Arresting Alzheimer's: CRISPR as a Cure to Neurodegenerative Diseases

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THE WEIGHT OF NEURODEGENERATIVE DISEASE

In 2021, 3.4 billion people globally faced harmful neurological conditions. Recent research has identified these conditions as the largest contributor of disease burden, which accounts for both the cost of living with a disability and premature death.[1] Moreover, the prevalence of this burden—especially from neurodegenerative diseases— is growing rapidly in aging populations.[2] Genetic-linked neurodegenerative diseases, such as Alzheimer's—which is estimated to affect 24 million people globally—are considered the most common and damaging, distinguished by their progressive destruction of the nervous system and brain.[3] Currently, the U.S. Food and Drug Administration approves nine prescription drugs that ameliorate symptoms of or aim at treating Alzheimer's disease (AD). However, there is no permanent cure.[4] That being said, discovering the genetic causes of AD has pointed scientists in a promising direction with the potential of improving millions of lives through gene editing.

HOPE IN CRISPR-CAS9 GENETIC ENGINEERING

Initially identified in the context of bacterial immunity, CRISPR-Cas9 plays an integral role in defending bacteria from the integration of viral genetic material during infection. The mechanism of this defense is like a pair of scissors with instructions on where to cut: a guide RNA provides the Cas9 enzyme directions for where to cut, and the enzyme cleaves these targets (Fig. 1).[5]

While this instruct-and-cut process was discovered in E. coli bacteria in 1987, revolutionary scientific advancement using the CRISPR system began in 2012, led by Jennifer Doudna and her lab at the University of California, Berkeley. Doudna's discoveries transformed CRISPR-Cas9 into a system useful beyond bacteria, allowing for programmable altering of the DNA sequence of any living organism, including humans. Now, gene editing using CRISPR tools has become routine and holds the potential to cure an abundance of genetic diseases.[6] Over the last decade, innovative research has greatly increased the editing efficiency of this technology, and off-target effects have been significantly reduced. In fact, by 2023, the first CRISPR-based drug—Casgevy—was approved as a cure for sickle cell disease. Today, many other CRISPR medicines are in the early phases of drug development, including proposed cures for urinary tract infections, cancers, heart disease, and diabetes (Fig. 2).[7]

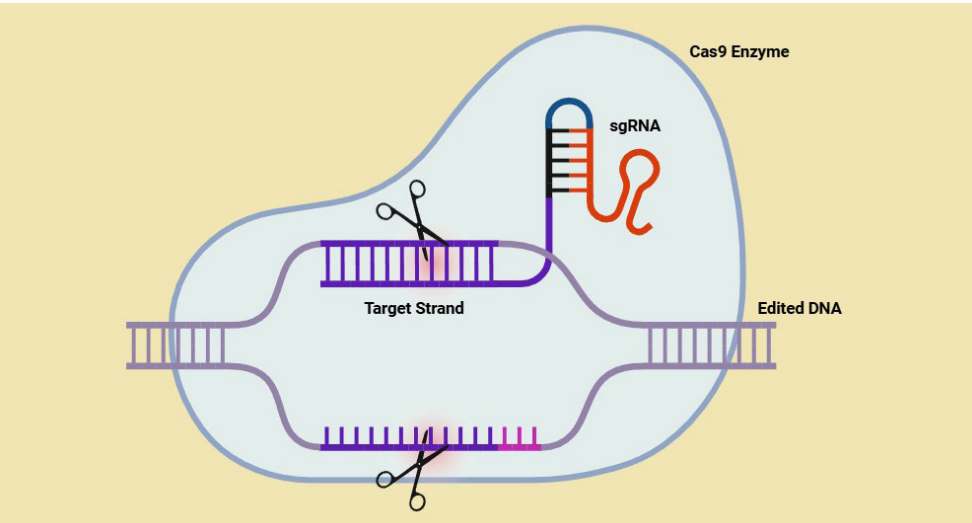

Figure 1: The Cas9 enzyme scans DNA until the guide RNA (sgRNA) recognizes the target strand. At this point, the enzyme acts as an endonuclease, cleaving both strands of DNA. Endogenous, or internal, repair mechanisms in cells fix this double-stranded break.

