

Gene Therapy in Modern Society
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Abstract

Gene therapy is a major area of current and potential medical treatment and has exploded into recent technological advances. Serving as the basis for many technological start-up companies as well as an increasingly dependable treatment method for major illnesses like cancer, gene therapy is fast evolving and multidimensional. With that evolution comes a considerable amount of controversy centered mostly on the safety and ethical concerns about research including germline gene therapy and embryonic stem cell use, health risks in clinical studies, and vector delivery methods. Although germline gene therapy is not being widely pursued at this time, it shares a similar ethical dilemma with embryonic stem cell use, which will soon play a crucial role in developing and regulating the most advanced gene therapy treatments. In any scientific pursuit concerning people's health it is important to strive towards making trials safer and keeping consumers informed and this will continue to be a priority as therapy advances. Ultimately, ethical dilemmas will be the most prominent factor holding gene therapy research back in the future, and society will need to somehow come to a consensus about these issues before science can reach its full potential.

Introduction

Gene therapy is quickly becoming one of the most controversial topics in modern medicine and research as technology continues to advance at a rapid rate. Modern research techniques including gene insertion and modification into organisms like plants and animals are becoming increasingly common and society is becoming closer to applying these techniques to human therapy and disease treatment. Gene therapy has the potential to unlock the secret to stopping degenerative diseases like M.S., remobilizing paralyzed

limbs or even curing cancer for good. As of now gene therapy is used on a limited basis and often applied only in cases where there are no other treatment options. Despite its potential to solve many health issues, people are scared that if gene therapy becomes too advanced it will be used to create “designer babies” or selection of superior traits to create the “super human”. Scientists have worked hard to ensure that these fantasy fears are not taken out of context and magnified, but the possibility of technology falling into the wrong hands always lurks and tends to consume people, especially in an era of such advanced terrorism and weaponry.

What is Gene Therapy?

Gene therapy is a method of disease treatment that has been under investigation since the 1980s (Chang, 1995). With the rapid evolution of biotechnology, the possibilities for gene therapy treatments are soaring. In order to understand gene therapy, it is essential to break down the topic into its core components.

Somatic vs. Germline Gene Therapy

It is first important to distinguish between somatic and germline gene therapy, the source of most controversy. Nearly all research being conducted in labs is geared towards somatic gene therapy, which means investigating the modification of genes in adult cells. Somatic gene therapy is the basis for groundbreaking treatments for diseases like cancer, hemophilia and some types of blindness. Germline gene therapy, however, is the modification of germ cells in order to change potentially inherited diseases or traits of an unborn person (What are the ethical issues surrounding gene therapy?, 2014). The idea behind germline gene therapy is that a gene can be inserted into sperm, egg, or blastocyst before development and alter a harmful genetic trait or condition (What are the ethical

issues surrounding gene therapy?, 2014). Despite popular belief, this type of modification is still in its infancy and not yet being researched on humans (Hanna, 2006).

Despite stereotypes of “designer babies”, germline gene therapy may have the potential to prevent children from inheriting serious diseases or birth defects. New techniques like Crispr, which involves editing very specific parts of the genome, could be very effective for curing diseases like HIV while also dramatically reducing risk for embryonic harm, a prominent ethical concern about germline gene therapy (Connor, 2013). Scientists are rather tentative about exploring how germline gene therapy may be used and to what extent (What is Germline Gene Therapy, 2011). According to Dr. Phillip Leopold, a researcher and professor at Stevens Institute of Technology, scientists are careful to stay away from research that may involve germ cells and jeopardize the integrity of work towards gene therapy to treat disease.

Methods of Delivering Gene Therapy

Gene therapy can be successfully delivered in a variety of ways depending on the disease and patient. The ex vivo method, inserting cultured cells into a person, was used through the early stages of gene therapy but the in vivo method, directly delivering genes through vectors, is where most modern development is concentrated (Chang, 1995). Many of the most effective treatments have come from developing harmless viruses or “vectors” to carry new genes into cells (Gene Therapy: Fact Sheet 27, 2012). The use of vectors has been so successful because viruses directly insert themselves into a host cell’s genome and take over. If successful, a modified copy of the gene is reproduced every time the cell divides and eventually rids the patient of the bad copies. Adenovirus treatments were the first delivered to patients back in 1993 and have been instrumental in understanding the

