**Implications of Viral Vector Use in Somatic Gene Therapy**

**Introduction**

Since the discovery of the DNA double helix in 1953 and the completion of the Human Genome Project in 2003, a multitude of new scientific procedures and medical advancements have come into existence - gene therapy is one of them. Gene therapy is the process of altering a patient’s genes to correct a genetic flaw that causes the patient to suffer from a disease. There are two types of gene therapy: somatic and germline. In somatic gene therapy, DNA is only inserted into somatic cells (non-reproductive cells) meaning that the genetic changes will not be passed onto the next generation. In germline gene therapy, the edited DNA is transferred into the germ cells (reproductive cells), meaning that the changes will be passed onto the next generation. Therefore, germline gene therapy is more controversial in terms of ethics and interference with the progress of natural human evolution. Though a relatively new procedure, viral vector somatic gene therapy has experienced incredible advancements in recent years, such as providing possible cures to common genetic diseases such as cancer, cystic fibrosis, and hemophilia, and continues to show great potential ("Gene Therapy," 2017).

**Viral Vector Somatic Gene Therapy Process Overview**

There are still ethical issues and scientific challenges surrounding somatic gene therapy, but as it is less controversial and scientifically consequential than germline gene therapy, it has been experimented and applied more than germline gene therapy. The procedure of in vivo viral vector somatic gene therapy can be roughly outlined as the following: the target human gene is cloned multiple times using bacteria, inserted into a virus, then the vector containing the gene is introduced to the organ where the dysfunctional gene is pathogenic and the viral gene is inserted into the nuclei of the target cells. Contrary to the in vivo process, ex vivo involves modifying the cells outside the body.

**Use of Viral Vectors**

In gene therapy, a vector is essentially a carrier to transport the DNA to the target cell. There is a large variety of vectors, classified as either non-viral or viral. Non-viral vectors include electroporation, microinjection, and gold particle bombardment. When deciding on the type of virus to use, scientists must weigh the efficiency of the virus (delivery and transgene expression) against its toxicity. The 2018 paper “Viral Vectors In Gene Therapy” written by Kenneth Lundstrom and published in the peer-reviewed journal MDPI clearly outlines the key characteristics of several viruses and how they have fared in past clinical trials, providing a comprehensive guide to the applications of a diverse array of functional and available viral vectors. The adenovirus is the most widely used viral vector due to its large transgene insert capacity and high transgene protein expression. In some cases regarded as the most efficient existing viral delivery system, it is used in over 20% of all gene therapy clinical trials (Lee, Bishop, Zhang, & Yu, 2017, p. 44). This procedure, however, does not come without risks and challenges. Multiple obstacles must be overcome to allow viral vector somatic gene therapy to become a reliable, safe, and regularly implemented procedure.

**Limitations of Viral Vectors: Immunogenicity & Insertional Mutagenesis**

Since the 1980s, when retroviruses were engineered to carry transgenes to target cells instead of their own viral DNA, viruses have been integral to the facilitation of transgene expression in gene therapy. However, in 1999, the tragic case of 18-year-old gene therapy patient Jesse Gelsinger forced scientists to take a step back and reevaluate the safety and viability of viral vectors. Gelsinger was brought in to The University of Pennsylvania as a patient who needed treatment for a “partial deficiency of ornithine transcarbamylase (OTC)”, an enzyme present in the liver that allows for the removal of excess nitrogen from amino acids and proteins, and the lack of which can lead to brain damage and coma. However, shortly after he was administered an adenovirus dosage of 3.8 × 1013 particles, he developed a high fever and died four days later. His unexpected death was attributed to a “massive systemic immune response” to the adenovirus particles that led to internal organ failure. In the 2003 paper “Progress and problems with the use of viral vectors for gene therapy” published in the Nature journal, the authors, members of the Stanford Departments of Pediatrics and Genetics, take an in-depth look at this particular clinical trial and determine the exact cause of the immune response to be that the adenovirus particles, which were targeting the liver, disseminated into the main circulation system and reached tissues they were not meant to come into contact with. This paper provides an all-inclusive viewpoint on the status of gene therapy, as it takes an unbiased perspective and considers both the successful clinical trials as well as an analysis of those that have gone wrong. The Gelsinger case mentioned above brings up a major obstacle regarding the use of viral vectors: immunogenicity.

According to Jeffrey Siegel, M.D., the Senior Group Medical Director of Immunology at GenenTech, immunogenicity is “the body’s response to a foreign protein that’s put into it, trying to fight it off”. Unfortunately for scientists, adenoviral vector particles provoke strong immune responses - in fact, “90% of vector DNA is cleared from the tissue within 24 hours of intravenous vector administration” (Nayak & Herzog, 2010, p. 5). The implications of the immune response can be detrimental to the host, and in Gelsinger’s case, it led to fever, “myalgia, nausea, hepatotoxicity” and eventually death (Sack & Herzog, 2009, p. 2).

Another unintended effect of viral vectors that has been identified is insertional mutagenesis where “a mutation [is] caused by the insertion of exogenous DNA into a genome” ("Insertional Mutagenesis," n.d.).  In 2002, a French gene therapy trial went wrong when 2 out of its 11 patients who were treated for severe combined immunodeficiency (SCID-X1) developed symptoms of leukemia. The patients were given bone marrow stem cells that had been modified to contain the working gene using retroviral vectors. However, the insertion of the functional gene using a retroviral vector possibly turned on the LMO2 tumor-causing gene, causing unregulated growth of bone marrow cells - causing leukemia (Anson, 2004, p. 9). This goes against the fundamental scientific principle of medicine, “primum non nocere”, which translates to “first, do no harm”.

**Addressing Limitations**

Since Jesse Gelsinger’s death in 1999, scientists have deliberated over the best strategies that can be implemented to reduce the anti-viral immune response in gene therapy patients. Katherine High, a pediatrician at the University of Pennsylvania and the president and chief scientific officer of Spark Therapeutics, proposed increasing the potency of the therapeutic protein that the transgene encodes for, allowing for a decrease in the dosage of virus particles that would need to be administered - effectively bypassing an immune response. Another strategy, as proposed by Casey Maguire, a microbiologist at Harvard Medical School, was to encapsulate the viral vector in an “extracellular vesicle”, hiding it from the immune system and allowing for more effective delivery.

**Conclusion**

The clinical applications of gene editing are vast and promising. Already, somatic gene therapy has shown success in treating multiple common and devastating diseases such as hemophilia, HIV, and cystic fibrosis. We are fast approaching the age of personalized treatment plans, and somatic gene therapy is at the forefront - attacking genetic disorders at the root of the problem - the genome. However, more clinical trials, experimentation, and enhancement are required before it can become an efficient and regularly implemented process that is safe and affordable for the general public.