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Whither Gene Therapy?

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Abstract: Human beings have participated in the evolution process by selectively breeding and domesticating certain kinds of plants and animals while crossbreeding others. Although it was never termed so, we were practising genetic engineering by keeping the ones that were desirable and eventually eliminating the other. Thanks to the many advances in genetics and genetic engineering today, we are in a position to treat or eliminate a disease from the very root itself, the genes. This is called gene therapy where the corrected genes are introduced into the affected cells either using a viral vector or nanoparticle. Depending on the target cell type, gene therapy can be divided into somatic cell gene therapy and germline gene therapy, which are non-transferable and transferable respectively, to future generations. There are many obstacles to the use of viral vectors, like the unnecessary immunogenic response that it stimulates in the patient and the potential uncertainties or the outcome of this novel therapy. Ethical issues involve sourcing

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embryonic cells for research, taking consent of the individual who is an embryo, clinical trials, the risk of misuse of this technology to create a superior human class, the affordability of such treatments and the regulations that will govern such therapies. In this essay we take a closer look at the various issues surrounding the use of stem cells and how we see it evolving in the future and if we could ever fully reap the benefits of this revolutionizing technology without compromising our "humanness".

Keywords: Gene Therapy, Stem cell, Genetic Disease, Risk-Benefit Ratio, Ethical Issues of Gene Editing

Introduction

"Many people say they are worried about the changes in our genetic instructions. But these (genetic instructions) are merely a product of evolution, shaped so we can adapt to certain conditions which might no longer exist. We all know how imperfect we are. Why not become a little better apt to survive?", said James Watson in 1991 (cited in Gonçalves and Paiva, 2017). Inheritance of hereditary characteristics has always been of great interest to mankind from the very beginning. In fact, it was in the very process of evolution that was anyways happening. Man too participated in the evolution process by selectively breeding and domesticating certain kinds of plants and animals while crossbreeding others. Although it was never termed so, we were actually practising genetic engineering by keeping the ones that were desirable and eventually eliminating the other. Genetic Engineering is thus not something new to humankind.

In the recent past, we have made further progress in understanding the mystery of genetics. It all began with the pea experiment by Gregor Mendel paving the way to the theory of inheritance. Years later, the chemical nature and the double-helical spiral structure of the DNA was proposed by James Watson and Francis Crick in 1950.

Further research helped identify the enzymes responsible for duplication, separation and reinsertion of genes at specific locations along with the DNA. This knowledge opened the door to a whole new field creating genetically modified bacteria and fungi to produce drugs, chemicals and antibodies (Gonçalves and Paiva, 2017). Today, we are at a point when we can treat or eliminate a disease from the very root itself, the genes. This is called gene therapy.

But is gene therapy a foolproof technology? There are many issues concerning the delivery system, efficiency and ethics when it comes to the actual use of the therapy. To top it all is the question of cost and the potential benefits as compared to the currently available therapies.

Gene Therapy

By 2003, the human genome project had mapped the human genome. This was a breakthrough event in understanding genetic information across populations. With such high-end techniques at disposal, scientists are now able to identify the genes responsible for any particular disease and hence find ways to rectify it. This local modification using correction of mutated genes or site-specific modifications is called gene therapy. Though currently limited to research laboratories, it promises to treat diseases such as sickle cell anaemia, haemophilia, cancer etc. (Gonçalves and Paiva, 2017).

The corrected genes are introduced into the affected cells either employing a viral vector or nanoparticles. Virus is most widely used because of their ability to infect and introduce genetic material into the cell. Viral vectors are however difficult to use in therapy because of our immune response that quickly neutralizes them. Therefore, nanotechnology using nanoparticles to deliver site-specific siRNA has proven to be a successful alternative (Bulaklak and Gersbach, 2020).

Depending on the target cell type, gene therapy can be divided into somatic cell gene therapy and germline gene therapy. When therapeutic genes are transferred to the somatic cells of the patients it is called somatic gene therapy and therefore the genes are restricted to the patient and are non-transferable to subsequent generations. However, in germline therapy, the stem cells are modified by introducing functional genes which are integrated into the genome. These are passed on to the next generations (Gonçalves and Paiva, 2017).

Scientific Obstacles in Gene Therapy

Viral vectors are often hindered by issues related to the patient's immune response, the specificity of delivery and insertional mutagenesis. As previously mentioned, the major obstacle in the use of viral vectors is our immune response, which attacks any foreign agent and neutralizes it, even the ones that are meant to deliver genes. In 1999, Jesse Gelsinger, a young man died during an experimental gene therapy due to his immune response to an adenoviral vector that was used in the study. The other concern of viral vector is its uptake by non-target cells in other organs that can lead to irreversible mutagenesis and other ill-effects (Hunt, 2008).

