Gene Therapy for Alzheimer’s Disease: A High-risk, High-reward Approach

An emerging treatment called gene therapy enables us to modify genes to correct defects that occur in inherited forms of disease, essentially stopping the progression of the disease in its tracks.

In fact, it has cured a neurological condition called spinal muscular atrophy, which affects children at birth. Its application in Alzheimer’s disease is untapped, holding the promise of conclusively addressing the genetic mutations that cause familial inherited forms of this disease. It is an entirely different approach to current treatments, which are based on remediating the pathologies of the disease, including amyloid plaques and tau neurofibrillary tangles, and have not yet achieved clinical success.

This approach is particularly compelling and is a focus of the Epstein Family Alzheimer’s Research Collaboration because of its profound potential implications. It is now possible to edit genomes to alter DNA sequences and modify gene function. If we are able to modify specific mutations that lead to Alzheimer’s disease, gene therapy could be the cure.

This effort will build on UC San Diego’s existing leadership in Alzheimer’s disease gene therapy treatment. For more than two decades, Mark Tuszyński, MD, PhD, distinguished professor of neuroscience and director of the Translational Neuroscience Institute at UC San Diego School of Medicine, and his colleagues have advanced foundational studies that lay the groundwork for this approach. He led a phase I clinical trial that assessed the safety and effects of injecting nerve growth factor into the brains of patients diagnosed with Alzheimer’s disease to slow or reverse neuronal degeneration.

“\nIt has required decades of focused work to get to this point, but we’ve found in animal studies that delivering BDNF to the parts of the brain that are affected earliest in Alzheimer’s disease results in reversal of loss of neuronal connections and protects against ongoing cell loss. Gene therapy isn’t new, but its potential in treating Alzheimer’s disease in people is largely untapped.”

~ MARK TUSZYSKII, MD, PHD
Distinguished Professor of Neuroscience
Director, Translational Neuroscience Institute
UC San Diego School of Medicine
That work led to the announcement last year of a new, first-in-human clinical trial to assess the safety and efficacy of delivering a specific protein called brain-derived neurotrophic factor (BDNF) into the brains of patients with Alzheimer’s disease or mild cognitive impairment. BDNF is part of a family of growth factors found in the brain and central nervous system that support the survival of existing neurons and promote growth and differentiation of new neurons and synapses. BDNF is particularly important in regions of the brain susceptible to Alzheimer’s disease degeneration.

The Epstein’s gift will also leverage the efforts of Subhojit Roy, MD, PhD, professor of neuroscience and pathology. Roy’s laboratory is developing a new Alzheimer’s gene therapy using CRISPR technology, targeting key genes that are involved early in the disease. His team will work with colleagues at USC who have identified and followed families with a specific gene mutation found in the Jalisco region in Mexico that predisposes them to early-onset Alzheimer’s disease, often appearing in their 30s and 40s.

While these efforts to advance gene therapy are exciting on their own, they become vastly more impactful when paired with the Alzheimer’s Disease Cooperative Study (ADCS)’s strengths in translational medicine. The ADCS is adept at taking new therapies through early clinical trials using innovative designs to more quickly identify the most significant findings.