GENE EDITING TECHNIQUE INFLUENCE AND POSITION TO HUMAN SOCIETY

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On my honor as a University Student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments

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Introduction:

Gene editing technology, or gene manipulation, began in 1970 with the successful isolation of the first restriction enzyme, that could be used for the precise cutting of DNA sequences. After Stanford University generated the first recombinant DNA molecules in 1972, the scientific revolution in gene manipulation started (Nicholl, 2008, p. 6). Various techniques have been developed since then, and some of them, like recombinant DNA, have now been applied to vaccines and pharmaceutical development, after most recombinant drugs were approved by U.S. Food and Drug Administration (FDA) since 1997 (Khan et al., 2016). Also, other newly developed techniques, like CRISPR-Cas9, are promoting "innovative applications from basic biology to biotechnology and medicine" (Hsu et al., 2014).

But just like other technology, the development of such techniques is always followed by concerns and debate. When recombinant DNA was just developed and applied in the 1970s to 1980s, board discussions occurred, topics like whether this technique will create novel organisms and infect the populace after escaping from laboratories, with concerns about scientists' responsibilities on proper usage for their research (Altimore, 1982). And ethical questions arise especially when it is applied to human gene editing or germline editing (Baumann, 2016). Therefore, this STS paper will investigate how gene editing techniques interact with different social groups, and how those techniques are situated in society through SCQT and System in Context framework.

STS Framework

The STS framework used for analysis is Social Construction of Technology (SCOT).

SCOT is a theory inspired by sociology of scientific knowledge (SSK), which developed a new way to analyze technological innovation's social context. Instead of treating technological innovation in a linear model, that is treating basic science, applied science, development, and commercialization in a linear way, SCOT sees different groups (relevant social groups) involved in technological innovation. Each social group has its own ideas, goals, and values about a new technological design, such as what problems of a new artifact should be solved, and where and when should a design be applied for. Through this interaction, new technological designs are both constructed by technological and social factors (STS Wiki)

Gene edit techniques introduction

The recombinant DNA technique aids people to be able to manipulate DNA segments from different species to create genes with new functions (National Human Genome Research Institute, 2023). Once scientists obtain the DNA molecule (gene) that encoded the protein of interest, they can insert that piece of DNA into a bacterial DNA molecule (plasmid). The modified bacterial plasmid (recombinant DNA molecule) would then be inserted into bacteria (host organism), and bacteria would make more copies of such plasmid, and produce proteins based on the recombinant DNA molecule. In short words, this technique makes scientists able to turn the bacterial cells into mini “factories” to produce proteins for further purification and use (Shaffer, 2023).

Another gene edit technique mostly discussed in this thesis is CRISPR-Cas9. This technique is developed from the CRISPR-Cas system (the acquired immunity systems that were discovered in archaea and bacteria) since the last decade. CRISPR is an enzyme that targets and removes viral DNA, and Cas9 is the protein that carries a guide RNA (gRNA) strand, normally

provided by scientists, which helps to target the specific area of DNA strand for cleavage, and further work like inserting DNA can then be facilitated (Ishino et al., 2018).

Analysis and discussions through Framework

As mentioned above, the SCOT framework is applied to investigate the interactions between different social groups and gene editing techniques, shown in Figure 1.

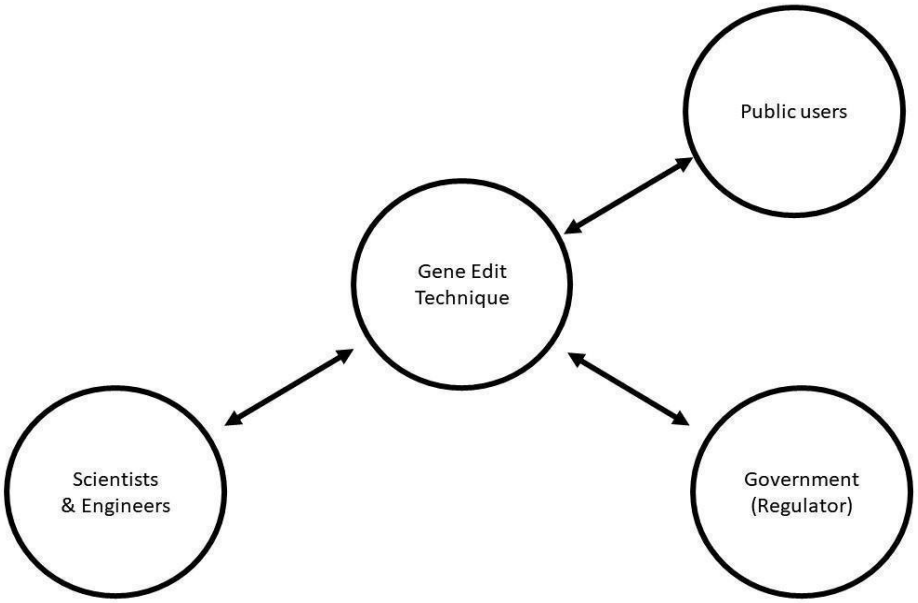

Figure 1: SCOT framework: Middle is gene edit technique, interacting with Public users, Scientists & Engineers, and Government (Adapted by Yixuan Yuan (2022) from Carlson (2009))

The first social group to be discussed is scientists and engineers. Over the last half-century, scientists and engineers are keeping developing and exploring potential applications of gene edit techniques. After the first recombinant DNA organism was made, recombinant DNA was tested for the insulin production process within a decade, and in 1982, this technique was applied to large quantities production of insulin and introduced to doctors and patients by Eli Lilly and Company after the approval from the government, and eventually become the primary

treatment for type 1 diabetes today. And because of the success of recombinant insulin, other recombinant protein drugs, for example, human growth hormone and erythropoietin, have been developed (Shaffer, 2023).