requirements of delivering a large molecule, said Dr. Leopold. Unfortunately they have also been known to cause major inflammatory reactions because of their size. Adeno-associated viruses, the smaller version of the adenovirus, are less likely to trigger an inflammatory response but can only accommodate genes smaller than 5,000 base pairs (Gene Therapy, 2014). Retrovirus treatments are a more recent development, but issues arise if they insert themselves into the wrong place in the host genome causing cancer or tumors (Gene Therapy, 2014). The herpes simplex virus is also very effective but only if therapy is required in the nervous system (Gene Therapy, 2014). Although viruses have proved to be the most effective method thus far, it is important to note that the use of the viral treatment can only work on a limited basis or else the body will have developed an immune response to the vector and reject the treatment, pointed out Dr. Leopold.

Scientists are also researching the use of stem cells to deliver gene therapy, but unless all treatments can be derived from adult stem cells this approach introduces a whole new layer of controversy (Gene Therapy: Fact Sheet 27, 2012). In a recent surgery Dr. Amit Patel of the University of Utah School of Medicine used stem cells to insert high dose of gene therapy directly into the heart to attract the patient's own cells to the site and hopefully cure his heart disease (KurzweilAI Accelerating Intelligence, 2013). Another alternative to viral delivery is the utilization of complexes of DNA with lipids and proteins (Hanna, 2006). Additionally, some researchers are experimenting with introducing an artificial 47th chromosome that could stand next to the standard 46 without negatively affecting their performance or causing any mutations. (Hanna, 2006).

Treatment of Diseases via Gene Therapy

Gene therapy for cancer, first approved in China in 2004, is the only disease approved for routine gene therapy (Gene Therapy: Fact Sheet 27, 2012). Gene therapy has been particularly successful in blood cancers like leukemia. Cancer has been the overwhelming focus of researchers around the world with 2/3 of clinical gene therapy trials and the most advanced techniques today focused on curing the disease (Gene Therapy for Diseases, nd). Some advanced research is in its final stages for the drug Ad.p53 targeting head and neck cancer, as well as gene vaccines for prostate and pancreatic cancer (Gene Therapy for Diseases, nd). Clinical trials are also under way to treat cancers in the brain, skin, liver, colon, breast and kidney (Gene Therapy for Diseases, nd). Sever Combined Immune Deficiency (SCID) realized some success from gene therapy when 7 out of 10 infants were treated successfully (Gene Therapy: Fact Sheet 27, 2012). However, two patients later developed cancer, which caused a hesitation to pursue the treatment on a wide scale because of the uncertainty of side effects (Gene Therapy: Fact Sheet 27, 2012).

Trials for hemophilia, neurodegenerative disease, AIDS and cystic fibrosis are underway but are still very novel and in early development phases (Gene Therapy for Diseases, n.d.). One particular clinical study infused CCR5 co-receptor genes with modified CR4 T analogous to those naturally found in the body then put them into an HIV patient in order to see if the cell can start working properly again. The trial was successful in diminishing the level of blood HIV DNA and was found to be safe within that study, but the modified cells have a much shorter lifespan than natural cells posing a problem for a long-term cure (Tebas et al, 2014). Another clinical success came from using an adeno-virus to treat choroideremia, a type of blindness, and it looks promising for clinical introduction (Ingenious, 2014). Other treatments, such as that for lipoprotein lipase deficiency, are

approved in Europe or other parts of the world but not in the United States (Ingenious, 2014). The earliest stages of testing done on mice have recognized success in treating heart conditions like Friedreich's ataxia and spinal cord injuries which could bring the use of gene therapy beyond the realm of autoimmune diseases and into treatment of bodily injuries and paralysis (Perdomini, Belbellaa, & Monnassier, 2014), (Bartus et al, 2014).

The Controversy Behind Gene Therapy

Gene therapy has several layers of controversy but one of the most prominent is actually grounded in a public misperception. Many people believe that the long-term goal of gene therapy is to ultimately develop germline gene therapy in a way to create "designer babies." In this light, people are understandably scared of and ethically opposed to any research that may support that notion. This is absolutely not the goal however, according to almost all scientists, including Dr. Leopold. The overarching driver behind gene therapy development is to cure disease and advance medicine. All credible research, even that testing germline techniques in animals like mice, is being conducted in order to come up with alternatives to mediocre or uncertain treatments like chemotherapy and to treat diseases that do not have a cure yet. This ethical dilemma is similar to that of stem cell research in that many people are opposed to altering or destroying a potential life. Although gene therapy in practice would benefit the child, the research would obviously not be perfected on the first try so surely some blastocysts would be lost. The hope of researchers is for gene therapy to become a safe, effective and cost-efficient way to treat disease both in adults and babies someday, however gene therapy in embryos will not see any progress until ethical concerns are addressed.

