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# The Clinical Progress of Gene Therapy and Its Ethical Standing

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## Introduction

Individuals suffering from cystic fibrosis, severe combined immunodeficiency, and many other diseases that result from genetic abnormalities often feel a cure is out of reach; treatment must rely on managing the symptoms in an attempt to slow the progression of the disease. However, by utilizing a vector to introduce healthy genes into an individual, the emerging field of gene therapy holds promise in its ability to treat genetically based diseases (Smith and Byers, 2002).

The concept of gene therapy emerged in the early 1960's with a new understanding of genetic inheritance (Wirth et al., 2013) (Gillet et al., 2009). In 1961, Howard Temin experimented with chicken cells that were infected with Rous Sarcoma Virus. He noticed that chicken cells inherited viral-specific mutations containing the genetic information for Rous Sarcoma Virus progenies (Temin, 1961). This led to the realization that new characteristics might be predictably inherited through the insertion of foreign genetic material into the host chromosome. Viruses were identified as a means to deliver genes into specific cells (Wirth et al., 2013). Gene therapy was viewed as the future of medicine, as described by Edward Tatum in a symposium. *"Finally we can anticipate that viruses will be used effectively for man's benefit, in theoretical studies concerning somatic cell genetics and possibly in genetic therapy.... We even can be somewhat optimistic about the long-range possibility of therapy based on the isolation or design, synthesis, and introduction of new genes into defective cells of particular organs"* (Gillet et al., 2009).

While various vectors and animal models were tested throughout the 1970's and 80's, the first human trial of gene therapy was not approved by the Food and Drug

Administration (FDA) until 1990 (Wirth et al., 2013). Two children with adenosine deaminase (ADA) deficiency, leading to severe combined immunodeficiency (SCID), were treated with their own blood cells that were modified ex vivo and reintroduced in an attempt to make proper adenosine deaminase. This trial yielded limited clinical benefit, but its safe completion paved the way for future human gene therapy clinical trials (Wirth et al., 2013).

Although the field of gene therapy appeared to be booming at the turn of the century, two failures led to major skepticism. Jesse Gelsinger, an 18 year old with ornithine transcarbamylase deficiency (OTC), enrolled in a phase I clinical trial conducted by the University of Pennsylvania to evaluate the safety of using an adenovirus vector to transfer OTC genes into patients. In 1999, the trial resulted in the death of Jesse Gelsinger, after the vector elicited a severe immune response and fulminate respiratory failure (Smith and Byers, 2002). Another setback in gene therapy's progress occurred during a trial treating severe combined immunodeficiency-X1 (SCID) in 1999. Using a  $\gamma$ -retroviral vector, they attempted to treat SCID-X1 by correcting a mutation in the  $\gamma$  chain of common cytokine receptors necessary to develop T-cells and NK-cells. While initial results seemed promising, the retrovirus' insertion led to T lymphoproliferation that resembled leukemia in 5 of the 20 patients involved in the trial (Shaw and Kohn, 2011). Both of these failures deterred optimistic feelings regarding the immediate benefit from therapeutic gene transfer.

The field of gene therapy continues to improve upon vectors and protocols and produced medications that are available to the public. China became the first country to approve a commercial gene therapy in 2003. The medication is called Gendicine® and it

replaces the p53 gene via a nonreplicative virus in order to treat head and neck squamous cell carcinoma (Wirth et al., 2013). China also approved Oncocrine® in 2005 to treat late-stage refractory nasopharyngeal cancer by inserting a gene with a deletion that will inactivate wild type p53 in host cells to limit replication and causing oncolysis in tumor cells. Lastly, in 2012 Glybera® was recommended by the European Medicines Agency for approval as a treatment for severe lipoprotein lipase deficiency. The adeno-associated viral vector inserts a gene to express lipoprotein lipase in muscle tissue (Wirth et al., 2013).