Although recombinant DNA has proven its success since the 1970s, scientists and engineers still want to find other simpler and more precise ways to edit genes in larger fragments (Service, 2019). Multiple techniques have already been developed, such as zinc-finger nuclease (ZFN) and transcription activator-liker effector nucleases (TALENs). However, scientists and engineers' later research showed the disadvantages of these techniques, such as complex design for DNA in interest, which limits their feasibility for further applications (Khan, 2019). Then in 2012, CRISPR-Cas9 was developed, which helped scientists to modify the gene more effectively and cheaply, compared with other methods like zinc-finger nucleases, which could take years to design (Bleicher, 2018). Due to these gene editing techniques' development, scientists and engineers are now more advanced to investigate the possibility to treat diseases through gene therapy, such as Type 2 diabetes. Type 2 diabetes is a metabolic disease resulting from insufficient insulin production due to genetic and environmental factors. As part of the pathogenesis of diabetes is the decline of the number of functional insulin secretion beta-cells, studies around beta-cells are mainly focused on areas like how to induce the existing beta-cells' self-renew and how to reprogram other cells or direct pluripotent stem cells to become beta-cells. The study has shown the success of producing beta-cells from pluripotent stem cells, both in human embryonic stem cells and induced pluripotent stem cells from reprogrammed somatic cells (Millete & Georgia, 2017). Moreover, gene editing technique in gene therapy has the potential that is not limited to diabetes treatment. Adrenal insufficiency, a disease caused by the inability to produce adequate levels of corticosteroids, attempts from gene editing to cure the

malfunction of the adrenal gland have been made to test the possibility (Mariniello & Guasti, 2021). Although there are still many steps that need to be accomplished to apply gene editing to cancer treatment, there is a growing number of reports of successful gene-edited cancer cell lines (Biagioni et al., 2018).

Another social group takes involved, is the public users, in this case, most are patients. For drugs, clinical trials are needed before they can be approved for wider use in society. During this process, some patients can be volunteers after they have a full understanding of the entire process and potential risks that could involve in drug testing (U.S. FDA, 2020). In this case, patients are testing the effectiveness of drugs and helping the pharmaceutical developers to eliminate the side effects and improve those drugs. And because gene editing techniques are used for producing necessary proteins, some techniques may be improved or abandoned due to being ineffective in producing desired proteins. In other words, patients interact with gene editing techniques indirectly. Moreover, patients and their family members have different views on whether using gene editing techniques more directly, like gene therapy, to cure their disease or cure their children exist. While some patients think their lives and success were shaped and affected by their disease, other patients reflect the idea that they will not consider if there is any moral issue in gene editing and will not hesitate to cure their diseases if those gene editing therapies are applicable (Hayden, 2016). But for patients, other factors like price, are also influencing their attitude toward gene editing. For instance, patients who take Glybera gene therapy, a therapy that treats adults with lipoprotein lipase deficiency due to the issues gene for lipoprotein lipase (EUROPEAN MEDICINES AGENCY, n.d.), each need to take 19 vials of Glybera on average, and each vial cost nearly $50,000 (Morrison, 2015). Such price creates a burden for patients to take therapy, and uncertainty about the benefits and risks associated with

these treatments are also challenging the patients (Koulianos, 2021).

Finally, the government also acts as an important group that interacts with gene editing techniques. In the therapeutics field, regulatory concerns always exist for issues like safety, efficiency, and quality control. Governments or agencies, such as US Food and Drug Administration (FDA) and European Medicines Agency (EMA) have published relevant guidelines for gene-editing therapeutics (Shim, G. et al). And for gene editing that focuses on human bodies, regulations that restrict further gene editing techniques' research are always followed by discussions about whether we need to change the rules based on current studies, for instance, the "14-day rule". This rule states that the maximum period time for research on human embryos is 14 days, as the 15^{th} day is the beginning of gastrulation, some believed this marked embryo is a distinct individual, and some suggest the time period should extend to 28 days, as the embryo will not experience any pain due to lack of functional neural system formation at that time (Appleby & Bredenoord, 2018).

As gene editing techniques are shaped through the above interactions with different social groups, the position of those techniques should be situated in society is another important issue to be considered.