In the case of germline gene therapy, potential parents who may want to use treatments to make sure their children are not born with certain serious, life-altering diseases like MS, are a major stakeholder group. People with a family history of an illness could be very interested in using gene therapy to eliminate the possibility of having children subject to the inherited disease. As technology improves and safer ways to delve more deeply into gene therapy emerge, germline gene therapy could be tentatively investigated, but for now many members of the scientific community remain opposed to opening that can of worms.

As in many medical pursuits, embryonic stem cells offer unprecedented potential to further gene therapy delivery. Of course, with the ethical dilemmas surrounding embryonic stem cell research these possibilities are not fully realized and scientists, whose livelihood depends on their research, are often not willing to risk losing all of their research funding in order to pursue embryonic stem cell research. Cultures used on a regular basis are adult stem cells, but the ability to use embryonic cells could open a whole new door (Murnaghan, 2010). For example, embryonic stem cells could be bred to match those of the person needing treatment and therefore the chance of an inflammatory reaction, like those may happen with vector delivery, is greatly decreased.

Safety is another major source of controversy accompanying gene therapy treatments. The lack of education and fear of horror stories about illness or death from trials may be contributing to concerns about testing of gene therapy. The death of an 18-year-old clinical trial patient in 1999 caused a great deal of hesitation about gene therapy trials and instilled a level of fear and uncertainty in people that has only recently been overcome (Deguilio, 2010). After the death, it was determined by the Subcommittee on

Public Health of the Committee on Health, Education, Labor, and Pensions that people do not have enough knowledge about clinical trials (Hearing before the subcommittee...., 2000). Clearly sick patients have a vested interest in the future of gene therapy and having those patients willing to cooperate in clinical trials is absolutely essential to the development of gene therapy. However, patients must also consider their own safety and wellbeing before consenting to try a new treatment so the perceived benefits from the gene therapy must outweigh concerns about potential harm from treatment. This can be a difficult decision to make when stories of clinical patients dying from side effects of treatment amass the media.

Because of the media's tendency towards sensationalism, any scientific research on people gone wrong will be widely reported, heightening public awareness of the risks involved in studies. Controversy revolving around preserving and saving lives is obviously a serious one, and if there is a high risk of human harm then the trials will not run and gene therapy advancement will be halted. Sick patients are stakeholders from a variety of different angles because they are the potential beneficiaries of advancement but also are the ones at the highest risk during the research phase.

As a result of the death of the clinical patient mentioned above, the FDA instilled surveillance inspections of clinical trials to make sure that they are safe and make an effort to better inform people before they participate (Hearing before the subcommittee...., 2000). Hopefully this movement has helped ease the decision of potential candidates for research studies and eliminated some of the dangers of participation so that the ill population will not need to worry about potential harm from their treatment.

Of course, knowing all of the risks of a gene therapy treatment beforehand can be extremely difficult because some of the more serious ones, like cancer, cannot be realized until years later. Similar to the lack of knowledge about the effects of dioxin in Agent Orange when it was first used, the development of cancer in two out of ten patients in a gene therapy trial to cure SCID was somewhat of a shock at the time (Gene Therapy: Fact Sheet 27, 2012). The government did not know the extent to which the contaminated Agent Orange would hurt people and they turned out to be much more severe than was initially thought just as scientists did not know that the effects of the therapy would be life-threatening. It would be a nightmare if gene therapy turned out to have unknown long-term effects that severely disable generations to come.

Gene therapy concerning the use of viruses to inject genes into the patient is another angle of the safety concern. Many people are concerned about viruses activating and getting them sick or causing an inflammatory response that causes more harm than good. Although some patients do have a negative inflammatory response, this is a risk that occurs with most any other type of drug or treatment. The viruses injected into people are variations of known strains, not copies, so contrary to popular belief, the viruses cannot become active and infect the host with a given disease. For example, one common vector used is a variation of the Herpes virus, but not the virus itself, so a patient receiving treatment cannot get herpes from that vector. This concept is extremely difficult to explain to people though and the term Herpes still instills fear in them.

