Collaborative Research on Gene Therapy's Clinical Benefits on Hereditary Diseases

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Abstract

This paper will study and discuss the benefits of gene therapy and how they combat hereditary diseases, as well as the drawbacks they may engender to human beings and society as a whole. Each article and research study mentioned in the following pages has given a different perspective on gene therapy and has pointed out, in one way or another, to how gene editing might provide a new lifestyle to those of us who suffer from genetic diseases. This technology is delivered through different techniques including somatic cell and germ-line gene therapy as well as CRISPR/CaS9 a technology described as an "evolving biological tool for cancer biology and oncology" by Tian et al. (2019).

We will later provide information that counteracts the benefits of gene therapy and review some of the criticism surrounding this field because of past outcomes. Since gene therapy and gene engineering in particular are still experimental methods that have just begun advancing in the right direction, scientists and researchers are still skeptical as to the safety measures around this branch of science, as well as the borderline ethical problems gene editing might cause as to the trouble it would bring to the natural selection of traits for example. This paper has analyzed seven different articles and came to the conclusion that gene therapy is an efficient way of treating genetic diseases that have no cure, or are inevitably contractible due to a person's hereditary background, but that doctors and scientists of the future should consider the unethical issues that it might bring up and adapt their environment accordingly.

Gene therapy is advised on and has clinical benefits on hereditary diseases

Introduction:

Gene therapy has made slow but substantial progress in today's society. Jafarlou et al (2016) discusses that the initial idea of gene therapy was brought up by Joshua Lederberg in 1963 but research on human genes didn't start until the 1980's (p.3). Verma and Somia (1997) adds on that it wasn't until the 1990's gene therapy was first used to combat diseases.

Imperatively, in gene therapy cells, tissues, and individuals changed by gene therapy are seen as genetically modified individuals ("Genome editing", 2019). Primarily there is the editing of chosen sequences of DNA in a living cell, then DNA is cut at specific point, cells repair themselves naturally, and DNA strands are then mended or swapped. New DNA sequences and gene functions occur because of the changed sequences (p# 3).

Given the potential that gene therapy can alter the genetic makeup, genetic therapy could be used to change the genetic makeup of crops and livestock and reproduction (p# 5). For example, gene therapy is used to increase plant produce, introduce the disinclination to disease and pests, the sufferance of different environmental conditions, and it could be utilized for the deletion of genes that contribute to the inheritance of a disease (para. 5).

In addition to these functions, gene therapy has been known to help combat hereditary diseases (p. 5).There are two gene therapy procedures which are effective at defying hereditary diseases. The first one is somatic cell gene therapy, which is efficient at

helping disabled organs function efficiently once again (Jafarlou et al, 2016). The second procedure is known as germ-line gene therapy, which creates a pleasing or advantageous genetic change that benefits the offspring. In this type of gene editing, genes could be passed on to the offspring of the offspring (Jafarlou et al, 2016, p.3).

In both cases, a vector which is a genetically modified, non-threatening virus, is responsible for carrying the gene into its designated cell. Gene therapy is essentially a great phenomenon which has to be dug up further. Without the power of this vector, there wouldn't be a chance for the advancement of gene therapy.

Literature review:

Gene therapy has been one of the most funded research fields in biomedical engineering the past 40 years, and that says lot about how puzzling a discipline it is for scientists, even after all these years of deciphering the mysteries hidden behind this revolutionary technology. In fact, genetic engineering has allowed us to regulate human conditions that weren't curable just half a century ago such as sickle-cell disease, and allowed us to cure genetic diseases in genomes as well (Park 2017). But that also reveals the unthinkable power of gene editing in controlling evolution, and that involves all of the issues that come with the liberty that this method gives us, human beings. Such liberties may give some people the opportunity to program the physical aspect of their offspring, eliminating all diversity that rules our society nowadays and overriding any natural selection for instance. All of the convenience that gene editing provides as well as some of the limitations it brings on the table are discussed in the articles and papers presented below.

Jafarlou, Baradaran, Saedi, Jafarlou, Shanehbandi, Maralani, and Othman (2016) examine the applications, as well as the advantages and disadvantages of gene therapy

treatments. After a rough history overview of the discovery of gene therapy in the 1960s, the *Journal of Biological Regulators & Homeostatic Agents* paper explores the different types of genes affected by gene therapy, and lists an exhaustive list of why one should consider gene therapy as an effective treatment for certain gene mutations causing hereditary diseases. According to this research paper, there are two gene editing procedures depending on the type of cell targeted by the treatment. Somatic cells are responsible for the wellbeing and normal functioning of organs, and they are not transmissible from one generation to another. Jafarlou et al. (2016) consider this kind of editing as the most promising so far, especially that 70% of the clinical trials are headed towards the use of viral vectors because of their better ability of transferring genes in vivo. The second type involving genes sexual chromosomes will not be discussed in depth in this paper because of the little discoveries made so far on the subject.

