuroprotective and neurite outgrowth effects. Neurite outgrowth is one of the necessary processes that underlie the development and plasticity of the nervous system. Enhancing neurite outgrowth, along with protecting neurons, is one of the most prominent therapeutic strategies currently being investigated to minimize neuron damage.

Toyama researchers are currently working to identify T-817's exact mechanism of action. Toyama has investigated the binding of T-817 to various receptors, and T-817 showed strong binding with certain receptors. Those receptors are known to be associated with neuroprotection, neuritegenesis and resistance to oxidative stress. Those receptors are reported to be decreased in the frontal and temporal lobes, cortex and hippocampus in Alzheimer patients. Toyama will continue to investigate the neuroprotection and the neurite outgrowth promotion effects related to those receptors and expects to provide an update in the near future.

Until next time,

Lon

Lon Schneider, M.D., M.S.,
Keck School of Medicine of USC



For country music fans it came as no surprise that 78 year-old Glen Campbell, the iconic and highly-celebrated country musician, won Best Country Song at the 2015 Grammy Awards. But for those fans and others it was the subject matter of the song that came as a shock. Campbell is in the late stages of Alzheimer's and living in a long-term care facility for Alzheimer's patients. He co-wrote 'I'm Not Gonna Miss You' with Julian Raymond while he was still lucid enough to form the words and melody. The song was featured in "Glen Campbell: I'll Be Me", a documentary that follows Campbell's journey through Alzheimer's. The bittersweet love song chronicles his battle with Alzheimer's and his affection for his family. The ode to Alzheimer's is both poignant and moving; Campbell performed it on stage numerous times during his final concert tour, two years ago. Unable to attend the Grammys, his wife Kim accepted his award. Kim Campbell said that she believed that it was her husband's love of music that has helped him survive. He was diagnosed in 2011. The song has also been nominated for an Oscar Award for Best Original Song at this year's Academy Awards. A video of the song can be viewed here: http://tinyurl.com/l96u2hy

Could a Compound in Hops Protect Brain Cells?

Wine has long been known for its health promoting advantages. Until now beer has languished on the sidelines as the poor unhealthy alcoholic relative. All that is changing with new research that examined a compound found in beer's key ingredient, hops.

Researchers at Lanzhou University, a major research university in Gansu Province, China, have identified a compound found in beer hops that could protect neuronal cells and could possibly slow the development of various brain disorders such as Alzheimer's, Parkinson's and other neurodegenerative diseases. Jianguo Fang and colleagues published their findings in the ACS' Journal of Agricultural and Food Chemistry.

They noticed increasing evidence suggesting that oxidative injury to neuronal cells is a factor in the development of brain diseases. With this in mind the researchers examined xanthohumol, a compound found in beer hops, for its potential benefits of antioxidation and anticancer properties, in addition to cardiovascular protection. In lab testing they found that xanthohumol could indeed protect neurons and possibly slow a variety of brain diseases.

Resources for AD Patients and Their Caregivers

- Sometimes caring for a loved one can feel overwhelming and justly so. With proper support and resources you can manage the byways and deal with the challenges that the disease brings.
- Check out local resources in your community by calling the local chapter of the Alzheimer's Association. They often offer a plethora of information and support. To find your local chapter visit the national website at **www.alz.org**
- The Alzheimer's Foundation also offers community resources. **www.alzfdn.org**
- The Alzheimer's Disease Education and Referral Center, part of the NIA, can provide you will more assistance than you could possibly need from brochures and books to caregiving tip sheets and resource lists to legal and financial issues to safety. Well worth spending time here. **http://www.nia.nih.gov/alzheimers/about-adear-center**
- Ask your research site or your local chapter of the Alzheimer's Association if they have a caregiver support group. Such support groups are immensely helpful with ideas and useful resources as your loved one's disease progresses. Start going to meetings as soon as possible.
- Study your and your loved one's day to determine the times of the day when your loved one is least confused and plan your routine around those times. Bear in mind that this could change so be flexible and adapt as necessary.
- Stay connected with friends and family; don't allow yourself to become isolated. Rekindle old friendships and find new ones.
- Friends and family may offer help from staying with your loved one while you go on errands to bringing over dinner. People often sincerely want to help but often don't know what to do or what you need. Let them help; don't be afraid to ask.
- Allow yourself to take a break. If you have a hobby, pursue it. Go to the movies, engage in a book club, keep up with your gardening. Ask family and friends to stay with your loved one if your interest involves leaving the house. Or if your hobby is collecting sea shells at the beach, take your loved one with you. Finding shells can be an easy and enjoyable activity for both of you.
- Take care of your own health. Don't allow yourself to become stressed or run down. If you get sick you won't be able to care for your loved one and that won't do either of you any good. Eat healthy, take your vitamins, go on a daily walk, and get plenty of sleep.
- Finally, begin to plan for the future. Waiting will not stop the inevitable. If you haven't already, pull together your financial and legal documents, investigate long term care options and determine what services are covered by health insurance and Medicare.

