Making a comeback

New ways to prevent — or even reverse — dementia, paralysis and blindness

By Ruthann Richter Oct. 14, 2021

Scientists long believed the brain was immutable, unable to recover functions lost to injury or disease. But in the past few decades, researchers have devised methods to manipulate the brain and central nervous system to help the paralyzed move and enable the blind to see, and they're moving closer to restoring lost cognitive abilities.

"We are at an inflection point where we are starting to give functions back to people," said Michael Lim, MD, professor and chair of neurosurgery.

Technological advances are driving the field's progress. Using new imaging methods, scientists can view cells in the brain in exquisite detail and monitor their activities in real time.

Powerful data science allows them to track the sequence of brain processes involved in human thought and quickly analyze the resulting terabytes of data. With advances in stem cell technology, they can also regenerate tissues to help people with severe brain injuries return to everyday activities like walking and talking.

At Stanford Medicine, these advances — plus a tradition that values collaboration and out-of-the-box thinking — are empowering innovations that were the stuff of science fiction just a few years ago.

Michael Lim, MD, professor and chair of neurosurgery at Stanford Medicine. (By Leslie Williamson)

Overcoming cognitive loss Taking a different approach on Alzheimer's

Much of the effort to treat Alzheimer's disease has focused on the protein known as amyloid, which forms sticky plaques that clog the brain and contribute to neurodegeneration.

But Longo has taken a different tack.

“I think that with Alzheimer’s and some of these other degenerative diseases, there are multiple forces that promote degeneration,” with amyloid being just one of them, he said. “We wanted to create a therapy that could address multiple mechanisms at one time.”

Normally, neurons respond to signals to maintain or shut down their synaptic connections, an essential part of the brain’s communication system. Some of these connections are lost naturally as we age, but in Alzheimer’s, the signal to kill these connections becomes overly active, Longo said. That leads to memory loss and other cognitive impairments.

Early in their Alzheimer’s research, Longo and his colleagues zeroed in on a molecule on the surface of neurons that regulates the network signals involved in this degenerative process. They then developed a synthetic molecule that binds to it to block the destructive process and promote regeneration. That molecule was C-31.

In studies with mice, they found that C-31 made the neurons resistant to the effects of amyloid, prevented the formation of the toxic tau proteins that occur in the brain in the later stages of Alzheimer’s, decreased inflammation and reversed some of the effects of aging on the cells, like the shrinkage of neurons, he said.

“Our hope was that doing all of these four things might have a more powerful effect than just removing amyloid,” Longo said.

“One of the great mysteries in our field now is that we see people — even at advanced ages — with a brain full of amyloid but with memory and other cognitive function intact. While we do not understand this phenomenon and why it occurs in only a minority of people, we think we have created a compound that confers a therapeutic version of amyloid resilience.”

In mouse studies, the compound not only prevented damage to the synapses but also restored one of their most delicate structures — the dendritic spine, a protrusion in nerve cells that helps them communicate.

Frank Longo, MD, PhD, the Stanford Medicine chair of neurology and neurological sciences. (By Leslie Williamson)

“We can apply it in a late state in the disease, when the dendritic spine is lost. The animal recovers to the levels of a young mouse,” he said. “It’s truly a regenerative effect.”

The beauty of the compound is that it can cross the blood-brain barrier, so it can be taken in pill form, making it easy and inexpensive to administer, Longo said.

Researchers in Europe recently completed a clinical trial to evaluate the molecule’s safety and explore ways to measure reductions in brain degeneration.

The trial included 242 patients with mild or moderate Alzheimer’s disease and was conducted by a company that Longo founded. Analysis of the trial is underway and, if indications are positive, the next step is a much larger trial to test for efficacy.

Longo and his research team are exploring how this experimental drug works and are finding additional conditions, such as Parkinson’s and Huntington’s disease, for which it might be useful. They have also found that C-31 may be able to counter nerve damage caused by the common cancer chemotherapy drug cisplatin.