Otsu (2015) delves into a third type of gene therapy that might be encouraging in the next decades, that is stem cell gene therapy. The very serious hematology specialized peer reviewed journal *Vox Sanguinis* considers that the use of edited Induced Pluripotent Stem Cells (iPSCs), which are reprogrammable cells derived from the skin or from blood, could successfully reverse genetic diseases, in other words, heritable illnesses. Otsu describes the use of Haematopoietic Stem Cells as one of the most promising and "advanced forms of experimental medicine" nowadays (p. 2). The current standards are based on an ex vivo introduction of a provirus in the genome of target cells to permanently reconstitute original haematopoietic cells and keep a healthy genetic lineage for the next generations (p. 2). The next step is to get the provirus to be inserted in the place of mutations on sex-linked chromosomes to fix any kind of ectopic transgene expression by correcting the genes loci for instance, and it seems like current trials on genetic disorders such as metachromatic leukodystrophy and Wiskott-Aldrich syndrome are very optimistic (Otsu, 2015, p. 3).

The plethora of techniques involving gene editing and gene engineering described in the previous articles have been quite successful in treating certain diseases, as well as picking and determining specific alleles in embryos. Also, a germline intervention might become the best preventive measure for certain heritable conditions, as it imposed itself as the only way for prosperity for people whose curing hopes were close to none. This is mostly due to the newest technology in the field of genomics, CRISPR/CaS9. This technology described by Tian, Gu, Patel, Bode, Lee, and Dong (2019) in a *Nature* article as an "adaptive immune system" (p# 2) consists of a protein system able to remove and replace DNA sections and fragments sequentially in order to change the genetic expression of different chromosomes in different organs, in order to treat different diseases ranging from monogenic diseases, which are disorders resulting from a single defective gene on non-sexual chromosomes, to all types of cancers (figure 1).

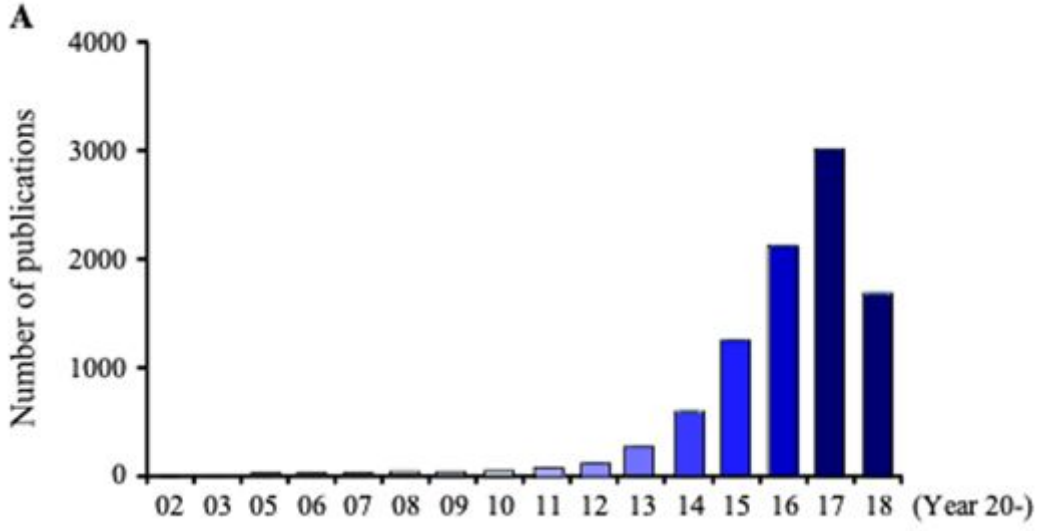

Figure 1. The number of publications on PubMed with the keyword "CRISPR" from 2002 to 2018. Reprinted from CRISPR/Cas9 – An evolving biological tool kit for cancer biology and oncology