With the momentum of commercially available gene therapy treatments, the use of gene transferring technology will continue developing and treating a large variety of genetically based diseases. However, the use of gene therapy technology has the potential to extend beyond the realm of strictly correcting disease-causing genetic abnormalities. Potential gene therapy procedures can be classified as somatic, germ-line, and enhancement (Anderson, 1985); as technology continues to develop, the viability of each type of gene therapy becomes a reality. Thus, the ethical standing of each application of gene therapy must be addressed along with its clinical successes in order to avoid unethical practices in research and medicine.

### **The Mechanism of Gene Therapy**

Gene therapy is performed either ex vivo or in vivo. Ex vivo procedures remove the cells from the patient's body, genetically alters them, and then reinserts them. In vivo procedures, however, genetically modify the cells inside the patient. Apart from the approach, gene therapy procedures can vary in the type of biological components utilized

to deliver the desired gene into the patient (Smith, 2003). These biological components, or vectors, are divided into the broad categories: viral and non-viral.

Liposomes and naked DNA are two examples of common non-viral vectors. Liposomes are spheres of a lipid bilayer that envelope a transgene, interacting with the host cell allowing for endocytosis of the exogenous genes. Naked DNA directly injects the transgene into the tissues for uptake and expression (Smith, 2003). Because these non-viral vectors are composed of typical cellular contents, they result in fewer toxic and immunological consequences during therapeutic use. However, the extent of successful gene transfer and the resulting transient gene expression limit the potential for current non-viral vectors (Somia and Verma, 2000).

While viral vectors can potentially result in more severe toxic or immunological consequences due to the insertion of viral components into the host, they can be modified to remove their pathogenic features to create safe and efficient vectors. The transgene that will fix the genetic abnormality in the patient is engineered to replace the pathogenic portion of the virus, and when the host cells are infected with the virus, the transgene is introduced into the host (Somia and Verma, 2000).

The two main classifications of viral vectors are integrating and non-integrating. Retroviruses, lentiviruses, and adeno-associated viruses are the common integrating vectors and they give the potential for life long transgene expression due to their ability to insert the transgene into the host cell's genome. Once in a chromosome, the inserted gene segment is replicated and transcribed as a normal sequence on the host's genetic material. The main type of non-integrating vector is an adenovirus, and it does not lead to

life-long gene expression because its genetic material is not inserted into the host chromosomes (Somia and Verma, 2000).

### **Ethical Concerns Following The Gelsinger Tragedy and Induced Leukemia**

The Gelsinger tragedy failed to uphold major ethical principles. Jesse Gelsinger, an 18 year old with OTC, was the first documented mortality of a therapeutic gene therapy clinical trial. Major ethical concerns surfaced surrounding the way the researchers, Dr. Wilson, his colleagues and the University of Pennsylvania conducted and reported the clinical trial. The researchers allegedly altered the consent form that was approved by the IRB to hide two primate deaths that resulted in an earlier version of the protocol from potential participants. The purposeful removal of adverse events from the informed consent resulted in trial participants that lacked sufficient information about the trial and its safety. They also were accused of failing to report other adverse events in animals and healthy human subjects to the FDA during the trial. In addition, they hid Wilson's conflict of interest as Novotech's founder, a biotechnology corporation that would reap financial benefits if this gene therapy were proven successful. Lastly, Gelsinger's blood ammonia levels were above the designated stop level outlined in the protocol before they began treating him. Due to the disregard of biomedical research ethics, further gene therapy research had to be conducted with increased scientific rigor to maintain public trust for its future clinical utility (Smith and Byers, 2002).

The OTC trial and the death of Jesse Gelsinger illuminated ethical concerns extending beyond the quality of the research; experimental gene therapy procedures on

humans was shown to be dangerous. The questions regarding its research were only heightened after the trials treating individuals with SCID-X1 produced 5 cases of induced leukemia out of the 20 individuals treated (Shaw and Kohn, 2011).

