

Gene Therapy- From Medicine to Perfection and the Ethical Arguments

Carl DeGuzman
Biochemistry 118Q
Professor Douglas Brutlag
12/3/09

One promising but somewhat less publicized branch of medicine is gene therapy, which involves the insertion of genes into an individual's cells and tissues in order to treat a disease. Gene therapy can be divided into two main types, somatic gene therapy and genetic gene therapy. Somatic gene therapy involves the transfer of therapeutic genes into the somatic cells of a patient. These cells include every cell type in the human body except for the cells which make up the sperm and ova and undifferentiated stem cells. The second type of gene therapy, genetic gene therapy, involves the modification of the germ cells or the sperm or eggs of the patient. The changed genes of the germ cells then become inheritable by the offspring of the patient. In theory, this approach could be used to treat diseases that are hereditary or passed down as genetic disorders. However, this passing down of traits to one's offspring is part of the reason that genetic gene therapy is surrounded by more ethical controversy than its somatic counterpart. Furthermore, the development of these two techniques has led to the possibility of genetic modification in not only those who are suffering from a disease, but also those who are in good health. Genetically altering one's genes could lead to enhancements in strength, cognition, mood, or height. This opens up a whole new side of the ethical debate, whether or not we should try to make ourselves "more perfect" through the use of gene therapy. Scientists however continue to perfect gene therapy and hope that soon it will be able to cure otherwise untreatable diseases.

Somatic gene therapy is at a much further stage of development than genetic gene therapy. There are two different types of somatic gene therapy, ex vivo and in vivo. Ex vivo involves altering the cells outside of the body and then transplanting them back in, while in vivo involves modifying the cells while they are still in the body. In order to introduce the necessary gene in a patient during somatic gene therapy, a vector is needed.

Most often, some sort of viral vector is used in order to implant the new DNA in the cell. Various types of viruses such as retroviruses, adenoviruses, and adeno-associated viruses are used which replace the target gene with a modified gene. Retroviruses must convert the RNA it carries into a strand of DNA before the cell's genetic make-up is changed, rather than carrying a copy of its own DNA to introduce to the cell. The strand of DNA made by the retrovirus is then introduced into the DNA of the cell by an integrase enzyme. Sometimes the DNA strand is placed in a part of the DNA where it does no good. Therefore, methods have been developed to insure that the DNA is introduced the right way. Unlike retroviruses, adenoviruses carry double-stranded DNA. They also do not integrate with the host cell's DNA, but instead float free in the nucleus of the host. The instructions in the strand are carried out normally, but when the cell replicates the DNA strand is not passed down to the replicated cell and therefore the therapy must be readministered as the cell population grows. Gendicine, the first gene therapy product to be licensed to treat cancer, is an adenovirus and is used to treat neck and head cancer. Finally, scientists use adeno-associated viruses (AAV), which are small viruses that contain a genome of single stranded DNA. It works either by inserting its genetic material on a certain site of chromosome 19, or by recombining with the host DNA. Although it carries such a small amount of DNA and is difficult to produce, AAV vectors are popular because people usually do not develop an immune system response to them. Also, AAV vectors are able to deliver genes to the

brain, unlike other vectors. Along with adenoviruses, AAV vectors are able to infect a wider range of cells than retroviruses, which infect only a limited number of host cell types. Although there are other methods that do not involve viral vectors, these vectors are the most used techniques in order to introduce the therapeutic DNA into the host cell.

Unlike somatic gene therapy, genetic gene therapy is still in a mostly theoretical stage of development. There are two stages of the germline that work well for genetic gene therapy: when the egg is released either before or after it is fertilized by the sperm, and when the egg is forming blastomeres. It is possible to simply inject DNA into the egg, and the DNA will integrate into one of the chromosomes. However, this method does not always work properly and can result in some cells of the embryo receiving the modified DNA while other cells do not. When the germline is in the blastomere stage it is manipulated in a test tube, creating embryonal stem cells. These cells can later be injected into a blastocyst and implanted in a surrogate mother. This gene therapy then results in an individual who has some cells that contain the modified embryonal stem cells, and some cells that do not have the modified DNA in them, but DNA which comes from the fertilized egg. So far, gene therapy has been successful in modifying various traits of animals, and scientists are rapidly learning more about this technique.

While the use of somatic gene therapy in medicine does not face much ethical scrutiny, the same cannot be said of genetic gene therapy. Opponents have two main issues with genetic gene therapy when describing why it is unethical. The first issue involves the progeny of the patient who are affected by the therapy. The second issue centers on the fact that in order to do the gene therapy, in vitro fertilization must be used. Proponents of this therapy point to the potential breakthrough treatments this therapy may offer when they try to answer these ethical problems.