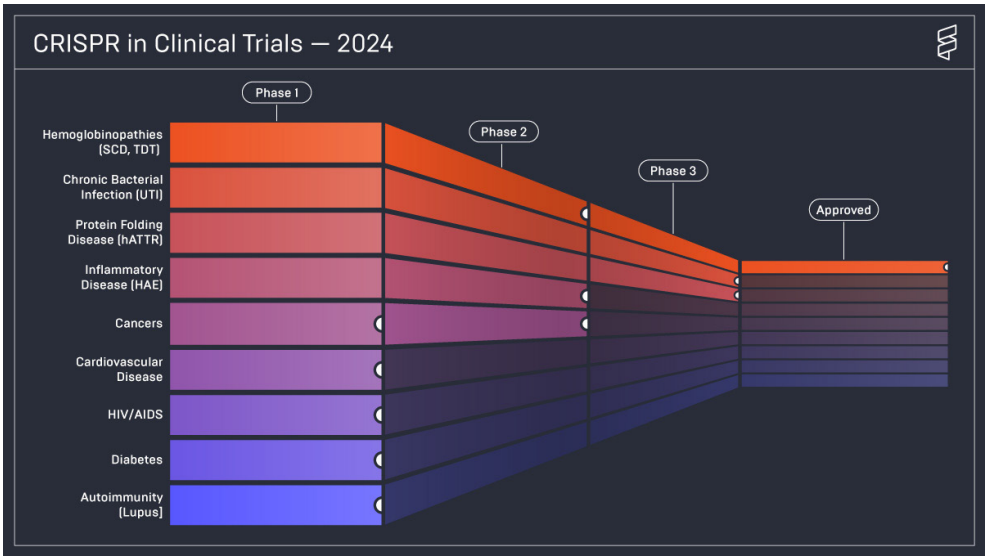

Figure 2: As of 2024, many CRISPR-based drugs are in different phases of clinical trials. A drug in Phase 1, like those addressing HIV/AIDS, indicates that a small number of participants are being tested for data about dosage and toxicity.[8] The amount of participants tested increases with each phase until the drug has enough safety information for approval. This process decreases patient risk but significantly increases the time and cost between a drug's invention and its accessibility.

THE GENETICS OF ALZHEIMER'S DISEASE AND RESEARCH RESULTS

How can CRISPR tools be applied to lessen the detrimental burden of neurodegenerative disease? Focusing on Alzheimer's disease, two major genetic factors can contribute to the disease's development: amyloid beta (Aβ) plaques and protein phosphorylation sites.

When deposited in the brain, Aβ plaque triggers an intense inflammatory response from the host's immune system, leading to progressive cell death and decline of brain function. This link to neurodegeneration makes Aβ plaque accumulation a hallmark of AD and has allowed geneticists to search for specific genes that could be contributing to the buildup. They have discovered that certain mutations in amyloid precursor protein (APP), presenilin-1 (PSEN1), presenilin-2 (PSEN2), and apolipoprotein E (APoE4) genes can elevate the production of Aβ plaque. This information alone has been significant in allowing people to test for susceptibility and prepare for the potential of future disease. However, using CRISPR-Cas9 to rid these specific sites of their plaque-increasing mutations would be revolutionary.

The second genetic factor is less established but still offers an alternative hypothesis about AD-related genetics. Tau proteins are fundamental in maintaining the proper cell structure of neurons. However, when they are modified with too many phosphate groups, hyperphosphorylation occurs and the tau protein's ability to support neuronal structure decreases. Eventually, these altered proteins end up aggregating in the brain, forming destructive tangles of neurons and proteins. This directly worsens neuronal and cognitive functioning and is associated with AD. Similar to Aβ plaque's genetic component, the hyperphosphorylation of tau has been linked to a specific genetic mutation causing overactivity of cyclin-dependent kinase-5 (CDK5), the enzyme involved in phosphorylation of tau. This CDK5 is detrimental, but has the potential to be addressed by gene editing.

With all these factors in mind, researchers set out to test whether editing these specific mutations could decrease the risk of AD. The findings are encouraging; significantly, two separate alterations of the APP gene linked to Aβ plaques resulted in reduced Aβ levels. Decreased accumulation of Aβ levels in general in fibroblasts, cells that aid in forming connective tissue, was also observed.[5] Lowering this destructive Aβ plaque buildup could directly improve brain function, which provides evidence that the progression of AD can be controlled by gene editing.

This success with APP gives insight into the future possibilities of altering PSEN1, PSEN2, APoE4, and CDK5 genes, and the immense new avenues of therapy—possibly even cures—for Alzheimer's disease.

