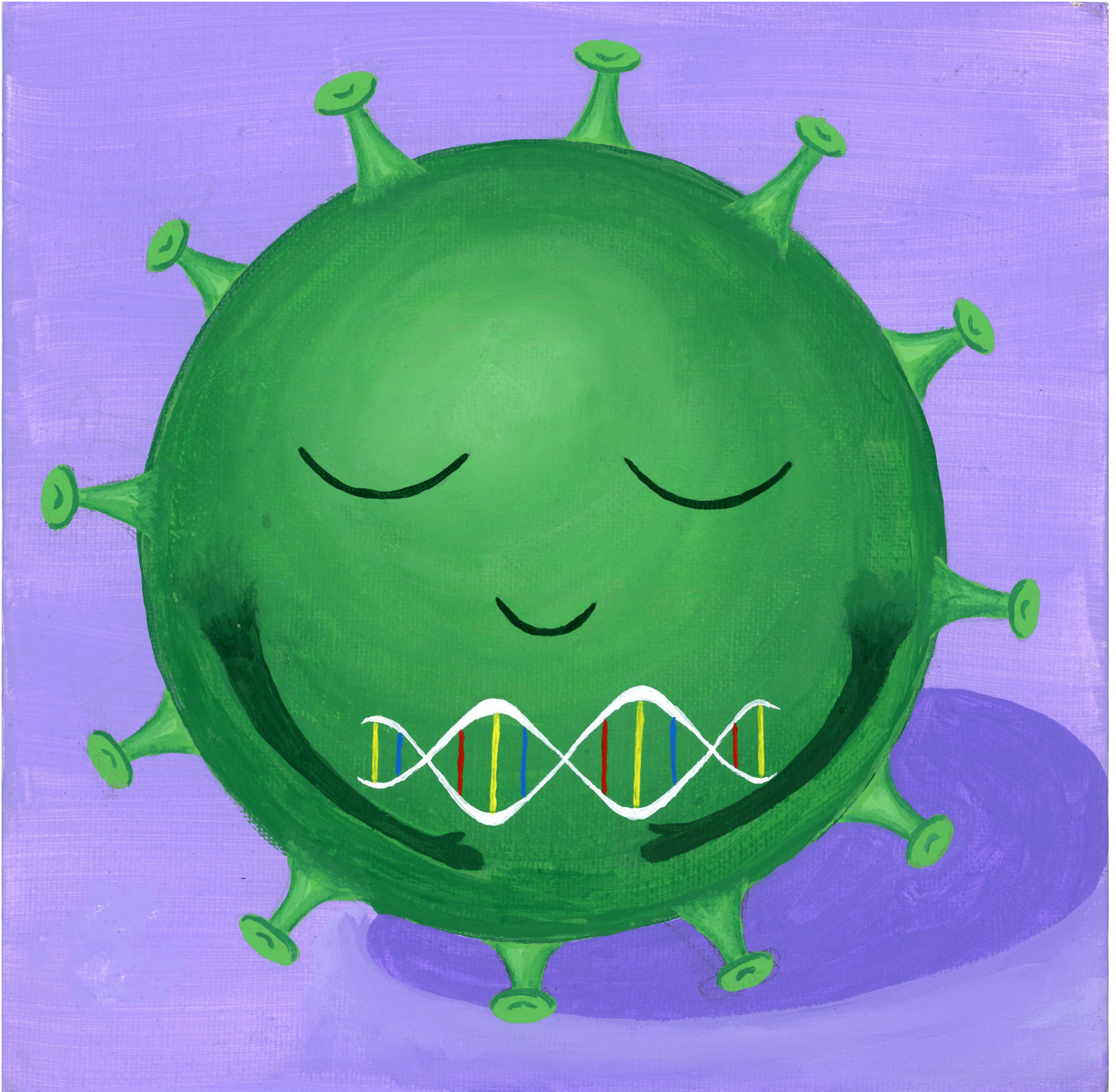


Gene-Based Therapies for Neurodegenerative Diseases

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INTRODUCTION

While infectious viruses have had devastating effects throughout history, recently developed virus-based biotechnologies have the potential to revolutionize treatment of genetic diseases. Specifically, viruses have been vital in the advancement of gene therapy [1]. Gene-based therapy treats diseases by altering the body at the cellular level with the potential to deliver longer-lasting and more personalized impacts than traditional drug-based therapies, making it an appealing route for “achieving permanent correction” [2],[3]. Gene therapy corrects mutated genes that have undergone alterations in their DNA sequence through the delivery of genetic material into cells [4]. A gene mutation occurs when there is a change in a DNA sequence that causes the sequence to be different from what is expected.

Gene mutations can be characterized as hereditary or acquired mutations. Hereditary mutations are inherited from parents, while acquired mutations are created at a particular time in a person’s life [5]. A tool known as a vector can act as a vessel for the genetic material to aid the delivery process [4].

Alongside plasmids and nanostructures, viruses can act as a type of viral vector to improve the efficiency of gene therapy [6].

Given the incurable nature of neurodegenerative diseases, which are characterized by the gradual loss of function and death of nerve cells, gene therapy is quickly emerging as a helpful method for improving their management [7]. This article will investigate the efficacy of applying gene-based therapies to the diagnosis and treatment of neurodegenerative diseases and the methodology available today.

WHAT IS NEURODEGENERATIVE DISEASE?