“It gives us another entry point to better understand the mechanisms underlying these diseases, and in an exciting way, to gain insight into the emerging topic of brain resilience. This knowledge will help us develop additional, entirely new approaches,” he said.

More information on active Alzheimer’s disease trials available at Stanford is on the website of the Iqbal Farrukh and Asad Jamal Alzheimer’s Disease Research Center, which was renamed in 2021 in recognition of a donation made by the Good Planet Foundation: med.stanford.edu/adrc.html.

Looking for new Alzheimer’s clues in the genes

Neurologist Michael Greicius, MD, began his latest quest for a new Alzheimer’s drug in 2014, when he met a 57-year-old woman in the throes of advanced disease. She came to the clinic with her parents, both in their 70s.

Genetic tests showed that the patient had one copy of the gene for APOE4, a protein involved in cholesterol metabolism that is also thought to affect brain function.

People with the gene are at greater risk of Alzheimer’s, but those with two copies carry a risk that is extremely high. Remarkably, the patient’s mother had two copies of the APOE4 gene, yet she was in excellent health.

“That is when I scratched my head,” said Greicius, the Iqbal Farrukh and Asad Jamal Professor. “She had a double risk. She’s perfectly healthy and yet her daughter, with only one APOE4 gene, is already affected. Something is protecting the mother. I pretty strongly suspect it’s a gene.”

He resolved to look for rare genetic variations that could be protective — something the mother had but her daughter hadn’t inherited.

“The idea would be to try to find drug targets in those molecular pathways — mimic what these people have in their natural genomes,” said Greicius, who directs the Stanford Center for Memory Disorders.

Greicius is four years into the NIH-funded study for which he and his colleagues have amassed a collection of sequenced genomes from more than 500 people with and without Alzheimer's. About half of these people are "protected" APOE4 carriers like the patient's mother.

The researchers have obtained extensive biologic data for some participants through clinical exams, spinal taps, brain imaging, immunologic testing and skin biopsies. Greicius is screening the material from these individuals, looking for genes that might have a protective effect.

He's also examining patients at the opposite end of the spectrum — those who don't have the high-risk APOE4 gene but who develop Alzheimer's at an earlier age, before they reach 65. This could point to previously unknown variants that could be implicated in the disease, he said.

Once these genes are identified, researchers can pinpoint the proteins they produce, then develop new drugs that may be able to block damaging proteins or enhance protective ones and, as a result, slow or stop the degenerative process.

Greicius' work has already borne fruit. He analyzed 25 independent studies and showed that a common genetic variation known as Klotho-VS, which protects against age-related cognitive decline, reduces the risk of Alzheimer's by 25% to 30% in older people who carry the risky APOE4 gene. He published papers on the work in *JAMA Neurology* in April 2020 and in *Neurobiology of Aging* in January 2021.

"That was a reassuring example that these variants are out there," he said. "Thirty percent is good. We're looking for variants that reduce risk by 80 or 90%. But this is certainly a good start."

More information is on the website of the Iqbal Farrukh and Asad Jamal Alzheimer's Disease Research Center: med.stanford.edu/adrc.html.

Fighting cognitive decline by taming inflammation

Scientists have long focused on inflammation as a major cause of cognitive decline among patients with Alzheimer's and other neurodegenerative diseases. But they have never understood the mechanisms behind it.

Katrin Andreasson, MD, a professor of neurology and neurological sciences, recently identified a possible pathway for inflammation in the brain and found a way to inhibit it to restore cognitive function, a finding she described in a January article in the journal *Nature*.

The key, she found, lies with a group of immune cells known as myeloid cells, which are among the body's first line of defenders. In the brain, myeloid cells are known as microglia, which also help clean up debris (like the plaques in brains of people with Alzheimer's) and control inflammation levels. In the blood, these cells are the macrophages and monocytes.