Since gene therapy involves using a living drug it has a lot of intrinsic variability in its behaviour and predictability in terms of efficiency. This is further exaggerated by the gene modification process and the environment in which it interacts with the living cells. Therefore, it is difficult to get a clear understanding of the cellular level interaction of these therapies. Unlike the drugs that are eliminated from the system through metabolic processes the effects of gene therapy are irreversible (Riva and Petrini, 2019). Gene therapy is still in its early stage of development and ongoing research has a lot to do to allay the fears of any unintended effect.

Despite these limitations, over the years many strategies to address these issues have evolved and have been tried in clinical trials. There is only an increase in the number of these trials. There have been

instances of success such as the curing of three children from a fatal immunodeficiency disorder in 2000. Another study reported partial restoration of eyesight to four young adults who were born blind, with the insertion of a single curative gene (Hunt, 2008). With new developments, gene therapy is going to revolutionize how we look at a disease and the human person.

Some Significant Ethical Issues

As we have seen, gene therapy is way different from conventional therapies based on drugs and other biologicals. This science is in its nascent stage and so are our understanding of its many complexities. Since genes involve alteration at the genetic level, it raises several other questions related to ethics not only those related to the very use of stem cells but also the viability of such therapy with the heavy price tag *vis-a-vis* the risks. We shall have a look at some of these issues.

a. Use of Embryonic Stem Cells

Adult stem cells are commonly used in cancer treatment even without the general awareness that we are using stem cells for therapy. Stem cell research involving germ lines need human embryos for research and development of potential therapies. This raises several moral and religious objections among people. No doubt embryonic stem cells have created a lot of debate not only regarding the consciousness in the embryo but also the source of these cells. Conception is considered as the beginning of life and therefore use of embryos is morally objectionable. Scientists counter this by saying that these embryos are outside a woman's body and is therefore not conceived in the usual sense. And to counter the argument of consciousness, they point out the lack of a nervous system in the embryo until implantation (Hunt, 2008).

The use of *in vitro* fertilization techniques has always been unacceptable practise on religious grounds. Therefore, claiming

that conception can take place in the womb alone and thus justifying the use of embryos seems very absurd. On the other hand, linking the nervous system to consciousness and thus justifying that an embryo outside a woman's womb lacks consciousness to use in research is equally debatable. As a matter of fact, we are still far from understanding what is consciousness. While the nervous system is an essential part of consciousness it is not the only thing that defines it. On the other hand, they are conveniently forgetting that the embryo has the potential to develop the nervous system if implanted in a womb. Thus, by depriving the embryo of what it rightfully deserves to grow into an individual, we cannot claim any moral ground to carry out our research for the wellbeing of humanity at the cost of anyone's life without even having an informed consent of that "potential individual" just because we claim that it lacks consciousness.

Currently, in the US, federal funds cannot be used for any research that creates or destroys embryos. In addition, NIH does not fund any use of gene editing in human embryos. While in some countries genome-editing research on non-viable embryos is allowed, in others there are approved genome-editing research studies with viable embryos. Each of these will have its own moral and ethical considerations to be made (NHGRI, 2017).

b. Identification of the Genetic Disorder

With the advances in the field of genetics, we can get a genetic map of potential diseases we are likely to be vulnerable to and the ones that could be passed on to the next generations. Being a genetic disorder, the disease is likely to dominate our family tree for many generations to come. Therefore, it would be highly desirable to fix this defect and ensure a better life for future generations. All said and done it may not be a welcome strategy to alleviate human susceptibility to genetic disorders.

The first issue is the usage of the type of stem cell for therapy. As discussed earlier only corrections in the genes of germline will be

inherited. But such an alteration seems to be highly debated because of the potentially irreversible threat to other genetic traits that may or may not be associated with the gene that is being treated. Moreover, it is also known that a trait is expressed by the interaction of several chromosomal and non-chromosomal genetic material. This increases the risk of untoward events that put the future progenies at risk. Thus, somatic cell therapy may seem a relatively easier option for the time being. But before that, we need to identify the disorder at a very early stage of embryonic development.

Prenatal screening for genetic disorders is a common practice today. The correct and timely identification of such diseases plays a decisive role for the parents to decide the next steps to be taken. Accordingly, the parents would choose either for termination of pregnancy or let the child be born with the anomaly. The decision for the treatment would also depend on the culture of the parents. In an Indian context, a male child is preferred over a female one, and therefore a female neonate is likely to be terminated despite the possibility of a cure.