Each year, the percentage of the United States population that is 65 and older increases and as a result there has also been an increase in the portion of Americans affected by neurodegenerative diseases [8]. The term neurodegeneration, when broken down, literally means the loss of structure and function of nerve cells [9]. Neurodegenerative disease (NDD) is characterized

by a continual loss of targeted populations of neurons in the brain [10]. For example, the loss of upper motor neurons distinguishes ALS while spinal muscular atrophy (SMA) is characterized by the loss of lower motor neurons [9]. There are over 600 types of neurodegenerative diseases which impact over 50 million Americans every year [8]. Some examples of NDD are Parkinson’s disease, Alzheimer’s disease, amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), and Huntington’s disease (HD) [8]. Huntington’s disease is characterized by serious disability to motor, cognitive and psychiatric function [11]. Alzheimer’s disease leads to the experience of changes such as short-term memory loss, agitation, and confusion [12]. Genetic modifications play an important role in the development of neurodegenerative diseases. For example, Huntington’s disease is

caused by mutation to the Huntington (HTT) gene, which encodes for the huntingtin protein [11]. Alzheimer’s disease is caused by mutation of the following genes: amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2) [12]. Neurodegenerative diseases can be differentiated from

one another by the following factors: 1) clinical symptoms and disease characteristics presented by a patient (ex: experiencing symptoms of dementia), 2) particular location of neurodegeneration, and 3) specific protein misfolding and aggregation which cause molecular abnormality [10, 13].

HOW DOES GENE THERAPY WORK?

Gene therapy, a potentially life-saving treatment method for patients, has the capability to manage neurodegenerative disease through repair of human genes by means of correcting mutated genes which have undergone a change in their DNA sequence [6]. Mutated genes are corrected through a tedious process of replacement with a normal, unaltered version of the gene in the genome – an individual’s complete set of genetic information [6]. Firstly, there is the challenge of targeting the replacement gene, containing the mutation, to the cell of interest [6]. There is also the difficulty of releasing the genes into



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their targeted cells, as they cannot be directly inserted into cells due to the DNA and the cell membrane repelling one another [6]. However, a tool known as vectors can address these issues by carrying and releasing genes to aid the delivery process [6]. There are two different types of vectors that can be utilized: viral and non-viral vectors [14]. The fundamental function of both types of vectors and overall goal of gene therapy is to ensure the delivery of genetic material across the cell membrane and eventually into the cell's nucleus [14]. Non-viral vectors help deliver genes by use of physical systems such as electroporation and ultrasound as well as chemical systems such as lipid polymers [14]. Viral vectors use viruses that act as vessels in the gene delivery process. These viruses are modified in certain parts of their genome to ensure they do not cause disease [14]. The idea of viral vectors can be applied to the treatment of neurodegenerative diseases. When gene therapy is carried out to treat neurodegenerative diseases, a common type of viral vector known as adeno-associated virus (AAV) has proven to be a potentially advantageous option [15].

TYPES OF GENE THERAPY (IN VIVO, EX VIVO, AND IN SITU) AND HOW VECTORS ARE ADMINISTERED

The process of gene therapy can be executed through one of three main mechanisms: in vivo, ex vivo, and in situ [16]. The ex vivo mechanism is carried out by removing diseased cells from the patient and correcting mutated genes or replacing it with a normal copy. The repaired genes are then reinserted into the patient's targeted cells. In the in vivo mechanism, the corrected version of the mutated gene is directly infused into the patient's target cells. This is done by infusion into the patient's blood circulation or cerebrospinal fluid [16]. While similar, the ex vivo and in vivo techniques differ in one main way. The ex vivo correction of mutated genes and subsequent insertion of repaired genes into patient cells are grown outside the body in a cell culture, while in in vivo the corrected genes are inserted directly inside the patient's body [17]. In In situ gene therapy, the corrected genes are injected directly into the diseased tissue such as a tumor or affected areas of the brain [16]. Ex vivo is only suitable for treatment of abnormal tissue that is able to be extracted

from the patient's body and then reintroduced after genetic manipulation [17]. On the other hand, in vivo is useful for treatment of diseased tissue that contains cells which are difficult to genetically alter in a cell culture outside the body [17]. For that reason, in vivo is particularly helpful in treating diseased cells from sensitive tissues such as the brain [16], making it the ideal type of gene therapy for the treatment of neurodegenerative diseases [16].

SPECIFIC APPLICATIONS OF GENE THERAPY TO NEURODEGENERATIVE DISEASES

The specific application of gene therapy using adeno-associated virus (AAV) viral vectors to several neurodegenerative diseases can be explored [18]. AAV gene therapy is characterized by the use of a type of non-enveloped virus known as an adeno-associated virus (AAV) [18]. The AAV acts as a viral vector to carry out in the delivery of genetic material to cells [18]. AAV are an ideal type of vector for management of NDD with gene therapy because they are unlikely to cause disease and invoke disease response in patients [15]. Gene therapy through use of the AAV viral vector has been successfully applied to Spinal

Muscular Atrophy type 1 (SMA1) [15]. SMA1 is characterized by the absence or mutation of the survival motor neuron gene 1 (SMN1) which creates the SMN protein [15]. Intravenous infusion of the adeno-associated virus 9 (AAV9) vector, which contains the missing SMN protein, led to improved health outcomes of longevity for patients with spinal muscular atrophy [15]. AAV gene therapy has also been successfully utilized to improve the management of Huntington's disease. For example, the delivery of the AAV5-miHTT-451 vector led to the repression of the mutated huntingtin (HTT) gene [15]. These exciting applications of gene-based therapy to neurodegenerative diseases such as spinal muscular atrophy and Huntington's disease show improved disease management and a hope for a better quality of life for patients affected by NDD. 🧠



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