Advancing Alzheimer's Research Without Animals

Could a lab-grown brain accelerate Alzheimer's disease research?

It’s a game changer, says Rene Anand, Ph.D. The Ohio State University scientist converted adult skin cells into pluripotent cells—immature stem cells that can be programmed to become any tissue in the body, including brain tissue that could replace the animals currently used in Alzheimer’s experiments.

Since 99.6 percent of Alzheimer’s drugs that test successfully in animals fail in humans, many researchers are turning toward promising new human-based technologies. Effective treatments are increasingly needed as the number of people with Alzheimer’s in the United States alone is expected to increase from 5.3 million in 2013 to 13.8 million in 2050.

Progressive and Fatal

Alzheimer’s is characterized by the development of clumps (amyloid plaques) and tangles of fibers (neurofibrillary tangles) in the brain, the loss of connections between brain cells, and the death of these cells.

The first symptoms are typically forgetfulness and difficulty performing routine, daily tasks. As it progresses, patients develop more severe memory loss, as well as speech impairment, visual-spatial problems (such as difficulty reading a map or drawing a clock), and loss of coordination and motor control. Behavioral and psychological symptoms, such as agitation, aggression, wandering, sleep disturbances, anxiety, depression, delusions, and hallucinations, can occur. On average, the survival time after diagnosis is about five to seven years.

Failure of Animal Experiments

To study the disease and test potential treatments, experimenters have developed “animal models” of Alzheimer’s in mice, nonhuman primates, rats, rabbits, dogs, and other animals. However, these “models” have a dismal record in Alzheimer’s research; experiments in animals have not translated into effective treatments for humans.

One of the most used mouse strains in Alzheimer’s experiments has a lifespan of less than 10 months. Over their short lives, the mice show features of accelerated aging including damage to the central nervous system and development of brain plaques. But there are many physiological differences between mice and humans, and there are no studies showing that the drugs tested on these mice help humans.

Alzheimer’s-in-a-Dish

Because of failures like these, scientists are developing more human-relevant technologies, such as “Alzheimer’s-in-a-dish.” Harvard Medical School researchers, including Rudolph Tanzi, Ph.D., have grown human neurons in a 3-D culture then introduced the
genetic traits associated with early-onset Alzheimer’s. The cells then produce the plaques and tangles that are the hallmarks of Alzheimer’s, paving the way for testing therapies.

“This new system should revolutionize drug discovery in terms of speed, costs, and physiologic relevance to disease,” says Dr. Tanzi, who helped develop the technology. “Testing drugs in mouse models that typically have brain deposits of either plaques or tangles, but not both, takes more than a year and is very costly. With our three-dimensional model that recapitulates both plaques and tangles, we now can screen hundreds of thousands of drugs in a matter of months without using animals in a system that is considerably more relevant to the events occurring in the brains of Alzheimer’s patients.”

Researchers are also using the cells of Alzheimer’s patients, which, unlike animals, carry the genes that contribute to the development of the disease. These cells can be tested with environmental and dietary Alzheimer’s triggers, such as metals and cholesterol, to assess disease initiation and progression. Other promising innovations include computational models and neuroimaging. See page 23 for an infographic about human-based Alzheimer’s research methods.

“Type 3 Diabetes”

Population and clinical studies are also providing answers. Several human studies have shown that nutritional interventions—the same ones that can prevent and reverse type 2 diabetes and other chronic diseases—might offer strategies to reduce the risk of Alzheimer’s.

Diets high in saturated or trans fats have been linked to high risk of
Alzheimer's disease, as has excessive copper intake.

Recently, evidence has shown a connection between diabetes and Alzheimer's. A study published in the Journal of the American Medical Association Neurology found that insulin resistance may increase Alzheimer's risk. Because of this connection to diabetes and metabolic syndrome, scientists have suggested that Alzheimer's—late-onset, in particular—could be redefined as "type 3 diabetes."

But just 10 percent of Alzheimer's research projects funded by the National Institutes of Health focus on prevention, despite the fact that research shows that the same plant-based diet that can help prevent type 2 diabetes may also play a role in reducing Alzheimer's risk.

The MIND diet, developed by Martha Clare Morris, Sc.D., a nutritional epidemiologist, and her colleagues at Rush University Medical Center may slow cognitive decline in aging adults and reduce a person's risk in developing Alzheimer's.

The diet includes eating at least three servings of whole grains, a green leafy vegetable, and one other vegetable every day, snacking on nuts most days, having beans at least every other day, and eating berries at least twice a week. In addition, the study found that it’s best to avoid butter, sweets and pastries, cheese, and fried or fast food.

"There is still a great deal of study we need to do in this area, and I expect that we’ll make further modifications as the science on diet and the brain advances," Dr. Morris says.

Dr. Morris presented at the Physicians Committee's International Conference on Nutrition in the Brain, where seven dietary and lifestyle guidelines to boost brain health and reduce the risk of Alzheimer's were presented before being published in Neurobiology of Aging.

Paradigm Shift

A new commentary in the Journal of Alzheimer's Disease by Physicians Committee medical research specialist Francesca Pistollato, Ph.D., and colleagues, addresses the need to refocus current research efforts on human-based methods, such as human cells and computational models, together with epidemiological and clinical studies.

"Animal models of Alzheimer's disease (AD) have been extensively utilized for decades... However, research success has not effectively translated into therapeutic success for human patients," writes Dr. Pistollato. "Our analysis indicates that a paradigm shift toward human-based, rather than animal-based research is required in the face of the ever-increasing prevalence of AD in the 21st century."
Why Animal Models Fail in Alzheimer’s Disease Research

In the last decade, ZERO new drugs have been developed that can effectively treat Alzheimer’s.

Today, 5.3 million Americans suffer from Alzheimer’s. Rates are expected to triple by 2050.

Currently, Alzheimer’s research relies on animal models but animals do not develop the disease as it develops in humans.

99.6% of Alzheimer’s drugs that test successfully in animals fail in human trials.

A shift toward human-relevant Alzheimer’s research

**Alzheimer’s-in-a-Dish**
Human brain cells are grown in a 3-D gel and then induced to develop plaques and tangles. Scientists can study how the disease progresses and test new therapies.

**Brain-on-a-Chip**
Brain cells are embedded on a small chip, allowing researchers to quickly test the safety of new treatments.

**Neuroimaging**
Researchers can monitor patients’ brain health—the severity of plaques and tangles—by taking images before and after a drug or nutrition intervention.

**Patient-Derived Samples**
Patient-derived brain tissues, blood, and cerebrospinal fluid samples are essential to discovering early diagnostic biomarkers of the disease.

**Clinical Trials**
Researchers use epidemiological studies to determine how and why the disease develops in certain groups of people. Clinical studies help model disease progression and test new treatment options within groups of people.