Add Nature, Art and Religion to Life's Best Anti-Inflammatories

By Yasmin Anwar, UC Berkeley

Taking in such spine-tingling wonders as the Grand Canyon, Sistine Chapel ceiling or Schubert's "Ave Maria" may give a boost to the body's defense system, according to new research from UC Berkeley.

Researchers have linked positive emotions – especially the awe we feel when touched by the beauty of nature, art and spirituality – with lower levels of pro-inflammatory cytokines, which are proteins that signal the immune system to work harder.

"Our findings demonstrate that positive emotions are associated with the markers of good health," said Jennifer Stellar, a postdoctoral researcher at the University of Toronto and lead author of the study, which she conducted while at UC Berkeley.

While cytokines are necessary for herding cells to the body's battlegrounds to fight infection, disease and trauma, sustained high levels of cytokines are associated with poorer health and such disorders as type-2 diabetes, heart disease, arthritis and even Alzheimer's disease and clinical depression.

It has long been established that a healthy diet and lots of sleep and exercise bolster the body's defenses against physical and mental illnesses. But the Berkeley study, whose findings were just published in the journal Emotion, is one of the first to look at the role of positive emotions in that arsenal.

"That awe, wonder and beauty promote healthier levels of cytokines suggests that the things we do to experience these emotions – a walk in nature, losing oneself in music, beholding art – has a direct influence upon health and life expectancy," said UC Berkeley psychologist Dacher Keltner, a co-author of the study.

In two separate experiments, more than 200 young adults reported on a given day the extent to which they had experienced such positive emotions as amusement, awe, compassion, contentment, joy, love and pride. Samples of gum and cheek tissue, known as oral mucosal transudate, taken that same day showed that those who experienced more of these positive emotions, especially awe, wonder and amazement, had the lowest levels of the cytokine, Interleukin 6, a marker of inflammation.
In addition to autoimmune diseases, elevated cytokines have been tied to depression. One

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recent study found that depressed patients had higher levels of the pro-inflammatory cytokine known as TNF-alpha than their non-depressed counterparts. It is believed that by signaling the brain to produce inflammatory molecules, cytokines can block key hormones and neurotransmitters – such as serotonin and dopamine – that control moods, appetite, sleep and memory.

In answer to why awe would be a potent predictor of reduced pro-inflammatory cytokines, this latest study posits that "awe is associated with curiosity and a desire to explore, suggesting antithetical behavioral responses to those found during inflammation, where individuals typically withdraw from others in their environment," Stellar said.

As for which came first – the low cytokines or the positive feelings – Stellar said she can't say for sure: "It is possible that having lower cytokines makes people feel more positive emotions, or that the relationship is bidirectional," Stellar said.

In addition to Stellar and Keltner, other co-authors and researchers on the study are Neha John-Henderson at the University of Pittsburgh and Craig Anderson, Amie Gordon and Galen McNeil at UC Berkeley.