In the wake of these experimental failures, public opposition to gene therapy trials began to rise. This included a proposal to the Recombinant DNA Advisory Committee calling for an immediate moratorium on somatic gene therapy experiments using viral vectors, unless in the case of certain patient death without the experimental treatment. However, the committee spoke against the proposal and no action was taken to discontinue human gene therapy experiments (SoRelle, 2000).

Similarly, the American Association for the Advancement of Science called for a total moratorium on experimental germ-line gene therapy, which is defined as genetic alteration of germ cells that would effect future generations (Marshall, 2000). This decision was determined because they saw the risks to the individuals undergoing the therapy, as well as the future generations, to outweigh potential benefits and thus make the procedures unethical (Marshall, 2000). While Austria, France, Germany, Denmark, Sweden, and the UK have legislation that blatantly prohibits germ-line gene therapy, the USA does not have explicitly limit its use (Pattinson, 2000).

### **Successful Gene Therapy Treatment of ADA and Commercial Use of Gendicine**

While the tragic death of Jesse Gelsinger and the induced Leukemia justify the questioning of future experiments if they can have such devastating results, gene therapy trials have also lead to significant clinical benefit for individuals suffering from previously incurable diseases. Ashanti DeSilva was one of the two children suffering from ADA deficiency treated in 1990. Before the trial, she was no longer responding to



her treatment and there were no available donor matches to undergo a bone-marrow transplant. Ashanti was likely to die within the next few years and her parents felt they had no choice but to enroll in the trial. Within six months after the trial, her T-cell count rose to a normal level, and with the continued low dose treatment she took before the trial, she is now a healthy and active individual (Naam, 2005).

Tracking the success of Gendicine<sup>®</sup> after its approval for commercial use in China results in further optimism for the clinical potential of gene therapy. A review of multiple clinical trials has shown synergistic effects of using Gendicine<sup>®</sup> with radiotherapy, chemotherapy, surgery, and hyperthermia in the treatment of various cancers (Peng, 2005). For example, in one trial with 135 patients having head and neck squamous cell carcinoma, Gendicine<sup>®</sup> in concordance with radiotherapy had a 64% complete regression and 29% partial regression. The complete regression of the combined therapy was 3-fold higher than the radiotherapy on its own. A similar trial on patients with advanced liver cancer found that the gene therapy along with transcatheter arterial chemoembolization had significantly better response rates (67.6%) than the control (51.2%). Yet another trial gave Gendicine<sup>®</sup> to patients with advanced solid tumors of 13 different kinds of cancer that did not respond to conventional therapies; clinical benefits were observed in 10 of the 21 patients that completed that trial (Peng, 2005).

With a split history of fatal consequences and clinical successes, an ethical debate is justified surrounding the appropriate conditions for and the application of gene therapy research.

## **Ethics of Therapeutic Somatic Gene Therapy**

Therapeutic somatic gene therapy is the application of genetic modification in somatic cells to correct an established genetic defect in the patient (Anderson, 1985). The main concerns surrounding this type of gene therapy are questions of safety and consent (Smith, 2003). As mentioned previously in the instances of Jesse Gelsinger and induced leukemia, gene therapy trials have resulted in serious and potentially fatal side effects. However, these ethical concerns of safety are common in conventional medicine and many clinical trials attempting to discover novel treatments (Smith 2003). In Phase I clinical trials, when determining a safe dose to use in future clinical trials the conventional threshold for toxicity due to the treatment is 33% (Le Tourneau et al., 2009). Though the 25% rate of induced leukemia in the SCID-X1 trial seems large, it falls within acceptable limit for clinical trials. In order to continue with trials of somatic gene therapy in an ethical manner, individual patients must be provided all the relevant information regarding the trial and must consent despite the possible risks (Smith, 2003).