Doctors and hospitals using gene therapy remain as prominent stakeholders because they must not only be up-to-date enough to know when to use gene therapy but also know how to convince patients of its effectiveness. This is especially true for

organizations like the Nationwide Children's Center in Columbus, Ohio, which invests a significant portion of time and resources into gene therapy. If patients do not have faith in the process they will not seek treatment from that hospital and it will ultimately go under (Center for Gene Therapy, 2014). The center has set up a detailed website highlighting the major progressions of gene therapy and the good it has done while highlighting the fact that clinical trials are looking for patients to participate. Combining information with advertising is a clever way to draw patients in and hopefully keep them from straying to unreliable sources for information. Although concerns about utilizing viruses to deliver therapy is a separate issue from the safety concerns about gene therapy in general, many of the same concerns about long term sickness or delayed reactions to a virus backfiring are similar. Hospitals must not only keep track of treatments but also decide which research areas to invest in and further convince patients to pursue these options.

Crosscuts in Gene Therapy

The ethical and religious conflict surrounding gene therapy is a prominent issue with people concerned about "playing God." Although treatments may be extremely helpful for curing diseases, some individuals believe that science should not be changing what is fundamentally human: the genome. This is a common view about many aspects of genetic research and it is important to consider how far is too far when using gene therapy. For instance, should gene therapy only be allowed to treat life-threatening illnesses or should it be extended in the future to include less serious diseases? If gene therapy is used now for serious diseases, what is stopping it from developing into frivolous practice for the rich?

A debate then arises about whether people have the right to gene therapy or if it should only be available to those who can afford it. According to Dr. Leopold, gene therapy

actually has the potential to save insurance companies a lot of money, but for the uninsured therapy costs may seem impossibly high. Gene therapy is not limited the same way as organs needed for an organ transplant, so there is no quantitative limit on the number of patients that can receive therapy. The cost now is high, and for a while price unfortunately may determine whether a person lives or dies. A great deal of ethical concern then arises again when germline gene therapy is brought into the picture. As discussed above, many people do not consider germline gene therapy ethical and this aspect of therapy alone has the power to significantly sway public opinion despite the fact that it really should be a completely isolated issue from somatic gene therapy.

Over the years, public opinion of gene therapy has been generally positive with controversy arising mostly about certain issues like germline gene therapy and the use of embryonic stem cells to do gene therapy research. When questions about public opinion are framed around using gene therapy solely to treat disease and improve lives there is little controversy, but once germline gene therapy enters the picture people are much more afraid to support the research. Leroy Walters, a prominent ethicist, published a paper in *Human Gene Therapy* stating his opinion on why somatic gene therapy is perfectly ethical but recognizes that the focus now needs to shift into deciding the boundaries of germline gene therapy (Walters, 1991). Public opinion polling has been somewhat limited because of the fast-paced change occurring, but a national mail survey from Japan in the early 1990's concluded that the majority of the general public, high school biology teachers and scientists would all use gene therapy to treat diseases (Walters, 1991).

Scientists often believe that controversy arises due to public misperception and simply more education will make the difference. However, it seems to be the lack of trust

rather than lack of knowledge between scientists and the public that leads people believe that unethical practices in research are not far-fetched (Gottweis, 2002). The relationship between scientists and the public remains rocky and unfortunately has not significantly improved with time. Public support will ultimately determine the success of gene therapy because those people are the ones making decisions about their health when choosing a treatment plan. If people do not trust scientists telling them about gene therapy they will not be inclined to help it persist and funding will dwindle.

The funding problem leads to the industry aspect of gene therapy, which depends on both federal and private dollars to progress. For over 30 years significant time and monetary resources have been pooled into gene therapy research and clinical trials. The National Institutes of Health has received the U.S. patent for ex vivo gene therapy and companies have been trying to patent various gene therapy techniques since as early as 1980 (NIH/Genetic Therapy Inc. Receive..., nd). According to Dr. Leopold, patents for new technology or methodology in gene therapy are not particularly difficult to obtain but rather just time-consuming and expensive. Patents are an integral part of the research and development process because without them companies would have no incentive to develop new products because it would be nearly impossible to make a profit once others copied the technology without any development costs.