In her experiments, Andreasson compared these immune cells from older people (over 65) with those from younger people (under 35) and found the cells change dramatically as we age. In older brains, microglia promote a damaging, hyper-inflammatory environment instead of maintaining calm.

Andreasson's research revealed a downward spiral of events that begins with older cells producing significantly more of the hormone prostaglandin E2, which regulates inflammation in the body.

She detailed other molecular changes in which more of the hormone molecules bind to cells, ultimately depleting the cells' energy stores and leaving them in a perpetually exhausted state. The cells essentially devolve from young to old. Surprisingly, the changes occur not only in the immune cells in the brain but also in the macrophages in the blood, she said.

Most importantly, Andreasson and her colleagues tested older and younger lab mice using two compounds known to block the binding of the hormone and the molecule it attaches to on the cell — the EP2 receptor. They were able to stop the damage from occurring in the cells in the brain, as well as in the blood.

"We were able to restore cognition to a youthful level," she said, as the older mice were able to navigate a maze just as well as young ones. "What was a real shock was when we tested it in the circulating blood (outside the brain). ... We found if you block an EP2 receptor in a macrophage, you could restore youthful metabolism."

That means it may be possible to devise a drug that preserves cognitive function but doesn't have to reach the brain. "That's good news," she said, "because every time you put something into the brain, there is potential for side effects."

Scientists haven't tested either compound in humans, so the drugs' toxicities aren't known, Andreasson said. But it's a promising avenue for scientists to pursue in preventing cognitive decline.

"If we could somehow change our microglia so they are behaving in a healthier way, that might go a long way toward slowing down the process of Alzheimer's disease," she said.

More information about Alzheimer's disease research and treatment is on the National Institutes of Health website: nia.nih.gov/health/alzheimers.

Restoring movement for stroke patients through stem cell transplant

Neurosurgeries with stem cells have demonstrated just how resilient and adaptable the brain can be. In multiple studies, Gary Steinberg, MD, PhD, has used stem cells in stroke and traumatic brain injury patients to restore their ability to walk, speak and return to some of their normal activities.

Steinberg published results from a landmark trial in 2016 in the journal *Stroke* in which he injected bone marrow-derived stem cells into an injured area of the brains of 18 patients.

Three-quarters of the patients had clinically meaningful recoveries, meaning their daily lives were changed for the better. The others had slightly less improvement or remained the same. The recovery of some of the patients was dramatic — they were able to run and speak again after having been trapped in their injured bodies.

"Those circuits that we thought were dead in stroke patients were not irreversibly damaged," said Steinberg, the Bernard and Ronni Lacroute-William Randolph Hearst Professor in Neurosurgery and Neurosciences. "They were repressed and could be resurrected."

Steinberg has since been examining the underlying mechanisms of these recoveries. In MRI images of patients taken after the procedures, he observed a transient signal near the injured area — a bright spot — that correlated with how well the patients fared over the longer term. He speculated that this signal might indicate a beneficial inflammatory response, which his recent lab studies have borne out.

He found that the stem cells were not creating new neurons, as he initially thought, but were releasing dozens, if not hundreds, of different healing molecules. These molecules include growth factors that build new nerve fibers and proteins that help create blood vessels, as well as a number of immune system cells that can enhance brain repair.

"It turns out that the beneficial inflammatory response is present not just where the lesion is but is more widespread throughout the brain," he said. "It probably stimulates circuits very widely throughout the brain."

Steinberg has tested the same stem cells as part of a multi-center trial involving patients who suffered traumatic brain injuries at least a year before the treatment. As in the stroke study, after six months, the treated patients showed significant improvement in their ability to move and walk, compared with control patients. The researchers reported the results in the journal *Neurology* in January 2021. The most common side effect was headaches, likely related to the surgical procedure, the scientists reported.

Steinberg is embarking on a study of a different kind of stem cell — neural stem cells derived from human embryonic tissue, known as NR1 cells. These stem cells, which he developed 20 years ago, have advantages: They are easier to grow than bone marrow-derived cells, can be manufactured in large quantities and are not genetically altered.

