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Searching for a Cure in All the Right Places

Robert Mahley's hunt for a cure to Alzheimer's disease begins with a protein called apoE.

BY ANNE D. HOLDEN, PHD

Alzheimer's disease is one of the greatest challenges facing modern medicine. Already, more than five million people in the United States are struggling with the disease, a number that stands to grow exponentially as the world's population ages. But even more sobering is what cannot be quantified—countless memories lost; a child's helplessness as he watches a parent fade into isolation; a patient's long, slow march into darkness.

The leading hypothesis about the cause of the disease focused on a plaque-like substance, called *amyloid*, which accumulates in the brain and is thought to destroy nerve cells. Unfortunately, multiple drug trials targeting amyloid plaques have all failed, and there remains no drug available that can slow or halt the disease's progression. But thanks to four decades of research by Gladstone scientists into a protein called *apoE*—there is now a Plan B.

“Several decades ago my research team first established the link between apoE and heart disease,” explained [Robert Mahley, MD, PhD](#), Gladstone Investigator and President Emeritus. “Soon after, scientists began to see connections between a type of apoE, known as apoE4, and the kinds of severe neurological damage seen in Alzheimer's. As the pace of this research accelerated, the link between apoE4 and Alzheimer's became unmistakable. We now recognize apoE4 as the strongest genetic risk factor for Alzheimer's.”

More remarkably, Alzheimer's is not the only condition influenced by apoE4. Traumatic brain injuries—the sort suffered by combat soldiers, professional athletes and car-accident victims—as well as multiple sclerosis, Parkinson's disease and strokes, all are likely to have a worse outcome in patients with apoE4.

ApoE and Brain Damage

Living cells make thousands of proteins, each with a specific role and each with the same goal: keeping the organism healthy. Normally, apoE is involved in repairing nerve cells that have been injured, for example, by a concussion. It does this by transporting fats, such as cholesterol, to these injured nerve cells, which can then restore crucial nerve-cell connections.

But apoE comes in several forms: one that repairs cells as it should (called apoE3) but another that does not and, thus, is detrimental (called apoE4). This form is not rare—as many as one in four people have a gene for apoE4.

Surprisingly, the “good” and “bad” forms of apoE have only one chemical difference. But the end result is two proteins with different shapes that behave in very different ways. ApoE3 is transported to the outside of the neuron, where it does its repair work. But apoE4, because of its improper shape, gets stuck inside the cell.

And that’s where the problems begin. The cell, considering apoE4 an intruder, attacks it with a special enzyme called a *protease*. This molecule cuts the protein into smaller fragments, which float aimlessly around in the cell and wreak havoc on many vital cell structures.

“The result is neuronal death—a process multiplied many millions of times and affecting entire regions of the brain,” explained Dr. Mahley. “Because these parts of the brain are associated with some of our most important human functions, including memory and social interactions, the result is the progressive dementia and devastating isolation we see in Alzheimer’s patients.”

Mounting Evidence that ApoE4 Is the Culprit

Gladstone scientists have been studying apoE for more than three decades. As a result, they now know the exact genetic code responsible for making apoE and how the different forms of apoE arise. They can also track, step-by-step, the destruction apoE4 causes inside neurons. And considerable evidence suggests that apoE4 actually *causes* conditions such as Alzheimer’s, rather than simply being *linked* to them.

For example, 65–80% of all Alzheimer’s patients have apoE4. In addition, studies of people who have suffered traumatic brain injuries reveal that those with apoE4 have consistently poorer clinical outcomes than those without it. That means they are significantly more likely to develop neurological diseases.

There is even more compelling evidence about apoE4 from laboratory animal models. Mice bred with apoE4 in their brains perform significantly worse on standard lab tests that measure learning and memory than mice with apoE3. And postmortem brain examinations of mice with apoE4 show the same regions of dead, shriveled neurons that we see in Alzheimer’s patients.

Racing to a Cure

Decades of research into apoE4’s destructive mechanisms point to a combination of therapies not only for Alzheimer’s, but also for a range of neurological diseases that threaten our elderly populations:

- **A structure corrector.** The difference between apoE3 and apoE4 involves a minute change in the structure, which has a profound effect on its function. Drugs that can repair this defect, making the harmful apoE4 indistinguishable from the good apoE3, could prevent the cascade of cellular mayhem before it even begins. Gladstone scientists, including Dr. Mahley and his colleague [Yadong Huang, MD](#),

[PhD](#), have already identified molecules that correct apoE4's structure. They are now exploring how these molecules could be used for drug development.

- **A protease inhibitor.** An existing category of drugs, known as protease inhibitors, has played a key role in the fight against HIV/AIDS. Now, new inhibitors may also prevent the protease from cutting apoE4 into dangerous fragments, fragments that attack and destroy critical cell structures and kill nerve cells.
- **Protective drugs.** Gladstone scientists are exploring drugs that would shield both the mitochondria and the cytoskeletal systems from damage by the apoE4 fragments.

Dr. Mahley expects the first human tests of these proposed therapies to focus on people who have suffered traumatic brain injuries, such as professional athletes or war veterans. If patients receiving therapy have better outcomes after six or eight months compared to those who didn't receive the treatment, researchers could then expand the testing to other groups, including Alzheimer's patients.

"We may not be able to change things for patients currently suffering with Alzheimer's," added Dr. Mahley. "But hope remains that a multipronged approach, which targets apoE4 and the damage it can cause, will help our children—and our children's children—grow old with peace of mind, and without the fear of neurodegenerative disease."