ETHICAL CONSIDERATIONS OF ADENOVIRUS-MEDIATED GENE THERAPY

Hannah Liu (hkl11@pitt.edu)

INTRODUCTION

For several years I have worked with neural stem cells, cells that still possess a certain amount of potential to divide into several specific cell types and also have the ability to self-renew [1]. I have used them as vectors for gene therapy to treat patients with glioblastomas\(^1\). These stem cells have the ability to house “suicide genes”—genes that disrupt DNA synthesis in cancer cells—and systematically deliver them directly to these cells. Once the transgenes are successfully transported to the cancer cells, an enzyme is expressed. This enzyme can then convert a non-toxic prodrug into a cytotoxic agent [1]. A prodrug is a precursor of a drug and is subsequently chemically converted by the expressed enzymes into a toxic, anti-cancer agent [2]. While traditional methods of surgery, radiation and chemotherapy are still widely used today, gene therapy shows promise for a less toxic and more accurate therapeutic approach.

Recently my supervisor approached me, asking if I would be interested in joining him in a clinical study testing a new method for treating glioblastomas. This research would entail using a different vector as opposed to the stem cells. This vector would be an inactivated adenovirus, carrying the same type of suicide genes which would act similarly to those within stem cell vectors once introduced into the body. Also, the subjects would be almost fully developed fetuses as opposed to grown adults, with whom I usually work. These fetuses do not possess developed judgement skills and would therefore not be able to give explicit consent. A main issue is if we consider consent by the parents to be the consent of the fetus. Also, adenoviral vectors raise multiple safety concerns, such as their immunogenicity\(^2\) and lack of specificity when attempting to target just the cancer cells instead of other surrounding, healthy cells.

In light of these concerns, I must make a decision on whether or not I would like to be involved in this study. While I find the clinical study risky and out of my specialty, my supervisor has given me this responsibility and I do not want to disappoint him as this will not only advance our lab, but it will also enhance the bioengineering field and widespread education of gene therapy techniques. Also, I need to consider that glioblastomas are one of the most common types of brain tumors in humans. The need for a new, efficient, and reliable form of therapy is constantly growing. The prognosis of patients diagnosed with glioblastoma is terminal, with a 5-year survival of less than 3% of patients despite “multi-modal treatment” approaches consisting of surgery and radio- and chemotherapy [3]. If this study were to be successful, we would be participating in a crucial medical breakthrough. I have to consider my personal ethics as well as multiple other implications—including safety, societal, and economical—resulting from this research before I can accept his offer.

BRIEF OVERVIEW OF GENE THERAPY AND TECHNIQUES

Initial gene therapy trials began more than two decades ago, including around 1700 approved clinical trials; through this time many medical advances have been made as well as the realization of societal concerns [4].

What is Gene Therapy?

The European Medicines Agency (EMA) defines that a gene therapy medicinal product is one that “contains an active substance which contains a recombinant nucleic acid\(^3\) administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence” [4]. Essentially, gene therapy entails the use of a vector which houses genes that, once expressed, can eradicate a tumor directly, as opposed to the “blindness” of chemotherapy or radiation. There are two types of gene therapy: somatic and germ line. My research is somatic gene therapy, which only changes a select group of somatic cells, while germ line affects gametes\(^4\) and can be passed on to future generations.

What is an Adenovirus/Adenoviral Vector?

The vectors being used in the gene therapy proposed for this new clinical trial are called adenoviral vectors. These vectors are genetically engineered versions of an active adenovirus. Adenoviruses (Ads) have a genome that encodes approximately 35 proteins which are expressed in order to initiate and complete viral DNA replication in a host...
[5]. Virions\(^5\) assemble inside the adenovirus and after several days the cell lyses, or breaks, to release the infectious virus to the rest of the host [5].

An adenoviral vector is a genetically modified version of the virus, thus providing an open space for the new genes to be housed and delivered. The vectors have their essential viral DNA removed and replaced by a high activity promoter that drives expression of the new transgenes that will be introduced into the body [5]. The main advantages of adenoviral vectors are that the efficiency of transduction is high, as is the level of gene expression [5]. In other words, adenoviral vectors provide an environment in which the transgenes are able to replicate well, leading to mass expression of the proteins that interfere with DNA replication of the cancer cells.