He plans to begin testing them this year in a Stanford-sponsored, first human trial in about 20 chronic stroke patients with partial paralysis. The procedure involves transplanting the cells directly into the brain near the area of the injury. Steinberg

is the only investigator in North America using direct brain transplantation of stem cells for stroke.

"We expect that if this strategy works, we will be extending it to other indications like traumatic brain injury, spinal cord injury and, hopefully, even neurodegenerative diseases like Parkinson's, ALS or, ultimately, Alzheimer's, though that's quite a bit in the future," he said.

For more information on participating in the trial, email stemcellstudy@stanford.edu.

A high-tech glove could enable stroke patients to rehab at home

Another new approach to treating patients who've suffered strokes could come from the wearable technology field.

By 2030, nearly 4% of American adults will have had a stroke, according to the American Heart Association, and as many as 80% of those who survive will end up with weakness and loss of sensation in their arms and hands.

"Having the use of two hands is absolutely essential for normal functioning. But currently there aren't many effective interventions that can help people get that function back following a stroke," said Caitlyn Seim, PhD, a research fellow at the Wu Tsai Neurosciences Institute at Stanford.

Most health insurers cover a limited amount of exercise-based stroke rehabilitation, and half of stroke survivors don't have the mobility to even access these programs. To close this gap, Seim engineered a high-tech glove that she and her collaborators hope will one day let stroke survivors recover lost function in the comfort of their homes.

The gloves use haptic technology — originally developed for the video game industry to simulate interacting with objects and other sensory experiences — to stimulate patients' hands with programmed patterns of vibration.

Researchers have hypothesized that applying vibration to specific muscle and sensory receptors in the hands could trigger a long-term rewiring of the brain, allowing people to regain control of their weakened limbs.

More immediately, the vibrations could also help relieve involuntary muscle contractions which distort patients' limbs and constrict movement.

This idea has not been tested outside of limited laboratory studies, but that will change with Seim's new wearable technology, which she is designing for real-world use in collaboration with Stanford Medicine stroke expert Maarten Lansberg, MD, PhD, a professor of neurology, and haptics expert Allison Okamura, PhD, a professor of mechanical engineering.

"A vibrating glove that improves hand function after stroke would be a breakthrough in the field of stroke rehabilitation," said Lansberg. "Dr. Okamura and I are very excited about this technology, which can be easily used by people in almost any environment."

The research team has designed the gloves to be easy to use in a home setting by patients who suffer a wide variety of stroke-related symptoms.

"Patients need to be able to put them on themselves and wear them comfortably at home, whether they have really tight fingers or really weak fingers," said Seim, whose work is supported by grants from the Wu Tsai Neurosciences Institute and the National Center for Medical Rehabilitation Research.

The team has enrolled 20 patients in a clinical trial to test how well the gloves work in a home setting. Patients will use the gloves for two months, then researchers will monitor hand function for up to six months. A second trial is underway to determine how haptic stimulation affects communication between hand and brain.

"So far, everyone who's finished with the device says they miss it, they want it back, they love it," Seim said. "And this is after we made them wear the glove for 160 hours. So I think that's a promising sign."

Lansberg and neurology and neurosurgery professor Marion Buckwalter, MD, PhD, who direct the Stanford Stroke Recovery Program, are also adapting gaming technology to help patients recover hand function. A study published in March in the rehab-focused journal *PM&R* found that patients who used a virtual reality rehabilitation gaming device for eight weeks at home showed marked improvement of hand function and were highly satisfied with the device. The team is testing this approach in a larger, randomized controlled clinical trial.

More about efforts to improve mobility and other functions after stroke is on the Stanford Stroke Recovery Program website at stan.md/strokerehab.

The above is a redacted version of:
https://stanmed.stanford.edu/2021issue2/restoring-lost-abilities-neurological-damage.html