Alzheimer’s Memory Loss Reversed for First Time

By Mark Wheeler, University of California Los Angeles

Patient One had two years of progressive memory loss. She was considering quitting her job, which involved analyzing data and writing reports, she got disoriented driving, and mixed up the names of her pets. Patient Two kept forgetting once familiar faces at work, forgot his gym locker combination, and had to have his assistants constantly remind him of his work schedule. Patient Three’s memory was so bad she used an iPad to record everything, then forgot her password. Her children noticed she commonly lost her train of thought in mid-sentence, and often asked them if they had carried out the tasks that she mistakenly thought she had asked them to do.

Since its first description over 100 years ago, Alzheimer’s disease has been without effective treatment. That may finally be about to change: in the first, small study of a novel, personalized and comprehensive program to reverse memory loss, nine of 10 participants, including the ones above, displayed subjective or objective improvement in their memories beginning within 3-to-6 months after the program’s start. Of the six patients who had to discontinue working or were struggling with their jobs at the time they joined the study, all were able to return to work or continue working with improved performance. Improvements have been sustained, and as of this patient follow-up is two and one-half years from initial treatment. These first memory loss associated (AD), amnestic mild cognitive or subjective cognitive impairment reports cognitive diagnosed with late stage prove.
The study, which comes jointly from the UCLA Mary S. Easton Center for Alzheimer’s Disease Research and the Buck Institute for Research on Aging, is the first to suggest that memory loss in patients may be reversed, and improvement sustained, using a complex, 36-point therapeutic program that involves comprehensive changes in diet, brain stimulation, exercise, optimization of sleep, specific pharmaceuticals and vitamins, and multiple additional steps that affect brain chemistry.

The findings, published in the current online edition of the journal Aging, “are very encouraging. However, at the current time the results are anecdotal, and therefore a more extensive, controlled clinical trial is warranted,” said Dale Bredesen, the Augustus Rose Professor of Neurology and Director of the Easton Center at UCLA, a professor at the Buck Institute, and the author of the paper.

**Web Service Offers Visual Reminders to Dementia Patients**

A new web service, MyOwnMemoryLane.com, helps support the memories of people with any form of memory loss or impairment. After users register, the patient or caregiver can upload images of the people and places in the patient's environment and provide captions. These captioned images appear in a simple slideshow which serves as a reference guide to help remember important people and places. You can watch a demo here: [http://www.myownmemorylane.com/demo.html](http://www.myownmemorylane.com/demo.html) The man featured in the demo is the grandfather of Sean Rooney who created the web service.
Over 700 Alzheimer's disease researchers from around the world converged on Philadelphia for the 7th annual Clinical Trials in Alzheimer's Disease (CTAD) conference. Rachelle Doody, M.D., Ph.D., from Baylor College of Medicine in Houston, Texas, kicked off the conference with an overview of where the field stands with respect to developing new treatments for the progressive neurodegenerative disease, which currently affects some 35 million people worldwide. Doody cited numerous potential strategies for treating dementia, including drugs and nutraceuticals that target risk factors, neurotransmitter-based therapies, neuroprotective or regenerative drugs, and drugs that modify proteins thought to be involved in AD pathogenesis. Moreover, she urged investigators to reject the distinction between symptomatic and disease-modifying drugs and instead focus on developing drugs that provide a clinical benefit. Such drugs, she said, will most likely modify the disease even if that is not the intended goal.

Collaborations for Alzheimer’s Prevention

An umbrella group called the Collaboration for Alzheimer's Prevention (CAP) was created in 2012 to coordinate efforts from three – now four - prevention initiatives: the Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU), the Alzheimer’s Prevention Initiative (API), the Anti-Amyloid Treatment in Asymptomatic Alzheimer’s (A4) study, and the newest member, the TOMMORROW Study, that will enroll people with a genetically-based increased risk of AD. TOMMORROW will test a drug that is used to treat diabetes that has been shown to slow cognitive decline.

CTAD provided an opportunity for the CAP members to share progress from each of their studies with the Alzheimer's community. The goal of CAP is to harmonize biomarker, clinical, and cognitive measures to maximize their utility for the entire field, said Randall Bateman, M.D., director of the DIAN-TU and a neurologist at the Washington University School of Medicine.