As many genetic disorders are detected at birth, the process of consent is often complex. There is the potential of an ethical debate with older children as to who has the right to consent, the child or the parents. However, standard medical ethics have a procedure dealing with children's consent on a case-by-case basis; if it is determined that the child is capable of making a rational decision when consenting or withholding consent, they are able to proceed with a gene therapy trial as desired (Smith, 2003). Somatic cell therapy trials that are properly monitored for consent and safety are considered to be ethically sound because of the principle of beneficence; this therapy

would result in a greater good for the human race by relieving the suffering from genetic defects (Anderson, 1989).

### **Ethics of Somatic Gene Enhancement Therapy**

Somatic cell gene modification can also be used to insert a gene in the effort to enhance a certain characteristic (Anderson, 1985). Gene enhancement has been successfully completed in mice by inducing the production of more type-I muscle fibers. By inserting a gene that increases the activation of PPAR $\delta$ , a “long distance-running” strain of mice was created due to the increased presence of fatigue-resistant type-I muscle fibers (Wang et al., 2004). Enhancement gene therapy, also called gene doping in an athletic context, has been used in humans with recombinant erythropoietin (EPO) that can increase oxygen delivery to muscles. Another potential use of enhancement gene therapy in humans could insert insulin-like growth factor 1 (IGF-1) and growth hormone (GH) to stimulate body growth and increased protein synthesis (Brzeziańska et al., 2014).

One major difference in enhancement genetic modification is that it produces additional gene products in order to have an increased effect instead of merely correcting a genetic disorder. With new metabolic pathways, regulators, and hormones being discovered every year, altering the metabolic equilibrium may have increased implications on the safety of enhancement procedures. The genetic alteration of cells to increase their production of certain products, such as GH, may affect numerous metabolic pathways in an irreversible manner (Anderson, 1985).

Apart from the potential dangers of gene enhancement therapies, there are further ethical issues about the procedure. One argument proposes the gene enhancement of a neurotransmitter that can enhance memory capacity, or the increased production of GH to

a child of two short parents, and identifies problems with determining who should receive the gene and how to prevent discrimination against those who do or don't receive the gene (Anderson, 1989).

Anderson describes potential criteria that could be used to pick those treated for enhanced memory capacity, such as those best able to benefit society (most intelligent), those most in need (least intelligent), those picked by a lottery system, or those that could pay for the treatment. Without a societal consensus on how to proceed with distribution of the treatment, Anderson suggests that this technology be limited to treatment based on greatest medical need, meaning therapeutic therapy. He believes that gene enhancement therapy could result in a separation and discrimination against individuals that were fortunate to receive the enhancement therapy (Anderson, 1989).

A differing argument examines the ability to distinguish between therapeutic and enhancement procedures. The ability to define a "normal" individual and quality of life has already been complicated by modern medicine's ability to prolong lifespan, increase fertility and increase the survival capabilities of the unfit. Thus, the difference between therapy and enhancement is not discernable, and instead is a moral continuum. Further, the desire to better ourselves has been a driving force for human evolution and thus gene enhancement procedures are morally sound (Chan and Harris, 2006).

### **Germ-line Gene Therapy**

Germ-line gene therapy is the insertion of a gene into the reproductive cells of a patient in order to correct a genetic disorder in their offspring. Just like somatic gene therapy, treatments in theory could both be therapeutic and enhancing (Anderson, 1985). A very important difference in the ethical consideration of germ-line genetic modification

from somatic cell therapy is the presence of safe and effective means of gene insertion. Currently, attempting germ-line therapy would be immoral due to the lack of safe technology (Smith, 2003).

Even when sufficient germ-line gene transfer techniques have been developed, there are some ethical concerns regarding its practice. Germ-line therapy's clinical effects would not be limited to the individual receiving the therapy; its inserted genes will affect that individual's future generations. Because of this, the long term safety of this type of genetic modification should be initially tested thoroughly for generations in animal models before it is attempted in humans (Anderson, 1985). These inserted genes also have the potential to spread throughout the population once they have been accepted as a part of an individual's germ line genetics (Smith, 2003). Because of this, general public approval should be achieved before a medical therapy with the potential to effect the genetic makeup of the entire population is performed (Anderson, 1985).