Study of Former NFL Players Reveals Specifics of Concussive Brain Damage

A team of Johns Hopkins specialists, using a battery of imaging and cognitive tests, has gathered evidence of accumulated brain damage that could be linked to specific memory deficits in former National Football League (NFL) players experienced decades after they stopped playing the game.

Results of the small study of nine men provide further evidence for potential long-term neurological risk to football players who sustain repeated concussions and support calls for better player protections.

"We're hoping that our findings are going to further inform the game," says Jennifer Coughlin, M.D., assistant professor of psychiatry and behavioral sciences at the Johns Hopkins University School of Medicine. "That may mean individuals are able to make more educated decisions about whether they're susceptible to brain injury, advise how helmets are structured or inform guidelines for the game to better protect players."

Several anecdotal accounts and studies have suggested that athletes, such as collegiate and professional football, hockey, and soccer players, exposed to repeat concussions could suffer permanent brain damage and deficits from these events. However, the mechanism of damage and the source of these deficits have been unclear.

To reveal them, Coughlin; Yuchuan Wang, Ph.D., assistant professor of radiology and radiological science at the Johns Hopkins University School of Medicine; and their colleagues used tests to directly detect deficits and to quantify localized molecular differences between the brains of former players and healthy people who didn't play football.

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Study of Former NFL Players

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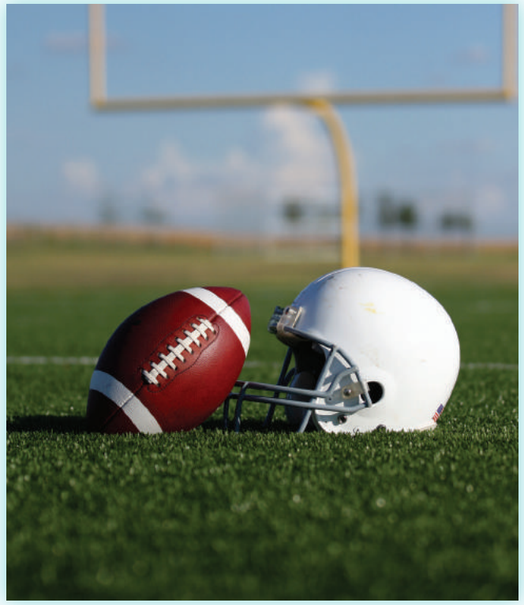
he researchers recruited nine former NFL players who retired decades ago and ranged in age from 57 to 74. The men had played a variety of team positions and had a wide range of self-reported, historical concussions, varying from none for a running back to 40 for a defensive tackle. The researchers also recruited nine age-matched "controls" — healthy individuals who had no reason to suspect they had brain injuries.

Each of the volunteers underwent a positron emission tomography (PET) scan, a test in which an injected radioactive chemical binds to a specific biological molecule, allowing researchers to physically see and measure its presence throughout the body. In this case, the research team focused on the translocator protein, which signals the degree of damage and repair in the brain. While healthy individuals have low levels of this protein spread throughout the brain, those with brain injuries tend to have concentrated zones with high levels of translocator protein wherever an injury has occurred.

The volunteers also underwent MRIs, which allowed the researchers to match up the PET scan findings with anatomical locations in the volunteers' brains and check for structural abnormalities. In addition, they took a battery of memory tests.

While the control volunteers' tests showed no evidence of brain damage, PET scans showed that on average, the group of former NFL players had evidence of brain injury in several temporal medial lobe regions, including the amygdala, a region that plays a significant role in regulating mood. Imaging also identified injuries in many players' supramarginal gyrus, an area linked to verbal memory.

While the hippocampus, an area that plays a role in several aspects of memory, didn't show evidence of damage in the PET scans, MRIs of



the former players' brains showed atrophy of the right-side hippocampus, suggesting that this region may have shrunk in size due to previous damage.

Though the researchers emphasize that this pilot study, published in the February 2015 issue of the journal *Neurobiology of Disease*, is small in size, they say that the evidence among just nine former NFL players suggests that there are molecular and structural changes in specific brain regions of athletes who have a history of repetitive hits to the head, even many years after they've left active play.