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While each trial focuses on a different population and tests a different compound, the investigators hope that by sharing expertise and data, converging on common outcome measures, standardized sample and data collection, and developing common participant recruitment and retention strategies, they will collectively answer critical questions in AD prevention. For example, while the studies have created different cognitive composite measures, through their work with CAP they converged on a similar set of cognitive domains to be tested, so that results can be compared across trials. In addition, thanks to support from the Alzheimer's Association and the Accelerating Medicines Partnership (AMP), a public-private partnership between the NIH and ten industry partners, tau imaging will now be included in all of these prevention trials. Each of these studies faces tremendous hurdles in terms of recruiting, screening, enrolling, evaluating, and retaining large numbers of subjects over a long period of time and across dozens of trial sites.

“It doesn’t take a village to do one of these trials, it takes a confederacy,” said Pierre Tariot, M.D., director of the API.

Reisa Sperling, M.D., director of the A4 study went even further. “I think it’s actually going to take a globe to defeat this disease.”

It will also take new tools, novel trial designs, new analytical methods, and other shared resources, all of which were topics of discussion at CTAD. For example, Jessica Langbaum, Ph.D., of the Banner Alzheimer's Institute in Phoenix, Arizona described the evolution of the Alzheimer's Prevention Registry. Launched in May 2012 to accelerate enrollment in coming prevention trials including Banner’s API trial, the registry is intended to be a shared resource for the scientific community as well as an awareness-raising tool for the general population. Now, after a series of refinements, including an interactive U.S. map that lists study opportunities, the registry has enrolled over 45,000 individuals toward their eventual goal of 250,000 enrollees. An interactive world map is planned, as well as a researcher portal that will allow tracking recruitment success for various projects.

**New investigational compounds**

Discovery and development of new drugs to treat dementia is indeed proceeding across diverse mechanisms. Some of the highlights from sessions include:

- R. Scott Turner, M.D., Ph.D., a neurologist at Georgetown University described a study to examine the effects of resveratrol on CSF biomarkers. The safety and tolerability trial enrolled 120 patients with mild-to-moderate AD. Patients were given placebo or escalating doses of resveratrol over 52 weeks. The drug was well tolerated and appeared to penetrate the blood-brain barrier to get into the central nervous system. No significant differences were seen in the primary outcome measures, but there were some signs that it may have stabilized deposition of amyloid in the brain and, similar to other anti-amyloid strategies, there was an increase in brain shrinkage, although the mechanisms involved in this are not clear. While the trial lacked a good clinical readout, Dr. Turner suggested that further study is warranted.
CTAD cont’d......

- Shifu Xiao, M.D., Ph.D., from the Shanghai Jiaotong University School of Medicine, presented the results of a phase II clinical trial of GV-971 in mild-to-moderate AD. GV-971 is a compound extracted from seaweed that appears to prevent the aggregation and deposition of amyloid beta. Patients were randomized to placebo, low dose, or high dose of the drug. Cognitive, behavioral, and functional improvement was seen only in those receiving the highest dose of the drug. The drug is now being tested in a phase III study in China.

- Alireza Atri, M.D., from the Massachusetts General Hospital described an ongoing phase III program of a drug called idalopiridine, which blocks receptors that bind the neurotransmitter serotonin in the brain. In animal studies the drug appeared to reverse cognitive deficits; and in a completed phase II study, it improved cognition in patients with moderate AD who were also being treated with donepezil. Interestingly, the drug also appeared to decrease anxiety, which is a significant and disturbing problem for patients with AD and their caregivers.

- Stephen Salloway, M.D., Ph.D., from Butler Hospital and Brown University presented results from the BLAZE study of crenezumab which looked at beta amyloid deposition in the brain using positron emission tomography (PET) scans. Crenezumab is an investigational, fully humanized, monoclonal antibody designed to target all forms of beta amyloid. Discovered by Swiss biotechnology company, AC Immune, crenezumab is being developed by Genentech, a member of the Roche Group. Using the standard technique for analyzing amyloid PET scans, Dr. Salloway reported no difference between the treatment groups receiving a low dose of the drug injected under the skin, a high dose infused intravenously, and a placebo. In exploratory analysis using an alternative technique in collaboration with Eric Reiman from the Banner Alzheimer’s Institute, suggested less beta amyloid accumulation in the high dose group after 18 months of treatment.