While they may be able to propagate well, adenoviral vectors are not cell-specific, which can lead to uptake in other cell types such as healthy, neighboring cells, thereby reducing the specificity of the therapy [6]. Adenoviral vectors are not entirely reliable as they may interfere with healthy cells as opposed to solely cancer cells. Also, adenoviral vectors show a possibility of provoking an immunological response in the patient since it can still be seen as a foreign invader of the body [6]. Since the body may not recognize the vector, its immune system will begin to attack it, causing inflammatory responses, especially after repeated administration [6]. In practice, using adenoviral vectors is much more efficient, easier to acquire, and cheaper to produce as opposed to other gene therapy vectors. However, one has to consider the ethical implications of trading welfare of the patient for ease for the researcher.

**SAFETY AND ETHICAL CONCERNS OF ADENOVIRAL VECTORS**

As previously mentioned, adenoviral vectors pose many medical risks and a major concern in my situation is if I approve of the use of these vectors as opposed to stem cells. According to Article II Section 1 of the National Society of Professional Engineers (NSPE) Code of Ethics, “Engineers shall hold paramount the safety, health, and welfare of the public” [9]. This statement is not necessarily so black and white in my situation, however. If I consider the general public, then this research would not violate the code of ethics; I would be searching for an alternative solution to the treatment of glioblastomas, or at the very least eliminating other options, pushing us closer to another possible long term resolution. However, it is not ethically sound to subject the fetuses to a technique that I do not find beneficial to their safety, health or welfare. Thomas Wirth of the Dept. of Biotechnology and Molecular Medicine at the University of Eastern Finland asserts that “the use of viral gene transfer vectors has raised skepticism about their safety, as it was shown that integration of the transgene may occur in an actively expressed site, presenting a possible threat to patients” [4]. Moreover, since adenoviral vectors do not exhibit tumor tropism\(^6\), the vectors may accidentally transport the transgenes to healthy cells as opposed to just the cancer cells. This can in turn cause insertional mutagenesis\(^7\) or oncogenesis\(^8\).

In addition to their lack of specificity, adenoviral vectors have proven to be immunogenic, or capable of causing an immune response from the body, which can be fatal. For example, the recent tragic and widely publicized death of Jesse Gelsinger in a gene therapy trial at the University of Pennsylvania raised many ethical concerns of using adenoviral vectors. Gelsinger was an 18-year-old male with a mild form of ornithine transcarbamylase (OTC) deficiency, a disorder of nitrogen metabolism [8]. In 1999 a team of researchers at the University of Pennsylvania’s Institute for Human Gene Therapy, injected adenoviral vectors into his body, containing a gene to correct his genetic defect [8]. He had received the largest number of virus particles in the gene therapy trial, and four days later he died from an immune reaction to the virus vector [8]. Since the virus is seen as foreign to the body, the body’s immune system begins to attack the virus, causing a plethora of side effects. Additionally, only 1% of the transferred gene reached the target cells, which shows the inability of adenoviral vectors to reliably attack cancer cells as opposed to healthy cells [8].

Paul Gelsinger, Jesse Gelsinger’s father, asserted that his son had not been told important preclinical evidence of the vectors’ toxicity [8]. Julian Savulescu, Director of the Ethics of Genetics Unit at the Murdoch Children’s Research Institute, states that two main ethical goals of research include “ensuring that the expected harm involved in participation is reasonable and that participants give valid consent” [8]. However, in my situation, a fetus is the subject. Although we may acquire consent from the fetus’ parents, the fetus is the one being affected. According to Article II Section 1 of the Biomedical Engineering Society (BMES) Code of Ethics, “Biomedical engineers involved in research shall [respect] the rights of...human and animal subjects” [11]. To be ethically sound, I need to protect my subjects if I believe that adenoviral vector use is not the best option for treatment. I cannot restrict their voices, even if they do not have one yet. Julian Savulescu additionally stresses that if “there are serious risks including a risk of death associated with participation in this trial, it is better

\(^5\) The infectious form of a virus as it exists outside the host cell, consisting of a nucleic acid core, a protein coat, and, in some species, an external envelope [14].

\(^6\) Tropism in the context of glioblastomas is a biological phenomenon that is characterized as an innate tendency of injected NSCs to migrate towards areas of the central nervous system with injury or pathology [7].

\(^7\) Mutation caused by the insertion of new genetic material into a normal gene [14].

\(^8\) The generation of tumors [14].
that the trial be conducted on humans who consent to those risks rather than on those who cannot consent" [8]. This means that transparency and honesty in research must be held with the highest priority. However, performing gene therapy on fetuses violates this principle as well as the oath to protect the public health.

**POPULAR PUBLIC PERCEPTIONS OF GENE THERAPY**

Not only does adenoviral gene therapy pose safety concerns, but it also raises questions of consent and the societal implications of costs. While this therapy holds great potential for the treatment of both genetic and nongenetic conditions, I must consider my personal ethics as well as those of the general public. Julie M. Robillard, Assistant Professor of Neuroethics at the University of British Columbia, conducted a survey study of the popular opinions of the public on multiple gene therapy topics. Issues included explicit consent as well as costs. These are relevant to my situation as a fetus is the subject, instead of a fully cognizant adult. I must reflect upon my obligation to my subjects, the general public, as well as my supervisor.