Smith states that the future of germ-line gene therapy must be approved on a case-by-case basis of an ethics committee that has carefully weighed the benefits and risks of the procedure. The benefits of the therapy must take into account the severity of the disease or disorder being treated and the success of conventional treatments for the disease or disorder. Conversely, the risks of the procedure would examine the safety of the proposed treatment (Smith, 2003).

Smith also identifies the potential to use germ-line genetic modification as a form of enhancement for future generations as a form of eugenics. While it seems attractive to have legislatures get involved to ban germ-line gene therapy on the basis of its eugenic-like applications, it would limit the medical potential of this technique as a treatment for

serious diseases. On the other hand, an unchecked potential of this type of procedure could lead to the formation of a genetic elite and a genetic underclass. Similar to somatic therapies, there is not a line easily differentiating between therapeutic and enhancement administrations of germ-line therapy, and it would be difficult to permit one without the other (Smith, 2003).

## **Conclusion**

Gene therapy has made some incredible strides since its first human trials. Even with the tragedies of the Jesse Gelsinger trial and the induced leukemia in SCID-X1 trials, optimism surrounds this developing field. As vectors are improved for safety and efficacy, even more medications will join Gendicine<sup>®</sup>, Glybera<sup>®</sup> and Oncocrine<sup>®</sup> as commercially available and approved gene therapies.

The only application of gene therapy that has limited controversy is therapeutic somatic gene therapy. By affecting the somatic cells of the individual receiving the treatment in order to treat a genetic defect, the only ethical considerations that need to be examined are the safety and consent of the patient. The Gelsinger tragedy provides an example of a trial that disregarded ethical practices by hiding deleterious effects in animal trials when receiving consent, as well as continuing the trial despite warning signs. However, with proper adherence to traditional biomedical research ethics, therapeutic somatic gene therapy is an ethically sound practice.

When examining the use of somatic gene therapy for enhancement, a more substantial ethical argument exists. First, this type of treatment poses additional safety concerns; by increasing the expression of certain genes instead of strictly replacing a nonfunctional gene, gene enhancement may throw off the metabolite balance and affect

multiple pathways. Second, even if the procedure is determined to be safe, how should it be determined who deserves access to the treatment. Third, the ability to distinguish between therapy and enhancement is becoming increasingly difficult as conventional medical practices have altered what a “normal” individual is. It would be difficult to ban the use of somatic gene therapy for enhancement if it were determined in rigorous clinical trials to be a safe practice. With the presence of cosmetic surgery, various diet pills, and supplements to increase muscle mass, there are already approved procedures used to enhance individual characteristics. Similar obstacles, such as financial resources, would be present in receiving both gene therapy and other enhancement therapies. Thus, enhancing somatic gene therapy should be treated in a similar manner ethically as cosmetic surgery and dietary supplements.

Germ line gene therapy poses similar ethical questions as somatic gene enhancement therapy. First, the current status of the research and the lack of a safe therapy limit its current ethical footing. However, with the production of an efficacious and reliable therapy, each application must be examined on a case-by-case basis to determine the ethical stance of its use. The potential for germ line therapy as a form of eugenics should not incite legislation banning the whole practice; it has legitimate potential to treat incurable diseases that result from genetic abnormalities. While it is difficult to clearly distinguish between therapy and enhancement, I feel only grave medical conditions should be considered to have sound ethical use in order to avoid the creation of a genetic elite that results from unequal access to treatment.

The future of gene therapy will bring about increased clinical utility for all three types described in this review. While I feel somatic gene enhancement therapy fits into

the current ethical scope of conventional medicine, a precedent will need to be set when distinguishing between therapy and enhancement if germ line therapy will ever be clinically available.



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