Those who support genetic gene therapy bring up two strong arguments in favor of it. The first is that by modifying the genes of the embryo, they believe one will be able to avoid the onset of diseases that would have been unavoidable otherwise. Embryos could be screened to determine the likelihood of developing certain diseases, and could be treated accordingly. Very severe genetic disorders that do not allow the embryo to develop properly could be treated before they are able to affect the growth of the embryo, allowing the baby to be born in the first place. Also, since the genes are passed on to the progeny of the patient, somatic gene therapy will not have to be used repeatedly on each generation. The transmission of genetic diseases would be stopped, removing the cost and risk involved when these diseases are treated. The second argument that they bring forth is that with germline therapy, the cause of the disease would be treated, not just the symptoms, and it would therefore be a true cure. This would be much better than other traditional treatments, such as chemotherapy, which the patient may have to endure for a number of years (Bushelle).

In spite of these potential benefits, opponents of germline gene therapy such as the Catholic Church strongly hold that it is unethical. One reason genetic gene therapy is found to be unethical is the potential harm that may be caused to the generations that come after the patient. In *Dignitas Personae*, a 2008 document released by the Congregation of the Doctrine of the Faith of the Catholic Church, the Church states that “Because the risks connected to any genetic manipulation are considerable and as yet not fully controllable, in the present state of research, it is not morally permissible to act in a way that may cause possible harm to the resulting progeny.” Gene line therapy basically changes the lives of future people who are unable to consent to the altering of their genes. They would possibly be subject to a lifestyle that they would not have been free to choose for themselves. Also, because there is the risk that the

therapy may not go as planned, more people than just the person who is first treated could be affected in an adverse way. A second reason given in *Dignitas Personae* is that in vitro fertilization must be used in order to do the therapy. *Dignitas Personae* says that, “In the hypothesis of gene therapy on the embryo, it needs to be added that this only takes place in the context of *in vitro* fertilization and thus runs up against all the ethical objections to such procedures.” One of these objections is the fact that many embryos are discarded during the process of in vitro fertilization. The Church sees that each and every embryo is a full human being, and so cannot be treated as just “a mass of cells to be used, selected, and discarded.” Invasive experimentation also must be done on the embryo, which the Church and many other moral groups oppose. The ethical standing of the human embryo remains a major point for those who are opposed to genetic gene therapy and other procedures that involve human embryos in general.

In spite of the controversy that surrounds genetic gene therapy, much progress has been made in the area of somatic gene therapy which shows that there is great potential in this type of therapy. In April of 2008, British researchers announced they were able to improve the sight of those who suffered from inherited blindness. Those tested were young patients who suffered from Leber’s congenital amaurosis (LCA), a disease that affects the RPE65 gene and causes the retinal cells to not function properly. Normally, LCA appears very early in life and causes progressive vision loss until the person can no longer see. The patients were given a healthy RPE65 gene by delivering the normal genes to the retina using a viral vector. A fine needle was used to access the cells beneath retina by a controlled retinal detachment, which heals once the viral vector is absorbed. This technique proved to be safe, as it both did not affect the extremely fragile tissue in the surrounding areas or produce any adverse or noticeable side effects. Those

treated experienced vision at least as effective as before they were treated, and one patient experienced significantly improved night vision. These results showed the scientists that nothing bad came from injecting the gene into the patients, and that if treatment was started early enough it was possible to improve the sight of those who suffered from the disease. Because of somatic gene therapy, those who suffered from LCA can now hope for restored sight, something that was impossible before the new therapy (UCL Institute of Ophthalmology). Even more recently, scientists have been working on a way to cure cancer through somatic gene therapy. By combining nanoparticles and the necessary genes, scientists are researching a way to target cancer cells but not the healthy cells surrounding them. The altered genes are wrapped up in microscopic nanoparticles which are taken up by cancer cells but not healthy cells. They then activate the production of a protein which kills the cancer cells. This is unlike traditional chemotherapy which kills all the cells in the cancerous area. Although this technique has only been tested on mice, scientists hope to start human testing in just a few years. Even cancers that are impossible to reach through therapy would be able to be treated by this method, and scientists hope they can also use this to treat a cancer that has spread (BBC).

All of this progress inevitably leads to more questions that raise even greater ethical issues: should somatic and genetic gene therapy be used on people with no actual diseases but want to improve certain parts of their genetic make-up? One example is brought up by ethicists to show how easy it may be to make the jump from using gene therapy for medical purposes to using it for non-medical ones. A technique has been developed to transfer genes into hair follicles, and now scientists are searching for the genes that promote hair growth. Research began in order to help treat cancer patients who had lost hair as a result of chemotherapy. However, once this technique is perfected, what would stop those who are suffering from natural

balding from pursuing the same treatment in order to reverse the balding? Although this is a small example, it can be applied to a wide range of other enhancements. Scientists have been able to insert memory-related genes into mouse embryos, and these mice are able to learn quicker and remember longer than their non-enhanced counterparts (Sandel). The potential impact of gene therapy outside of medicine sparks a heated ethical debate between those who believe these therapies should be open for all and those who believe gene therapy should only be used in a medical setting.