Companies are investing and committing to finding gene therapy treatments more frequently than ever. For example, "Oxford BioMedica, has established a collaboration with Sanofi-Aventis, a major international pharmaceutical company, to develop and commercialize gene therapy treatments for vision-robbing retinal degenerative diseases that affect tens of millions of people around the world," ("New Investment to Boost Gene

Therapy Development, 2009). Gene therapy is the basis for many new biotech start-up companies such as Voyager Therapeutics aimed to treat ALS and Parkinson's (Borchers, 2014). In a bad economy this could be an important industry and source of long-term jobs. Entire academic institutions, such as Barts Cancer Institute, are also dedicated to gene therapy development, particularly for cancer research (Cancer Gene Therapy, 2013). Additionally, once research is conducted many manufacturing companies depend on the demand for this newly developed, expensive technology to keep their businesses profitable. Without any advancement, many specialized medical companies would likely not make it. Gene therapy stakes clearly span across many facets of industry and daily life and must be evaluated from a variety of viewpoints in order to make the best possible decisions about the direction of technology as it becomes more prominent in the health field.

Conclusion

Gene therapy is a controversy that is important to a subset of sick people right now but will likely affect a large percentage of the population over the course of a lifetime. Rather than trying to gain support from a specific subset, gene therapy needs to be embraced by everyone in order to succeed. This is a perspective not often considered by groups indirectly affected by research and this paper has raised my awareness about the span of gene therapy. Also, I found it surprising that it seems as though despite concerns about side effects, very few people take a strong stance against somatic gene therapy. Most of the controversial aspects of gene therapy revolve around germline research and the potential for embryonic stem cell use. Finally, gene therapy encompasses many more techniques than I had initially thought. Each type of delivery has its distinct pros and cons

and there really is no decisive best method because each is so different. The prospect of so many undiscovered possibilities is exciting, but the uncertainty can be overwhelming for journalists and so far have dealt with it poorly. News coverage of gene therapy has been extremely product-oriented, as S. Holly Stocking in *Creating Uncertainty* would say, and journalists tend to cover the results of a study, good or bad, in a way that makes them seem clear-cut and definitive (Friedman, 1999). Gene therapy is far from being a defined process with predictable end results so media coverage claiming that there are now cures for genetic diseases is very misleading.

Measures have already improved dramatically to help ensure patients participating in trials and undergoing treatment are as safe as possible and this will continue to be a paramount concern as research advances. People will hopefully grow to trust the safety of gene therapy and eventually settle the controversy. Katherine E. Rowan, professor at Purdue University, hits the nail on the head when she explains how the source of concern or confusion for people is not necessarily due to the lack of knowledge but rather difficulty of the audience in overcoming counterintuitive information (Friedman, 1999). Although the science is complex, most people are hung up on the fact that a virus has always been associated with sickness rather than a cure and therefore do not trust the science.

Both mass and social media have blown up the controversy considerably and now people are afraid for their safety because of publicized horror stories about clinical trials. They are worried about their treatment cost and privacy because of the shifting health care environment as well, but most of all they have become strongly devoted to their opinions about research and manipulation of germline cells. The ethical concerns about these procedures are deep-rooted and often religious, making them difficult to overcome. Issues

about legal and monetary compensation can eventually be sorted out systematically, but ethical and religious issues are much more difficult because they are not necessarily guided by logic. We have seen repeatedly in the context of embryonic stem cell research that one group cannot easily sway the core values or beliefs of another and there is no real “right” answer. Opposition may be tamed if some of the newest technologies really do prove to be extremely safe, but widespread approval is likely far-off. The media has traditionally made germline gene therapy seem much more mainstream than it actually is and audiences seem to be convinced that scientists will be playing Frankenstein. That falsehood can be battled with constant education for now, but it is only a matter of time before scientists start pushing to investigate the possibilities germline gene therapy has to offer.

Genetics is somewhat of a new frontier therefore industry and legal regulations are shaky at best. Insurance companies will need to continue to adjust their coverage plans and hospitals reassess the cost of treating patients. The times will catch up to these material concerns and develop a plan as needed, but the big hurdle will be the ethical dilemma over safety of treatment, embryonic stem cell research and germline gene therapy.

Gene therapy has the potential to work medical miracles by today’s standards. Although curing genetic diseases may have foreseeable negative effects like a population explosion, the benefits of curing the sick outweigh the rest. There are many ways to combat a growing population and as people many of us cannot imagine many things greater than curing human suffering from disease. If we can achieve a healthier tomorrow for present and future generations, then the scientific and ethical battles being fought now are worth it.