The researchers are currently looking for translocator protein hotspots in both active and recently retired players to help determine whether these changes develop close to the time of play or whether they're a result of a more delayed response to injury with similarities to other degenerative brain disorders.

If these findings are seen in studies with larger numbers of participants, they say, use of this molecular brain imaging technique could eventually lead to changes in the way players are

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USC study finds blood vessels in older brains break down, possibly leading to Alzheimer's

By Alison Trinidad,
University of Southern California

Advanced image analysis suggests breakdown in brain's memory and learning center can be detected before cognitive loss begins, suggesting important implications for Alzheimer's and dementia patients.

University of Southern California (USC) neuroscientists may have unlocked another puzzle to preventing risks that can lead to Alzheimer's disease. Researchers at Keck Medicine of USC used high-resolution imaging of the living human brain to show for the first time that the brain's protective blood barrier becomes leaky with age, starting at the hippocampus, a critical learning and memory center that is damaged by Alzheimer's disease.

The study indicates it may be possible to use brain scans to detect changes in blood vessels in the hippocampus before they cause irreversible damage leading to dementia in neurological disorders characterized by progressive loss of memory, cognition and learning. These findings would have broad implications on conditions that will affect 16 million Americans over age 65 by 2050, according to the latest figures from the Alzheimer's Association. The research appears in the Jan. 21, 2015, edition of the peer-reviewed scientific journal *Neuron.*

"This is a significant step in understanding how the vascular system affects the health of our brains," said Berislav V. Zlokovic, M.D., Ph.D., director of the Zilkha Neurogenetic Institute (ZNI) at the Keck School of Medicine, the Mary Hayley and Selim Zilkha Chair for Alzheimer's Disease Research and the study's principal investigator. "To prevent dementias including Alzheimer's, we may need to come up with ways to reseal the blood-brain barrier and prevent the brain from being flooded with toxic chemicals in the blood. Pericytes are the gate-keepers of the blood-brain barrier and may be an important target for prevention of dementia."

Alzheimer's disease is the most common type of dementia, a general term for loss of memory and other mental abilities. According to the Alzheimer's Association, roughly 5.2 million people of all ages in the United States today have Alzheimer's disease, an irreversible, progressive brain disease that causes problems with memory, thinking and behavior. Postmortem studies of brains with Alzheimer's disease show damage to the blood-brain barrier, a cellular layer that regulates entry of blood and pathogens into the brain. The reasons why and when this damage occurs, however, remain unclear.

In the Neuron study, Zlokovic's research team examined contrast-enhanced brain images

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Study of Former NFL Players

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treated after experiencing concussion or how contact sports are played.

Other Johns Hopkins researchers who contributed to this study include Cynthia A. Munroe, Shuangchao Ma, Chen Yue, Shaojie Chen, Raag Airan, Pearl K. Kim, Ashley V. Adams, Cinthya Garcia, Cecilia Higgs, Haris I. Sair, Akira Sawa, Gwenn Smith, Constantine G. Lyketsos, Brian Caffo and Martin G. Pomper.

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USC study
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from 64 human subjects of various ages and found that early vascular leakage in the normally aging human brain occurs in the hippocampus, which normally shows the highest barrier properties compared to other brain regions. The blood-brain barrier also showed more damage in the hippocampal area among people with dementia than those without dementia, when controlling for age.

To validate the research method, the USC team examined brain scans of young people with multiple sclerosis without cognitive impairment, finding no difference in barrier integrity in the hippocampus between those of the same age with and without the disease. The researchers also looked at the subjects' cerebrospinal fluid (CSF), which flows through the brain and spinal cord. Individuals who showed signs of mild dementia had 30 percent more albumin, a blood protein, in their CSF than age-matched controls, further indicating a leaky blood-brain barrier. The CSF of individuals with dementia also showed a 115 percent increase of a protein related to pericyte injury. Pericytes are cells that surround blood vessels and help maintain the blood brain barrier; previous research has linked pericytes to dementia and aging.

Brain Games

Can you read the following paragraphs?

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