Tian et al (2019) illustrates the way CRISPR/Cas9 works as a combination of a programmable RNA molecule associated with a Cas9 endonuclease that are directed to the

defective gene sequence of the phenotype in question. The genome modifications are made by "small insertions and deletions" (p# 2), as the Cas9 enzymes cut through the mutated genes in cells, binds to them through the single-stranded guide RNA, and start deleting the base pairs affected by the anomaly and replacing them by duplicating the correct RNA injected by the researchers (p# 2). The paper thoroughly inspects the different variations of CRISPR/Cas9 which mainly depend on the possible mutations made on HNH and RuvC, which are the two functional domains of the nuclease lobe of the Cas9 enzyme of the protein. Such mutations can lead to the activation of certain gene expressions or fix overexpression issues for example (p# 3). In an attempt to the decipher the mystery of genetic diseases such as different types of cancer, researchers and scientists have put a considerable amount of effort, time, and resources into developing the CRISPR/Cas9 technology. Pushing the boundaries of the realm of gene therapy is especially shown in the number of publications mentioning CRISPR these last years. Tian et al. (2019) showed that over 9000 publications included a correlation between cancer and gene engineering in the past 16 years only (figure 2). That's why Tian et al. consider that the cancer and tumor outbreak is only treatable using innovative, genetically engineered proteins such as CRISPR/Cas9 (Tian et al., 2019, p# 4).

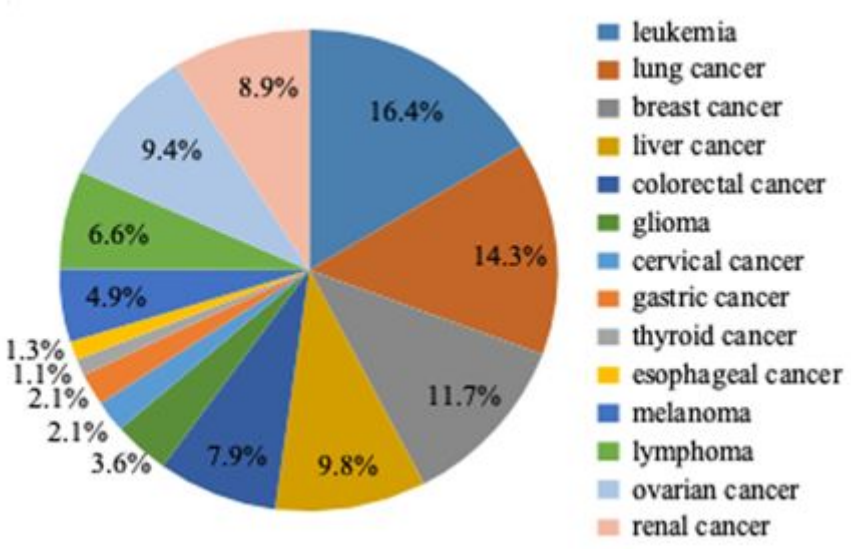

Figure 2. CRISPR/Cas9 applications in different cancers as reported on PubMed. Reprinted from CRISPR/Cas9 – An evolving biological tool kit for cancer biology and oncology

Verma and Somia (1997) inspect the feasibility of putting gene therapy into practice, and efficient delivery ways to swap defective genes with healthy ones. Although this *Nature* article is 22 years old, its content is somewhat still up to date, and points out to different issues we might encounter with using genetically modified somatic cells to remove or replace defective genes in different organs in the human body. Both authors agree that the concept of adding new genes to existing ones to potentially eliminate malfunctioning or unexisting genes is promising, and that it might actually help treating heritable diseases, slow down a tumor formation, and more. However, Somia and Verma based their skepticism on the fact that out of 200 trials done back at that time, no one was really cured with the treatment injected. As far as gene editing is concerned, their apprehension is still valid nowadays because scientists haven't found a viable solution for some of the problems they mentioned. A non exhaustive list of the limitations the authors mention and explain in the article includes the narrow number of somatic cell capable of transferring correct genes to certain targeted organs, the

quantity of therapeutic protein needed for each transfusion, and the inability of retroviral vectors containing the right corrected genes to infect non-dividing cells such as neurons and liver cells. However, Verma and Somia (1997) are still confident about science being able to solve these issues, and are rooting for bright prospects in the near future.

Discussion:

Gene Therapy has been around since the 1960s but it was not until recently that there has been successful outcomes and major breakthroughs.There have been cases where someone had no evidence of cancer in their body after going through gene therapy, and another case where they grew skin for a boy with a disorder called epidermolysis bullosa (Mullin, 2018).

The use of gene therapy has been used to treat hereditary diseases such as sickle cell disease and cancer. This is a huge advancement for medicine and gives hope to those combating hereditary diseases and much more. Gene therapy essentially fixes any faulty genes that are the cause behind the disease. With this treatment, it removes the gene that is causing the person to be sick and replaces it with a non-faulty gene. This treatment is not only limited to treating hereditary diseases but also biological issues such as infertility.

