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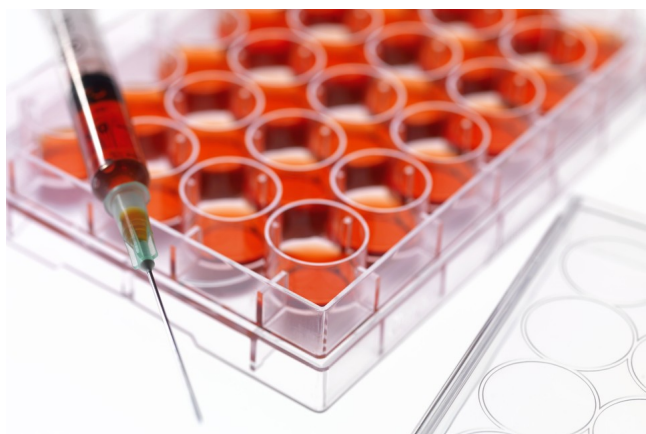
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## Stem Cells Help Evaluate Experimental Alzheimer's Drugs

Researchers evaluate new treatments by observing their effects on neurons derived from stem cells



Researchers evaluate experimental Alzheimer's drugs by observing effects on neurons derived from stem cells. *PHOTO: GETTY IMAGES*



By

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Some Alzheimer's disease researchers are using stem cells in a novel way—as a model of the disease outside the human body, enabling more efficient testing of experimental drugs in the lab rather than in clinical trials with people.

Finding a drug to slow the onset of Alzheimer's, the major cause of dementia in older people, has been frustratingly elusive. That is partly because animal testing, where most research begins, doesn't often produce results that predict very well what will happen to people with Alzheimer's. And clinical trials of drugs in humans are costly and time consuming.

Though still early days in the field, scientists at the University of California, San Diego, Harvard University and a number of other

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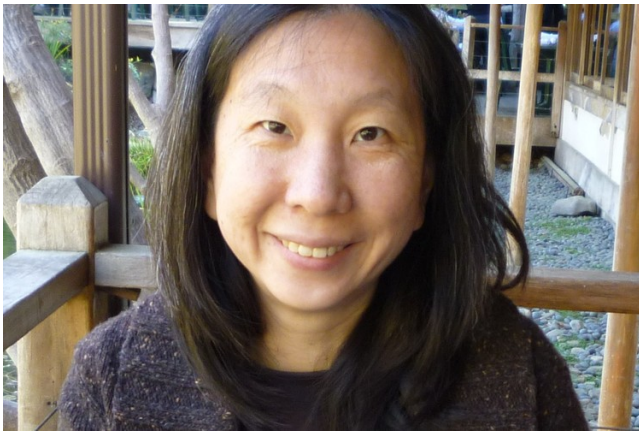
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institutions along with a growing bevy of biotech and pharmaceutical companies, are developing better ways to study the disease outside of the human body and without using animals.

In an early development, scientists at University of California, San Diego used stem cells, which can differentiate into a number of specialized cell types, to create neurons with characteristics of Alzheimer's. Then they tested two experimental drugs, including one that had previously been withdrawn from a clinical trial because it seemed to worsen disease symptoms rather than help. In testing the drug on the stem cell-derived neurons, the researchers found that for certain patients with a particular genetic mutation, the dosage received in the clinical trial was likely ineffective.



Dr. Shauna Yuan, of the University of California, San Diego, is leading Alzheimer's drug research using stem cell-derived neurons, which could one day help identify not only accurate doses for clinical trials, but also which compounds shouldn't move forward in development at all. *PHOTO: UNIVERSITY OF CALIFORNIA, SAN DIEGO*

Such "in vitro" testing of Alzheimer's drugs using human stem cells could potentially help researchers more quickly identify compounds that shouldn't move forward in development, as well as identify accurate doses of medicine for people in clinical trials, says Shauna Yuan, a professor in the department of neurosciences at UCSD and

lead researcher in the project.

For instance, scientists could test actual human brain cells more extensively in the lab, rather than jump quickly from animals to large, expensive human trials, which have become common in the field.

In the realm of treatment, one approach is to use a patient's own stem cells to repair damaged tissue—creating treatment specific to that individual. With some diseases, stem cells produce new, healthy tissue in place of damaged tissue, although it isn't clear how well that would work in the brain with neurological disorders. Another goal is to create stem cell lines that could be scaled up and used to treat larger patient populations, similar to the way small-molecule drugs and biologics therapies are used now.

There are currently more than 300 trials on stem cells happening world-wide across a variety of diseases; the largest number are focused on heart attack, and a few dozen on brain disorders like stroke or amyotrophic lateral sclerosis, often known as Lou Gehrig's disease. Many trials use mesenchymal stem cells, a subtype of adult stem cell that can be harvested from bone marrow or fat tissue, for instance. These stem cells can be delivered intravenously and tend to target damaged tissue with inflammation, according to P. Murali Doraiswamy, a psychiatry professor at Duke University and senior author of a recent paper published in *Lancet Neurology* that called for more research in the field on stem cells.

Mice and other lab animals make for poor models in which to test new medications in many neurodegenerative diseases like Alzheimer's. Lab animals don't get these types of diseases naturally, and the disease that scientists have genetically engineered into mice, for instance, translates imperfectly into what happens in humans.

"Stem cells give you a window into a living human being's brain, and that's really extraordinary," says Susan Solomon, chief executive of the nonprofit New York Stem Cell Foundation, which funds and conducts research involving stem cells.

Using DNA sequencing and neurons derived from stem cells that are genetically identical to a patient, researchers can observe how those cells are firing in either a normal way or whether they're struggling, Dr. Solomon says. One day scientists may be able to see the history of biological changes in the stem cell-derived neurons and replay how the disease developed and how processes went astray, she says.

Technological advances in genetic engineering and cell expansion now

make it feasible to develop large quantities of stem cells to enable trials, according to Dr. Doraiswamy.

There are many challenges with stem cell research in a disease as complex as Alzheimer's. It isn't clear what the optimal type of cell is to infuse into the brain, such as neurons that provide chemical messengers to the brain or support cells like glial cells. It's difficult to get the cells into the right place in the brain noninvasively and to track delivery to make sure the cells get to the target safely, says Dr. Doraiswamy.

Alzheimer's researchers have made progress in creating accurate models of Alzheimer's disease in the lab using stem cells. In research supported by the nonprofit Cure Alzheimer's Fund and published last year in the journal *Nature*, Rudolph Tanzi, a neurology professor at Harvard University, and collaborators at other institutions created a three-dimensional model of Alzheimer's using stem cell-derived neurons expressing certain mutations known to cause Alzheimer's. That is superior to mice designed to mimic the disease, which express only some types of brain changes associated with Alzheimer's.

The human stem cell model demonstrated that disease-related changes to amyloid plaques can trigger tangles in another protein called tau, says Dr. Tanzi. The relationship between amyloid plaques and tau tangles in the course of the disease has been a large source of debate in the field. Dr. Tanzi says the model makes drug screening for Alzheimer's 10 times as cheap and 10 times as fast as using animal models and other techniques.

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