Attachment A

Dr. Phillip Leopold is a researcher and professor at Stevens Institute of Technology studying vector and virus interactions with gene expression especially through the use of nanotechnology in tissue engineering. Additionally, he the Education Committee Chair of the American Society for Gene Therapy and a member of both the New York Society for Microscopists and the Harvey Society.

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Below is the interview correspondence we had via e-mail.

1. I saw from your website that you are working with on research about vector and virus interactions with gene expression especially through the use of nanotechnology in tissue engineering, can you elaborate a little bit more on your current project?

Our laboratory works on the three major approaches to gene delivery: viral, chemical, and physical methods. In terms of viral gene delivery, we are working adenovirus, the first virus delivered to patients in a gene therapy protocol in 1993. Since that time, other viruses have been developed for delivery to patients, most notably, adeno-associated virus or AAV. Other viruses are used on patient cells outside the body, followed by return of the treated cells to the patient. Lentiviruses are often used in that setting. The study of the adenovirus infection pathway has been very instructive in terms of understanding the mechanisms that are required to move a large, hydrophilic molecule, like DNA, across a plasma membrane, through a viscous cytoplasm and through a nuclear pore into the nucleus of a target cell. I believe that there are aspects of the infection pathway that remain poorly understood. One area that we focus on is the step between microtubule-mediated movement and nuclear binding. We study a variety of cell types, including enucleated cells (cells from which the nucleus have been removed), to understand this step in infection. I am also working with a team of Computer Science students who are creating a computational model of viral infection to allow us to test hypotheses about the various factors involved in the infection process.

While viruses provide a highly efficient way to deliver DNA to the nucleus of a target cell, a given virus can only be used once in an immuno-competent patient. Subsequent administrations will be inhibited by antibodies raised against the capsid of the virus due to the initial administration. Having a means of delivering DNA to patient cells without raising an immune response to the vector would be very valuable, hence the interest in developing physical and chemical gene therapy methods. Physical methods include electroporation (use of a rapid sequence of electrical currents to open hole in cell membranes that permit

DNA entry into cells) or pressure (hydrodynamic gene delivery). We have spent some time trying to re-create a prior report that electroporation can be done more gently by growing cells on a porous filter which serves to 'focus' the electric current through a small portion of the cell...not so much luck with that yet. Chemical gene delivery refers to methods of mixing DNA with chemicals to attempt to accomplish the same job that the viral coating (or capsid) performs. However, viral capsids are very, very complex, so re-creating those virus-cell interactions is a big challenge. My philosophy is based on the observation that viruses mimic parts of the cell as they enter during infection. If we could build a virus with 'self' proteins instead of foreign proteins, we may be able to avoid the immune response.

Right now, we are particularly interested in developing a therapy for polycythemia vera, a disease of the bone marrow in which an overabundance of red blood cells are formed. The challenge of this disease is that it is caused by a single nucleotide change in the JAK2 gene, producing a dominant mutant form of the disease gene. We either have to edit the gene or selectively eliminate mRNAs that arise from the mutant gene without affecting mRNAs that arise from the 'good' JAK2 gene.

2. I also saw that you recently were granted a patent for your invention "*Crystal RG, Sato N, Leopold PL. Method of modulating hair growth. United States Patent #6,159,950*" can you describe how that process went for you? Was it difficult to patent your work? Do you know in general if patents are an issue in the gene therapy industry?

Patents are not hard. They are just laborious and expensive. Fortunately, the university often helps with the work (by hiring a patent attorney) and the expense if they believe that the patent has value. Patents are very valuable for any type of technology that is very expensive to develop. In general, drugs cost about \$1 billion and take 12 years to develop. A company will not make that investment unless they know that they will be able to sell the drug without competitors for a certain period of time...protection guaranteed by a patent. If companies did not have that protection, no one would invest the \$1 billion because they would not be able to make their money back by selling the drug because other companies would copy the drug and sell it for less since they had no development costs.

3. In your opinion what is the most effective delivery method of gene therapy now? Which has the most potential?

In my class on gene therapy, I stress that each delivery method has unique qualities that can make it the best choice for a given therapy. For example, for direct delivery to a patient with long term expression, it's hard to beat AAV, but AAV can only accommodate small genes. For larger genes, the helper-dependent adenovirus system would be a good choice. For permanent gene transfer by insertion into the host genome, lentiviral gene delivery to stem cells or progenitor cells (like bone marrow), is an excellent choice, but lentiviruses cannot be used for direct administration into the patient. Even first generation adenoviruses (like the one used in the Gelsinger case) still have value for delivering short term bursts of gene expression...for example when delivering a growth factor or a vaccination.