- SCarlet RoAD is the first study to test the efficacy of an anti-amyloid antibody in 800 patients with prodromal AD, an early stage of AD in defined by amnestic mild cognitive impairment and amyloid pathology as assessed by low levels of CSF beta amyloid. Phillip Scheltens, M.D. of VU University Medical Center in Amsterdam reported encouraging early screening data related to CSF amyloid pathology and the identification of patients that could most likely benefit from treatment with gantenerumab.
Ready or Not: Stem Cell Therapies Poised to Enter Trials for Alzheimer’s

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Stem cells have been hailed, and hailed some more, as a breakthrough technology. All the same, they have been slow to make real inroads in the understanding and treatment of Alzheimer’s disease. That is about to change, according to scientists who spoke at “Accelerating the Cure for Alzheimer’s Disease through Regenerative Medicine.” Held November 6 at Duke University, Durham, North Carolina, the symposium was co-chaired by Murali Doraiswamy and Joanne Kurtzberg. Kurtzberg is a pediatrician and cell therapy expert at Duke.

The first clinical trials of stem cells for AD are expected to begin in 2015, speakers said. Some cautioned that many questions remain about how stem cells affect the Alzheimer’s brain. They debated whether the move into the clinic is premature, noting the need for more research into where in the brain stem cells go and how long they last. On this, attendees were intrigued by some success tracking injected cells with MRI. In addition to therapeutic applications, induced stem cells made from patients with AD and related disorders are helping shed light on disease mechanisms and enabling screens for potentially therapeutic compounds. Research on stem cells remains limited, however, in part because it is largely supported by state initiatives, such as the California Institute for Regenerative Medicine, and private foundations, such as the New York Stem Cell Foundation.

Can Stem Cells Treat Alzheimer’s?

Therapies based on stem cells have had some success in other diseases. Transplants of cord blood, for example, are approved by the Food and Drug Administration to treat leukemia and inborn errors of metabolism, Kurtzberg said in a talk in which she described treatments pioneered by the Duke Stem Cell and Regenerative Medicine Program. Clinicians irradiate the patient’s bone marrow before administering cord blood, then stem cells in the donated blood engraft and replace unhealthy cells. In the last 25 years, more than 35,000 such life-saving transplants have taken place, Kurtzberg noted.

In Alzheimer’s disease, however, neurons die off in massive numbers throughout the brain, making cell replacement impractical. This has caused many researchers to overlook stem cell therapy as an option for AD, Mahendra Rao said in his keynote address. Rao leads regenerative medicine at the New York Stem Cell Foundation Research Institute, New York City. Nonetheless, stem cells have demonstrated the ability to improve cognition in animal models. Rather than replacing neurons, they may benefit the brain in other ways, such as by modulating inflammation, stimulating remyelination, and supplying trophic support. “This may enhance the life of dying neurons,” Rao said. Would injected cells succumb to the surrounding disease, as has been found to happen with fetal neuron grafts in Parkinson’s patients (see Apr 2008 news story; Jun 2014 news story)? Quite the opposite, Rao believes. Injected stem cells, which often mature into glia, may help modify the brain environment, thus lowering its toxicity.

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Stem Cells cont’d………..

One example of how stem cells can promote neuron health came some time ago from Frank LaFerla of the University of California, Irvine. LaFerla injected mouse neural stem cells into the brains of animals that modeled hippocampal sclerosis and Alzheimer’s disease. Treated mice improved cognitively but, in synch with what Rao said, injected cells neither became neurons nor lowered Aβ or tau pathology. Instead, they promoted formation of synapses in the CA1 region of the hippocampus, an effect LaFerla traced to stem cells releasing brain-derived neurotrophic factor (BDNF). Knocking down this growth factor in the cells before injecting them abrogated the treatment benefit. Could stem cells slow disease progression? When LaFerla modified neural stem cells to express the Aβ-degrading enzyme neprilysin, treatment with these cells lowered Aβ deposits throughout mouse brain. It is not clear if this step improves cognition further, LaFerla said in answer to an audience question.

Stem cells may also replace sick glia. Kurtzberg described the use of cord blood stem cells to treat Krabbe’s disease in children. This genetic disorder is caused by the lack of the enzyme galactosylceramidase, which helps maintain the myelin wrapped around axons. Babies born with this condition develop muscle weakness and seizures, and most die before they are 2 years old. However, those who receive cord blood transplants around one month of age, before symptoms appear, survive and generally thrive, with only mild development delays, Kurtzberg said.

Most of the stem cells that engraft in the brains of these children become glia. Studying engrafted cells in postmortem samples, Kurtzberg’s group found that they shared properties of microglia and oligodendrocytes. In mouse models, these cells secrete soluble anti-inflammatory factors, stimulate neurogenesis, and promote remyelination. The researchers are now generating these cells in vitro and are about to begin a Phase 1 trial to test whether delivering them into cerebrospinal fluid, in addition to the standard cord blood transplant, is safe in children with Krabbe’s disease. The differentiated cells should engraft more quickly than do stem cells, which take months to provide the full benefit, and thus may improve outcomes, Kurtzberg noted.

