Utilizing CRISPR-Cas9 Technology for Alzheimer's Disease

Understanding Accessibility and Equity Concerns with CRISPR Technology

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By
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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

The field of medicine has constantly been grappling with the challenges posed by a large number of currently incurable diseases. Despite large advancements in medical science over the years, large portions of the global population continue to suffer from conditions like sickle cell anemia, Huntington's disease, and various cancers – conditions that are currently incurable by standard medical therapies. Cystic fibrosis is another example of a currently incurable disease. It is a genetically inherited condition that affects the lungs and digestive system. Around 40,000 patients suffer from this condition in the United States, with more than 100,000 patients worldwide (National Institute of Health, 2023). Thus, this calls for urgent attention and innovative solutions to alleviate the suffering experienced by these individuals.

"Clustered Regularly Interspaced Short Palindromic Repeats", or CRISPR, for short, is a powerful technology that can be used to alter and modify the DNA sequencing of living organisms. It allows for revolutionized treatment of numerous, and often previously incurable medical diseases (FDA, 2023). Specifically, there have been no cures to diseases that are a result of an erroneous sequencing of one's DNA. Cystic fibrosis is one such disease, due to a mutation of the "cystic fibrosis transmembrane conductance regulator" (CFTR) gene that causes excess mucus buildup in the lungs (Cystic Fibrosis - Causes, 2023). With these gene editing capabilities in mind, the technical topic of this prospectus aims to utilize CRISPR technology to target the CFTR gene and enhance the effectiveness of current cystic fibrosis therapies, while the STS topic aims to understand issues with equity and affordability in healthcare.

Technical Topic: Utilizing CRISPR-Cas9 Technology for Cystic Fibrosis Therapy

The technical topic of this prospectus pertains to utilizing CRISPR gene editing capabilities to combat cystic fibrosis by targeting the faulty DNA base-pairs that cause these genetic conditions. As mentioned earlier, cystic fibrosis is caused by genetic mutations in the (CFTR) gene, affecting the movement of salt in and out of cells and causing extreme mucus blockage in and damage to the lungs and the digestive system. Current cystic fibrosis therapies do not cure the condition but rather merely manage symptoms like reducing inflammation in the lungs and opening up the airways. CRISPR capabilities, however, can be utilized to specifically target the faulty CFTR gene and perform the necessary modifications to rectify the mutated DNA segments, resulting in a potential cure for the condition.

The core component of CRISPR is the "CRISPR associated" (Cas) protein, and more specifically the Cas9 protein. Using this protein, the gene editing process is divided into three different steps: recognition, cleavage, and repair. First, the designated section of the DNA sequence (in this case, the faulty CFTR gene) is targeted within a genome. This step involves a molecule called "guide RNA" (gRNA) to guide the Cas9 enzyme to the specific location to bind with the DNA. The Cas9 enzyme is an endonuclease, which means that it has the ability to precisely cut strands of DNA at any given location. Thus, once the gRNA guides the Cas9 enzyme to the correct location, the enzyme performs a "double-stranded break" (DSB) (Asmamaw, 2021).

After the DSB, the cell undergoes two main molecular pathways to repair the cleaved site: Non-Homologous End Joining (NHEJ) and Homology-Directed Repair (HDR). NHEJ is the primary repair mechanism and is the fastest and most active in the cells, but it also tends to be prone to errors as it can sometimes lead to random insertions or deletions at the cleavage site.

HDR (see Figure 1), however, is far more precise in its repair, but it is slower and requires large amounts of donor DNA templates containing the target sequence (Asmamaw, 2021). Together, the gRNA, Cas9 enzyme, and the NHEJ and HDR pathways provide a robust mechanism for gene editing, leading to potential revolutionary discoveries with regards to medical therapies. The steps of the gene editing is illustrated by Figure 1, below:

Steps in the CRISPR-Cas9 editing process

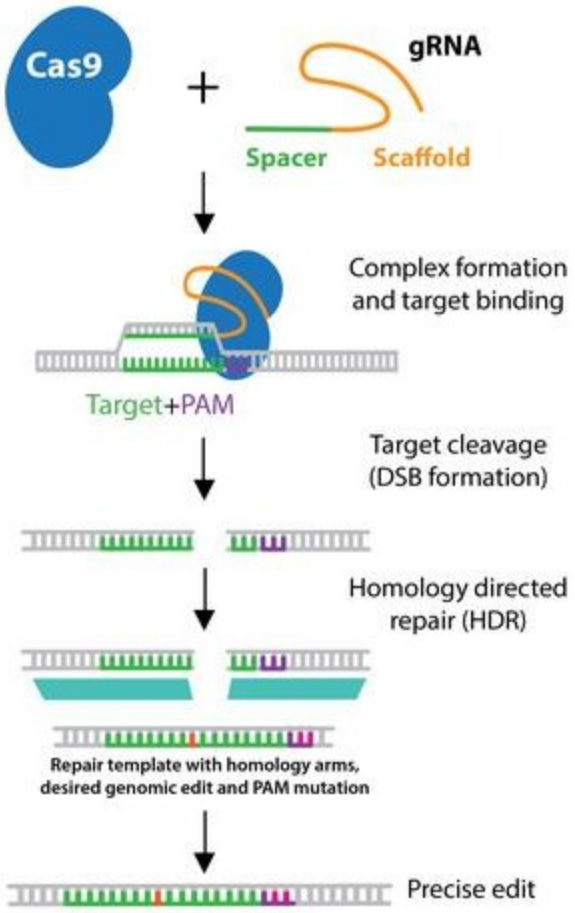

Figure 1: The figure above provides an illustration of the Double Stranded Break (DSB) Homology-Directed Repair (HDR) steps in the gene editing process (Addgene, 2015).