Supporters of genetic enhancement normally argue from a position based on expanding freedom of choice and liberty, and they claim that genetic enhancement will lead to happier lives by widening the scope of choices parents and children will have. More control would be given to the individual to do things as they see fit, which would not in any way hamper the future of that person since that is what they desired in the first place. They also argue that parents who want to modify their child's DNA before they are born are no different from parents who control what their children do after they are born. Another point brought up is that children will not have to suffer from their lack of natural abilities or traits. They would be able to avoid the bullying that comes from other children due to some trait or lack thereof that they possess. Gene therapy would allow these "designer humans" to lead more healthy and fulfilling lives, according to those who support genetic enhancement.

Opponents of genetic enhancement normally argue from a position based on one losing their sense of giftedness, which can be seen through both a religious and secular viewpoint. Opponents worry that people will soon play the role of God and come to believe that all of one's talents and powers are their own doing. The religious viewpoint is clearly expressed in *Dignitas Personae*, which states "it must also be noted that in the attempt to create *a new type of human*

being one can recognize *an ideological element* in which man tries to take the place of his Creator.” Other points made by the document include the creation of two social classes, those who have access to the therapy and those who do not. This would interfere with the equality of all human beings, as it would be impossible to fulfill the desires of every single individual. All of this implies “an unjust domination of man over man” which moves away from an attitude of caring for others and away from accepting human life in its natural form. The secular viewpoint against genetic enhancement is well laid out by Michael Sandel, a political philosopher at Harvard University, in his essay entitled “The Case Against Perfection”. He argues that by continuing to pursue genetic enhancement, three features of our moral landscape would be transformed: humility, responsibility, and solidarity. Humility would be the first feature to leave society because people would no longer view their talents as gifts, but as wholly their own doing. The recognition that our talents are not wholly one’s doing is what constrains the pride of many individuals. Responsibility would then increase immensely if people became responsible for their own genetic make-up. Less will be attributed to chance and more to choice, creating pressure on people to choose the right traits in order to be successful. Sandel says that “the more we become masters of our genetic endowments, the greater the burden we bear for the talents we have and the way we perform.” Finally, Sandel argues that it is the recognition that our talents are gifts that causes people to help others in the first place. Because people are not responsible for their genes, they are more willing to help out those who are not as fortunate genetically. By choosing gene therapy, Sandel says that people will slip into a “the rich are rich because they are more deserving than the poor” mentality. They would view themselves as self-made, and see those who cannot afford the gene therapy as simply unfit. Ethicists see the divide that would

inevitably come about between those with access to the therapy and those without access as something that cannot be tolerated.

Gene therapy is an extremely exciting branch of medicine that has enormous potential to cure a wide range of diseases. As shown in the case of LCA or cancer, gene therapy could someday be used to cure diseases that right now do not have any cures. However, the further this therapy progresses the more one must ask himself about the ethical issues that surround it. As scientists perfect techniques to alter the DNA of cells and are able to target with greater knowledge the necessary genes, genetic therapy will become more of a viable therapy in medicine. It will also inevitably become possible for genetic therapy to move outside of the boundaries of medicine and into the realm of enhancement. In spite of these ethical concerns, gene therapy will undoubtedly increase in importance as more applications for it are discovered by scientists.

Resources

Borenstein, Jason. "The Wisdom of Caution: Genetic Enhancement and Future Children." Springer. 16 July 2006. 3 Dec. 2009.
<<http://www.springerlink.com/content/w6127xx772143791/fulltext.pdf>>.

Bushelle E, Hertz E, Hubbard D, Saylor K, and Slyker A. "Gene Therapy Policy Statement." Macalester College. 6 May 2003.
<<http://www.macalester.edu/~montgomery/GeneTherapy.htm>>.

Instruction Dignitas Personae on Certain Bioethical Questions. Congregation for the Doctrine of the Faith. 8 Sep. 2008.

Mauron, Alex. "Ethical aspects of gene therapy." Geneva Foundation for Medical Education and Research. 4 Sep. 2008. 3 Dec. 2009.
<http://www.gfmer.ch/Endo/Lectures_09/ethical_aspects_of_gene_therapy.htm>.

"Nano-treatment to torpedo cancer." BBC News Online: Health. 10 Mar. 2009. 3 Dec. 2009.
<<http://news.bbc.co.uk/2/hi/health/7935592.stm>>.

"Results of world's first gene therapy for inherited blindness show sight improvement." UCL Institute of Ophthalmology. 28 Apr. 2008. 3 Dec. 2009.
<<http://www.ucl.ac.uk/media/library/Genetherapyblind>>.

Sandel, Michael J. "The Case Against Perfection." The Atlantic. Apr 2004. 3 Dec. 2009.
<<http://www.theatlantic.com/doc/200404/sandel>>.

"Types of Gene Therapy Explained." Alternate Heals. 3 Dec. 2009.
<<http://www.alternateheals.com/gene-therapy/types-of-gene-therapy.htm>>.

United States. U.S. Department of Energy. Gene Therapy. 11 June 2009. 3 Dec. 2009.
<http://www.ornl.gov/sci/techresources/Human_Genome/medicine/genetherapy.shtml#status>.