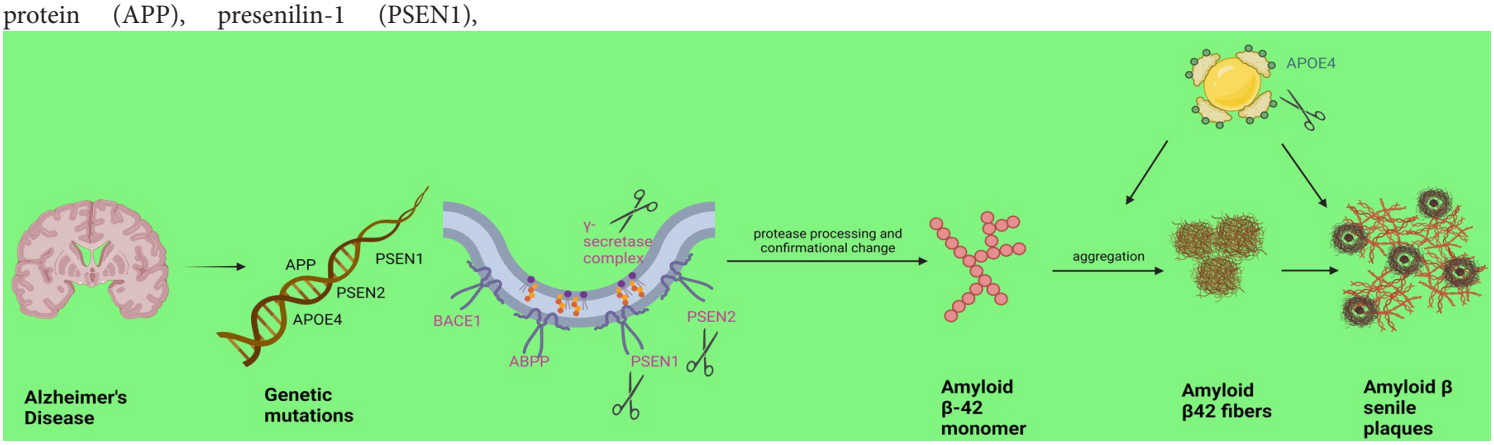

Figure 3: Genetic engineering of amyloid β protein-associated mutations can prevent the aggregation of neurodegeneration-causing plaque. This model highlights the progression of Aβ plaque build up in individuals with Alzheimer's, starting from specific genetic mutations (left of diagram). Each scissor symbol represents an area where CRISPR-Cas9 can edit the gene to make it less deleterious.

HIGH COSTS AND OTHER CAUSES: STILL A LONG WAY TO GO

Although this research provides evidence of an eagerly anticipated cure to neurodegenerative diseases like Alzheimer's, it is necessary to address where gene editing falls short. While there are clear genetic indicators of Alzheimer's, these hereditary signatures account for only around 1% of cases, with most Alzheimer's patients having sporadic (non-genetic) AD.[5]

In addition to gene editing, research around epigenetics has become a major topic of discussion. Epigenetics refers to changes in gene expression without alterations to the genome. These epigenetic modifications occur on DNA and proteins associated with DNA, often as a result of environmental factors and lifestyle. Scientists have observed epigenetic differences between healthy individuals and those with AD. The disease itself could account for these epigenetic abnormalities; however, external factors such as drug use, obesity, and stress can further epigenetic dysregulation, intensifying disease outcomes.[9,10] Taking this into account, thorough research and treatments beyond the scope of CRISPR-Cas9 are necessary to address all contributing factors of Alzheimer's.

For example, Casgevy was priced at 2.2 million dollars per patient when released, an amount unaffordable to almost all sickle cell disease patients.[11] At this point, the high price of gene editing limits the availability of life-saving drugs to only the upper class, posing a controversial ethical dilemma among scientists.

THE FUTURE FOR OUR BRAINS IS BRIGHT

Despite the limitation of cost, there remains hope as the issue of accessibility weighs heavily at the forefront of innovators' minds. For example, five of the worlds' leading genetic engineering labs, including Doudna's, are collaborating on the Innovative Genomic Institute (IGI)'s Delivery Collective, working urgently to develop a novel access-improving technology.[12] As Fyodor Urnov, Director of Technology and Translation at IGI and Professor of Molecular Therapeutics at UC Berkeley, explains, "The development of a new gene-editing medicine has to assume the same mindset as making pizza."[13] Essentially, cutting costs and time requires the ability to change toppings—or the disease CRISPR-Cas9 is addressing—without needing to re-toss the dough—or the technology and clinical trials. When the technology reaches this point of efficient adaptability, the time and costs of production will greatly decrease, and gene editing will be considered a truly accessible cure.

Though CRISPR-Cas9 is expensive and currently has the potential to aid only a limited number of neurodegenerative disease cases, any advancement towards curing conditions like AD means changing the lives of hundreds of thousands of people. This includes not only those fighting the disease, but also those at risk, as well as the large support system of caretakers, family, and friends whose lives are impacted by the destructive nature of neurodegeneration.

Furthermore, the novelty of CRISPR-Cas9 gene editing technology places an exorbitant price tag on any potential cure.

Figure 4: Epigenetic factors can contribute to the pathogenesis of Alzheimer's disease. Behavioral and environmental factors in an individual's life can alter gene expression through epigenetic changes. Contributing factors include diet, education, substance use, stress or mental wellbeing, and even socioeconomic status.

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IMAGE REFERENCES

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