Cleanup Crew?

Amyloid deposits (green) in cortex and hippocampus of mice treated with human mesenchymal stem cells (right) are reduced by one-third compared to untreated controls. [Image courtesy of Alexei Lukashev and Tristan Bolmont, Stemedica International.]

In other cases, it is not yet clear what the stem cells do. Researchers led by Alexei Lukashev of the biotech company Stemedica International, Epalinges, Switzerland, presented a poster on the use of human adult mesenchymal stem cells to combat Alzheimer’s disease. First author Tristan Bolmont injected the cells into the bloodstream of 15-month-old APP/PS1 mice once per week for 10 weeks. The amyloid load in the hippocampus of treated mice dropped by one-third compared with untreated controls. Meanwhile, more microglia clustered around plaques, while the number of pro-inflammatory microglia shrank, suggesting that the stem cells somehow influence this balance. In ongoing work, the authors are characterizing this, as well as testing behavior in treated mice. The cells appeared safe, with no increase in vascular amyloid or microhemorrhage.

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Human mesenchymal stem cells are currently in a Phase 1/2 clinical trial for stroke. Lukashev said he is applying for FDA approval for a Phase 2 Alzheimer’s study to start next year. Similar approaches by other groups are in trials for multiple sclerosis and amyotrophic lateral sclerosis (ALS).

Other stem cell-based Alzheimer’s treatments are also on the threshold of the clinic. Ellen Feigal, who leads research and development at the California Institute for Regenerative Medicine (CIRM), noted that her organization has given out 17 awards for Alzheimer’s projects; three of those are now applying for FDA approval for trials. Two academic studies identified small neuroprotective molecules through screens of stem cells; the third, led by Alexandra Capela at the biotech company StemCells Inc., Newark, California, proposes to transplant neural stem cells into AD patients.

Conference attendees disagree whether the technology is ready for human study. “We are rushing too fast to the clinic,” LaFerla cautioned, noting that many questions of basic science remained to be answered. Also, researchers do not yet know how many cells to deliver, where, and how often in order to optimize the response, he said. Bolmont conceded that questions remain, but said he felt many of them can be answered only by trials. “We could do two more years of mouse studies, and we would still have the same question about whether these treatments will work in humans,” he told Alzforum. Feigal urged that trials and research run in parallel. “We don’t need to paralyze trials while answering basic questions. Clinical trials can inform research. It is a two-way street,” she said.

Thomas Finn from the FDA spelled out potential safety concerns for which his agency will watch. They include whether intravenous injections of stem cells might block capillaries, causing embolisms and damaging brain tissue. Another question is whether stem cells might give rise to tumors, or make the wrong kind of cells or connections in the brain, leading to side effects like chronic pain.

Where Did the Injection Go?
Stem cells labeled with the MRI agent SPIO spread through one brain hemisphere after injection into a carotid artery. [Image courtesy of Piotr Walczak, Miroslaw Janowski, Jeff W.M. Bulte, et al.]

Tracking Cells in Vivo
To allay these concerns, researchers want to be able to follow injected stem cells to see where they go and what kind of cells they become. In his talk, Jeff Bulte, a radiologist at Johns Hopkins University, Baltimore, discussed ways to label stem cells with contrast agents so that MRI can tracked them. One such agent, superparamagnetic iron oxide (SPIO), is sensitive and appears safe, having been used in several clinical trials. In a human case study, SPIO maintained a signal for more than four months. However, this compound has been pulled from the market for economic reasons, Bulte told Alzforum.

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Stem Cells cont’d......

Probes containing the stable isotope fluorine-19 (19F) emit a bright signal but are less sensitive than SPIO. Celsense Inc. of Pittsburgh markets these probes, which are in use in at least one clinical trial. Bulte’s own company, SenCEST LLC, Fulton, Maryland, develops chemical exchange saturation transfer (CEST) agents. Instead of using metal, the exchange of a proton between the agent and surrounding water creates the signal. All three approaches demonstrate potential for human use at this time, Bulte said.

With all these labels, however, the signal fades over time. Bulte is experimenting with reporter genes that could give long-term information on injected cells, with the added advantage of turning off when cells die. As an example, he said that stem cells can be engineered to express a thymidine kinase from herpes simplex virus, which is then detected by a thymidine analogue probe using CEST. Bulte also found that stem cells can be targeted to areas of inflammation by making them express the docking protein VLA-4 on their cell surface. This molecule binds to VCAM-1, which is expressed by inflamed endothelial cells. This way, stem cells penetrate into the brain three- to fourfold better, Bulte claimed.