Limitations:

The advancement of clinical studies has been sluggish. Several deaths were reported because of gene therapy, the ill knowledge on the holistic nature of gene therapy being the primary cause of it (Jafarlou et al, 2016, p. 4-5). All factors of gene therapy need time to

manifest to our society, that's partly due to the contraventions in the monitoring and staging in trials.

In a specific trial involving a single gene mutation, a changed gene vector (Ad 5) was used to transport the gene of ornithischian decarboxylase (Jafarlou et al, 2019, p.5). However, the patient of this trial did not survive the experimentation. The life of this person would have been saved if he was tested for his immunity for the used gene vector. This case caused gene therapy to endure a lot of criticisms and this case highlighted the flaws in gene therapy. Much needed restricted regulations by FDA and NIH were established (p.5). Even after many cases benefitted from these regulations gene therapy still had predicted negative outcomes since gene therapy hasn't been around for long time and in gene therapy the target cell has to be fitted. The process of gene therapy doesn't always promise that the right gene will be delivered (p.5).

In a separate trial after the regulations passed, a curative gene that was transferred to two children enduring a harsh combined immunodeficiency disorder failed to provide a desirable effect (p.5). After the curative cells were escalated or in other words, the intensity of the cells was heightened and sent back to the patients, they lived normal lives. (p.5) but three out of the eleven patients who were cured using the vector were diagnosed with leukemia due to the gene transfer-ration. They were cured of an immunodeficiency disease but they subsequently developed leukemia.The MoMLV vector that transferred the curative cell came in contact with the LM02 gene that had similarities. Essentially, the formation of the MoMLV was particularly closer to the LM02 which resulted in leukemia for the patients (p.5-6). Although gene therapy is still in the development phase in the scientific world each day, it is extremely promising (Otsu, 2015, p.3). More effective therapies should be used by

scientists for delivering and placing genes into cells other than gene therapy until, people know gene therapy in and out.

Verma and Somia (1997) provide an argument that contradicts the thesis of this paper, gene therapy is beneficial on hereditary diseases. Verma addresses the idea that gene therapy can have a huge impact in the medical field by slowing the growth of tumors and slowing down the process of diseases such as alzheimer's. The only flaw being delivering the altered gene back into the body. Ayres (N.D) discusses the cons of gene therapy which ranges from the cost of this method, to the ethics behind gene therapy. Being able to change a person's' genetic quality. This being a possibility means children could have their genetic profiles altered *in vitro* so that a specific result is created. Being able to create the perfect human could create a separation between humans. Nevertheless the rest of the articles believe it is the future and support gene therapy and the benefits it can provide to hereditary diseases.

References

Ayres, C. (n.d.). 12 Pros and Cons of Gene Therapy. Retrieved from https://vittana.org/12-pros-and-cons-of-gene-therapy

Genome Editing in Brief: What, Why and How? (n.d). Retrieved from http://nuffieldbioethics.org/report/genome-editing-ethical-review/genome-editing

Jafarlou M., Baradaran B., Saedi T. A., Jafarlou V., Shanehbandi D., Maralani M., Othman F. (2016). An Overview of The History, Applications, Advantages, Disadvantages, and Prospects of Gene Therapy. Retrieved from https://web-a-ebscohost-com.ccny-proxy1.libr.ccny.cuny.edu/ehost/pdfviewer/pdfviewer?vid=4&sid=6ddb86bd-dab8-4592-9362-83a9a2ef5004%40sdc-v-sessmgr05 (Ebscohost database)

Mullin, E., & Mullin, E. (2018). 2017 was the year of gene-therapy breakthroughs. Retrieved from https://www.technologyreview.com/s/609643/2017-was-the-year-of-gene-therapy-breakthroughs/

Otsu, M. (2015). Perspectives on stem cell gene therapy for genetic disorders. Retrieved from https://onlinelibrary.wiley.com/doi/epdf/10.1111/voxs.12112?shared_access_token=p3qt02cMunOCjbij_tJC3ota6bR2k8jH0KrdpFOxC66tP7CQ_XkFQNXJL1a1XFGOKrDBWQ-gmXho1VYWTc_Hb-jC5pB0iS8WiPw4WlRE4EkrV1Mk8Ra5NbHnRNmZ4ti5&

Park, A. (2017). U.S. Scientists Use CRISPR to Fix Genetic Disease in Human Embryos For the First Time. Retrieved from http://time.com/4882855/crispr-gene- editing-human-embryo/

Tian, X., Gu, T., Patel, S., Bode, A. M., Lee, M., & Dong, Z. (2019). CRISPR/Cas9 – An evolving biological tool kit for cancer biology and oncology. Retrieved from https://www.nature.com/articles/s41698-019-0080-7#Bib1