In prenatal screening we also need to look at the individual's autonomy and the cost involved. In this case the individual's autonomy is out of question as we are talking of the embryo that doesn't have the capability to understand, reflect or reason to make an informed decision. It may be argued that the parents take the decision on behalf of the "unconsulted" foetus. On the other hand, is the moral question of passing on a genetic disease to the future generations even when a cure is available on the grounds of autonomy and consent of the individual (D and GA 2014).

c. Clinical Trials

Once a potential therapy is proven to be effective in the laboratory it needs to be taken the next level of first in human

trials. This poses ethical issues such as difficulty in evaluating preclinical research; difficulty in assessing the risk-to-benefit ratio; conceptualisation and estimation of patient benefits and/or social benefits; application of the principle of justice; criteria for inclusion/exclusion of participants; the process of information and consent; and risk of therapeutic misconception.

The general practice is to have basic laboratory and animal research at the preclinical stage before undertaking any human trials. The Nuremberg Code states that "The experiment should be so designed and based on the results of animal experimentation and knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment" (Nuremberg Military Tribunals, 1948–1953). The Declaration of Helsinki also states a similar requirement (WMA, 1964–2013, article 18) and provides that: "Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation".

As is known, every experimental study by its nature involves uncertainty and risks especially, when it comes to first-time human research. Therefore, a risk-benefit study is required before any clinical trial, to save the interests of the subjects in the trial. However, we still lack a quantitative technique to weigh the risk to benefit ratio. The three conditions that must be met include (i) the potential risks to individual subjects must be minimised; (ii) the potential benefits to individual subjects must be enhanced; and (iii) the potential benefits to individual subjects and society must be proportionate to or outweigh the risks. Thus, even if there are no potential benefits to the subject, the potential risks should be minimal to justify a potential benefit to society in the long run.

Coming to the point of subject selection for clinical trials, seriously ill patients who have exhausted the therapeutic possibilities are considered for gene therapy. Even in such cases, all risks may not be justified given that a viable alternative therapy is unavailable. Moreover, the patient must be aware of the uncertain nature of such therapies and the potential risks. Stem cell-based approaches are beginning to be tested in clinical trials on neurodegenerative disorders. These could also include first-in-human intracerebral transplantation of cells derived from human embryonic stem cells and inducible pluripotent cells. This involves inserting the cells into the brains of the patients and thus exposing non-target cells to potential risks and permanent impairment of brain functions. On the other hand, it is not possible to get informed consent from a cognitively impaired patient (Riva and Petrini, 2019).

d. **Safety**

There is always a likelihood of off-target effects or mosaicism (when some cells carry the edit but others do not), which brings the safety of patients as the primary concern. Some researchers are of the opinion that there may never be a time when genome editing in embryos will offer a benefit greater than that of existing technologies. Once proven successful, there is a likelihood that genome editing would also be used for non-therapeutic purposes such as the creation of individuals with certain behaviours or characters. There is also the likelihood of creating new human species with superior qualities (NHGRI, 2017).

e. Justice and Equity

Genome editing, as has been known, is an expensive affair and nothing less than an unrealistic dream for ordinary people, let alone the poorer nations. Thus, even among the wealthy a few are going to avail such a therapy. This would create an all-new class of genetically engineered who will claim superiority, not only based on wealth but also in the very essence of their genetic being (NHGRI, 2017).

Is it even ethical to modify the human genome? What is the definition of a disease and who decides? Wouldn't an undesirable behaviour be termed as disease for economical

Conclusion

Having looked at various aspects of gene therapy and the obstacles in this emerging field we still have some unanswered questions. Firstly, is it even ethical to modify the human genome? What is the definition of a disease and who decides? Wouldn't an undesirable behaviour be termed as the disease for economical exploitation? How are we to address the issues of eventual mishaps in gene editing? Is it really a boon when we think of creating a whole new superior human race? Who will take the onus of ensuring that it is used ethically without any ill intent to dominate or subjugate the other?

Any scientific discovery is to be welcomed. But when it comes to gene therapy or editing, we are putting at risk our human liberty, autonomy and the future of the entire human race. In the gene therapy ethics debate, science provides us with the facts. The facts are necessary for us to make informed decisions. But science cannot tell us what our choices ought to be (van Bogaert, and Ogunbanjo, 2014). Looking at the cost, ethical and scientific issues involved in gene therapy, currently the risks outweigh the potential benefits. Moreover, like nuclear energy, gene therapy too can be potentially misused against humanity.

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