Such tracking technologies provide a glimpse into the life of injected cells. Using MRI labels, Bulte found that stem cells injected into carotid arteries fanned out across the brain more broadly than cells injected into the brain’s ventricles or parenchyma (see image above). In an animal study, injection of large cells by this route did not disrupt the integrity of blood vessels in the brain, Bulte said.

Modeling Disease: What if Craig Had an Alzheimer Mutation?
Short of treating disease, researchers hope that stem cells will at least model human disease more faithfully than do animals or cell lines. Lawrence Goldstein of the University of California, San Diego, previously reported that induced neurons generated from people with APP mutations produced loads of Aβ40 and phosphorylated tau. At Duke, Goldstein noted that genetic variability between individual people poses a problem for modeling disease with induced pluripotent stem (iPS) cells. To address this, he generated iPS cells from a person whose genome was fully sequenced: genetics pioneer Craig Venter. Then he introduced mutations in either APP or presenilin and compared the results. To his surprise, presenilin mutations did not boost phosphorylated tau, while APP mutations did. Why this difference? Goldstein does not know yet. Currently, he is culturing induced Venter neurons with astrocytes to see if cellular interactions might influence tau processing.

Neurons in iPS cells can model other neurodegenerative diseases as well. Chris Henderson of Columbia University, New York City, generated induced corticospinal motor neurons, which selectively degenerate in ALS. Henderson compared their gene expression profile to that of oculomotor neurons, which remain intact throughout the disease, to learn what makes spinal motoneurons so vulnerable. He turned up 15 candidate susceptibility genes and four potential resistance genes. When he knocked out one of the susceptibility genes, matrix metalloproteinase-9 (MMP-9), from ALS mouse models, they lived 80 days longer than littermate controls, extending their lifespan by about one-quarter. MMP-9 is expressed almost exclusively by motor neurons and might make an attractive therapeutic target, Henderson suggested.

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Researchers also use induced neurons to screen drugs. Goldstein screened a library of 3,000 compounds on induced neurons from AD patients. He found four classes of drug that lowered Aβ, and said he is working on advancing some of them to the clinic. Henderson screened 50,000 compounds on induced motor neurons to find some that stimulated axon growth in an inhibitory environment. Surprisingly, statins boosted axon extension the most, leading to a 30-fold increase in growth. Henderson believes that the drugs are acting via a mechanism other than cholesterol. Statins themselves would not make good ALS therapeutics because they barely enter the brain and have systemic side effects, he noted. He is looking for other ways to stimulate the same pathway.

Attendees debated whether stem cells will lead to personalized medicine. In theory, clinicians could use iPS cells to generate replacement cells that contain a patient’s own DNA. By studying iPS cells from multiple donors, researchers could find specific genetic factors that predict whether a given patient will respond to a particular therapy. Clinicians want these options, speakers said, but pharmaceutical companies protest that such approaches would not be commercially viable. In practice, stem cell therapies will not attempt genetic matching in the foreseeable future, clinicians agreed. The question of whether autologous injected stem cells will last for a lifetime without inflaming the immune system will likely be answered sooner.—Madolyn Bowman Rogers

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ADCS Clinical Trials Enrolling...

For information on the following studies please visit:

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

A4 – Anti Amyloid in Asymptomatic Alzheimer’s Disease

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

On a temporary enrollment hold until late December:

SNIFF – the Study of Nasal Insulin to Fight Forgetfulness
The Dominantly Inherited Alzheimer Network (DIAN). DIAN is an international research partnership of leading scientists determined to understand a rare form of Alzheimer’s disease that is caused by a gene mutation. Understanding of this form of Alzheimer's disease may provide clues to decoding other dementias and developing dementia treatments.

Funded by a multiple-year research grant from the National Institute on Aging, DIAN currently involves thirteen outstanding research institutions in the United States, United Kingdom, Germany and Australia. John C. Morris, M.D., Friedman Distinguished Professor of Neurology at Washington University School of Medicine in St. Louis, is the project’s principal investigator.

DIAN is currently enrolling study participants who are biological adult children of a parent with a mutated gene known to cause dominantly inherited Alzheimer’s disease. Such individuals may or may not carry the gene themselves and may or may not have disease symptoms.

To register for DIAN drug trials or DIAN, visit www.DIANExpandedRegistry.org.