**Lack of Information**

A major concern with gene therapy is subjects not understanding or not being provided with all the necessary information regarding the therapy [10]. Essentially, people are afraid that they will not be fully prepared or debriefed on the procedure and its outcomes. This returns to the central canon of consent, as seen in Article III Section 3 Subsection A in the NSPE Code of Ethics. It is stated that “Engineers shall avoid the use of statements containing a material misrepresentation of fact or omitting a material fact” [9]. In my situation, I would not necessarily be lying, but I would not be properly telling the fetus what this procedure is and its potential consequences. Similarly, in Article III Section 1 of the BMES Code of Ethics, it is asserted that “Biomedical engineers involved in research shall comply fully with legal, ethical, institutional, governmental, and other applicable research guidelines, respecting the rights of and exercising the responsibilities to colleagues, human and animal subjects, and the scientific and general public” [11]. By performing gene therapy on a fetus I would be violating the principle of respecting human subjects [11].

An example of a possible violation of these principles occurred in June of 2000 when Dolores Aderman sued the University of Pennsylvania after having been a subject in one of their gene therapy experiments. She claims that the University “failed to disclose to her all the risks of the experimental treatment” [12]. She felt that this violated her “essential dignity” [12]. The principles behind this lawsuit translate to my situation. I find it unethical to subject a human being to treatment they do not necessarily want to receive or know they are receiving.

**Costs and its Societal Implications**

In addition to consent, the economic considerations of adenoviral gene therapy are just as important. Recently, the unit price of the first European Medicines Agency-approved human gene therapy product, alipogene tiparvovec was announced be approximately 1.11 million euros, or about 1.2 million dollars [13]. As a member of BMES, I must adhere to all principles of the code of ethics, including Section 2 of Article II that states “Biomedical engineers involved in health care activities shall consider the larger consequences of their work in regard to cost, availability, and delivery of health care” [11]. This is not entirely helpful when considering my situation as I cannot necessarily change the price tag on this therapy. The reason that it costs so much is that this therapy is mostly philanthropically funded and the techniques/procedures needed to construct the adenoviral vector/gene complexes are expensive in nature.

Considering this cost, is it ethical to provide this therapy that may be only available to the rich? This would be infringing upon the NSPE Code of ethics Article II Section 1 tenet that states “Engineers shall hold paramount the safety, health and welfare of the public” [9]. I would not be providing welfare for the public, rather I would only be providing to a select few. Expensive therapies contribute to widening healthcare disparities that exist between the rich and the poor [13]. However, this is not the fault of biopharmaceutical companies or the patients. Also, it would not make logical sense to just withhold treatment so to not contribute to the disparity between rich and poor. It can be argued that gene therapy can be beneficial to the general public as it provides funding to biomedical research as well as financial incentives for further investment in new therapies [13]. This means that as the cycle of money flows, more and more research can be conducted, possibly providing a better solution for cancer therapy in the future. Therefore, I can conclude that the costs of gene therapy are ethically sound.

**CONCLUSION**

Based solely on both codes of ethics, I would ultimately refuse to participate in this new clinical study involving adenoviral gene therapy on fetuses with glioblastomas. A major issue is the lack of consent from the fetus in an especially dangerous and risky form of therapy. Referring to Section 1 of Article II of the NSPE Code of Ethics, I personally do not find it ethical to participate in adenoviral gene therapy when I do not believe that it will maintain the safety, health or welfare of the public [9]. I am aware that glioblastomas are terminal and that chemotherapy and other treatment options are becoming unviable. I realize there is a
huge time crunch to find a new solution and this study could advance the biomedical engineering field and spread more knowledge. However, by considering all aspects such as consent, safety, other similar case studies, and the responsibility of the researcher to protect their subjects, I have come to the decision that I will not accept my supervisor’s offer. While it may be very difficult to turn down a superior, I advise all other engineers in a similar position to carefully consider the effects on not only the general public but also on their individual subjects. Engineers must remember their moral responsibility to not only advance the engineering field but also hold high the welfare of the public.

REFERENCES


ACKNOWLEDGEMENTS

I would like to acknowledge Jessie Liu, who took the time and had the patience to help me in proofreading this paper. I would also like to thank Shane McKeon for proofreading this paper for a final time. Lastly, I would like to thank Dr. Vidic for this opportunity.