4. How safe is using viruses to deliver treatment? It seems counterintuitive to use something such as a virus that people usually view as harmful to treat illness.

You are right! It is counterintuitive. However, the viruses used for gene therapy have been genetically modified so that they cannot mount a viral infection. So, the danger does not come from a potential multiplication of viruses in the patient's cells. However, there remains some risks associated with gene therapy. At least three areas of concern include: (1) the impact of delivery of a whopping amount of small particles to the body...it turns out that the body has mechanisms for eliminating small particles from the blood, but that a huge dose of small particles can over-stimulate that system leading to a huge, general inflammatory response...this is what happened to Jesse Gelsinger...ironically, delivery of 10^{13} particles of anything that was 100 nm in size, not just gene therapy vectors, probably would have had a similar effect; (2) insertional mutagenesis – in the case of lentiviruses that insert into the genome, the insertion site can disrupt regulation of a normal gene...when that gene is related to cell growth, a cancer can form... three children in the French severe, combined immunodeficiency (SCID) trial developed leukemia due to insertional mutagenesis...two were successfully treated and lived, but one child died; (3) the successful expression of the transgene can have unintended consequences – in one clinical trial aimed at calming an autoimmune condition by expressing an immune-suppressive protein, one patient died from an opportunistic infection due to the effectiveness of the therapy in preventing an immune response.

5. In what area do you believe gene therapy has the most potential? Most people say cancer or HIV but are there other significant uses for gene therapy being investigated besides just curing disease?

I believe that gene therapy will be a regular part of the medical toolbox in 30-50 years. Already, we have a tremendous ability (at least proof-of-principle in clinical trials) showing that we can replace genes in certain contexts such as alpha-1 antitrypsin deficiency, Batten disease, several blindnesses caused by defects in the retina, hemophilia, and several immunodeficiencies. We also have powerful genetic vaccines that have been demonstrated and a few good examples of cancer therapies. Look for genetically-enhanced engineered tissues, genetically-delivered growth factors to regenerate diseased tissues such as ischemic hearts or osteoporotic bones, and many other applications. 'Gene therapy,' in the future, will serve the same purpose that the syringe serves now. It will be a way to deliver any number of drugs to a patient.

6. Do you think that gene therapy will be a widespread treatment option for a large variety of illnesses anytime soon?

See above. Not too soon...but certainly in the future.

7. It seems as though the controversy about gene therapy in the public arises more from concerns about germline gene therapy than somatic gene therapy, what is your take on this controversy? Have you ever had to clear up any public misconceptions about your research goals due to this controversy?

Excellent question, and right on point! I think that people revere DNA as being the blueprint for the human body. Whether you believe in a divine origin of DNA or an evolutionary origin, I think that most people agree that changing the genetics of our species is something that should not be done lightly. I think that most gene therapists want to stay as far away from that type of debate as possible because of the potential for those issues to derail the very real potential for gene therapy as a drug delivery method. Before any gene therapy clinical trial is approved to advance to humans, the investigators must show that there has been no germ line transmission in animals. I can sleep at night because I know how hard it is to get genes into the intended target cells. Accidentally getting them into an unintended target cell seems like a very remote possibility, but one worth avoiding!

8. How are insurance companies dealing with gene therapy treatment? Do you know if patients trying to receive this groundbreaking treatment have been struggling to get companies to cover their treatment because it is so new?

No problem. This new question, like the last several questions, is tremendously important. Ensuring coverage of new therapies by 3rd party payers is a critically important strategy for all drug development. My guess is that, should a gene therapy be shown to be safe and effective and, thus, win FDA approval, the 3rd party payers are likely to permit reimbursement. In many cases, a genetic therapy may represent a tremendous cost savings. I believe that treatments for Gaucher Disease (patients are missing a lysosomal enzyme) run around \$100,000/yr for recombinant protein injections (you can check with Genzyme on the estimated cost). However, a single procedure costing \$100,000 using an AAV vector that expresses the enzyme may give years worth of correction. The insurance companies will be thrilled!

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