Among the above three social groups, scientists and engineers, and government are more closely interacting and influencing gene editing techniques. Scientists and engineers are more engaged with gene editing techniques as they are able to develop and explore the potential of those techniques through research. In some aspects, scientists and engineers could also be considered a regulator for gene editing techniques used. When recombinant DNA was just developed and applied in the 1970s to 1980s, board discussions occurred, topics like whether this technique will create novel organisms and infect the populace after escaping from laboratories,

with concerns about scientists' responsibilities on proper usage for their research (Altimore, 1982). Thus in 1975, molecular biologists, physicians, and lawyers created guidelines for altered DNA living organisms' research at the Asilomar conference, and years later, in 2015, scientists held another Asilomar, which focused on genetically engineered human beings (Vogel, 2015; Jasanoff & Hurlbut, 2018). All these efforts are reasonable as scientists have not understood all the possible side effects, especially of editing germ cells or embryos, and in some ways, make the public avoid direct contact with gene editing techniques, or be more specific, avoid the disease treatment based on those techniques that could lead to potential hazards.

But accidents still happen if just rely on scientists and engineers. In 2018, Chinese scientist Jiankui He claimed he successfully edited the human embryo of twin girls to resist HIV infection and made the embryo go through an in vitro fertilization pregnancy. This accident lead a broad discussion at that time, as Jiankui He not only violated international consensus about the editing of human embryos but also failed to prove his study had eliminated the potential risk, such as off-target effects, in using CRISPR-Cas9 (Krimsky, 2019). Because of his action, another social group engaged in: the Chinese government issued draft regulations about clinical research that have gene editing need to have national approval. Through this example and the above discussion, both government and scientists and engineers can be considered as the gatekeeper of gene editing techniques.

The left social group, public users, or patients are the social group that is most distant from gene editing techniques, as those pharmaceutical products or therapy that can be used for their treatment need to be tested by scientists and engineers and be approved by the government or other regulatory agencies. The social context situated between the public users and gene editing techniques represents any approved techniques applications in society. Gene editing

techniques and those three social groups' positions in society can now be represented by Figure 2: gene editing techniques are constrained by two groups, the scientists and engineers and government's regulations (gatekeepers), as they are either the direct users, developers, and regulators, that constrain the technique. Outside the circle, the social context includes aspects like pharmaceutical products and gene therapy. Finally, far from the technique, the Public, includes patients or people who are not the direct user of gene editing technique but are influenced by the products developed from gene editing technique.

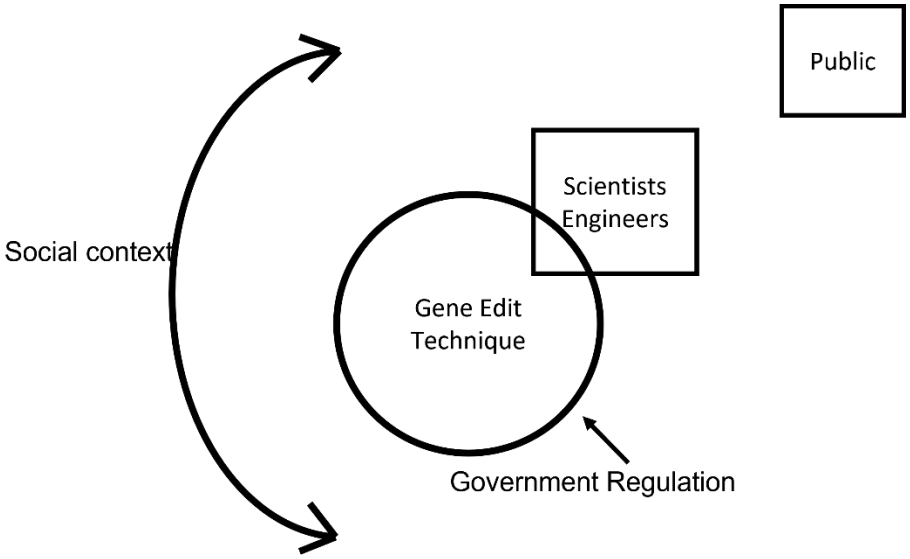

Figure 2: System in Context framework: Scientists and Engineers are gatekeepers with government regulation. Public is separated from gatekeeper, government regulation by Social context (Adapted by Yixuan Yuan (2022) from Carlson (2009))

Conclusion

Although manipulation of human genes has been a controversial topic for a long time, and cases that violate the regulations may still happen again in the future, it does not mean society should prohibit any research on gene editing techniques, as more advanced techniques may be the potential solutions for disease treatment, especially for those disease caused by

genetic defects. Looking at history, gene editing techniques' implications on pharmaceutical production have shown their potential and success in disease treatment. This is not only contributed by scientists' and engineers' years of technique improvements but also contributed by government or similar agencies that keep regulating those techniques' usage, and patient volunteers that support the gene editing based product development.

In this case, for exploring potentials of gene editing techniques and applying them on the right track in future, maybe better remaining the current position of gene editing techniques in society, that is avoid the public having contact with those techniques directly, and leave both scientists and engineers and government regulations to constrain gene editing techniques to avoid those techniques causing possible hazards on society, and making the decision on what gene editing techniques products can now be passed to the public.

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