Given the revolutionary nature of CRISPR, the technology poses a considerable amount of safety concerns, particularly with regard to genetic modifications made to germline cells. Germline editing refers to the modification of genetic material such as sperm, eggs, or embryos that can be passed onto future offspring. The process of genetically modifying these cells can have immense consequences as its impact would last across generations. This applies to cystic fibrosis as it is a condition that is genetically inherited, which means that therapies would target the germline cells of patients.

As a result, the possible side effects using CRISPR to modify the DNA in germline cells remains a significant area of uncertainty in the technology. Edits made in germline cells can sometimes cause unintended consequences, and since errors made during genetic modifications are almost impossible to reverse, it can pose serious harm to future generations. For example, a study led by Dr. Dieter Egli of Columbia University used CRISPR in human embryos to correct a genetic mutation that causes blindness. In this study, however, "more than half of the embryos ended up missing portions of the chromosome on which the genetic mutation was situated", and some cases resulted in losing the entire chromosome altogether (Frosch, 2022). Since embryos are germline cells, these unintended side effects of the technology harm not only the current embryo but will persist through all future generations as well.

The technical deliverable will build upon existing research in CRISPR technology to improve cystic fibrosis therapies – this approach should work, as cystic fibrosis is an inherited condition that can be fixed with genetic modification. The main challenge faced when implementing this deliverable will be the process of conducting clinical trials on patients. As mentioned earlier, any failures that may occur during these gene editing therapies can have potentially drastic consequences, which makes it imperative that rigorous trial and testing be

conducted before these therapies are released in the market. To do so, finding willing participants to take part in clinical trials before the treatments are released would be the largest hurdle as these treatments are still in their early phases and require much more testing for increased understanding of further side effects and unintended consequences.

STS Topic: Mitigating Accessibility and Equity Concerns with CRISPR Technology

A perspective on the multifaceted nature of adopting CRISPR-Cas9 into medicine is crucial to understanding the sociotechnical implications of utilizing this technology for disease treatment. Outside of just the patients receiving these therapies, there are numerous stakeholders at play; sociotechnical frameworks like the TOC (Technological, Organizational, Cultural) model provide a structured approach to analyzing these interplaying actors. Earlier sections have given insight into the technological nuances of CRISPR for gene editing treatment. On the organizational side of things, insurance providers, regulatory bodies, pharmaceutical companies, and associations for medical professionals play key roles in adopting CRISPR into therapies (Iltis, 2021). Additionally, understanding societal acceptance, issues with accessibility/equity, and other cultural aspects of this system are another important factor in the larger socio technical framework.

Specifically, the uncertainty or conflict that this STS research will attempt to resolve revolves around the societal and accessibility challenges associated with the widespread adoption of CRISPR-Cas9 technology. These concerns include equitable access to these therapies and proper, well-defined regulatory frameworks for these technologies. Regarding equity and accessibility, currently proposed CRISPR treatments for certain conditions like sickle cell anemia are wildly unaffordable for the vast majority of the population. For example, Vertex

Pharmaceuticals, a biotech company based in Boston, announced a one-dose gene editing therapy for sickle cell disease for a “cost-effective” price tag of almost $2 million. In another report, the Institute for Clinical and Economic Review (ICER) stated that a price range between $1.3 million and $1.9 million would be “cost-effective” (Reuters, 2023). A paper published by the National Institute of Health (NIH) researching the resulting impact on equity states that “health disparities persist in part because major advances in medicine and treatment overwhelmingly benefit society’s advantaged over its disadvantaged", which in turn excludes much of the population, “including many individuals from historically disadvantaged groups who are traditionally denied access to essential social, economic, and health care institutions owing to their minoritized status” (Subica, 2023).

The lack of insurance coverage for CRISPR treatments further exacerbates the issue of affordability. Due to its high cost for research and development, in addition to the long-term consequences that may result from genome editing, a handful of insurance companies have issued plans that entirely exclude CRISPR and gene-editing therapies from their coverage. Without insurance coverage, being able to afford such expensive treatments will continue to be a major deterrent for most patients in need of these therapies (Kozubek, 2017). On the policy side of things, CRISPR “remains largely unregulated due to the United States’ outdated regulatory scheme for biotechnology”, and due to fears of ethical misuse, human embryo research is is not easily undertaken by scientists due to a number of federal and state restrictions aimed at preventing such research” (Tomlinson, 2018). Thus, underlying equity issues, combined with a lack of proper regulation and societal fears of misuse, have stunted the advancement of CRISPR into medical therapies.

Taking these concerns and uncertainties into consideration, the proposed approach to resolution expands upon previous research by Bruno Latour and his extensive work in actor-network-theory by understanding the historical precedence of currently affordable therapies and examining the factors that led to its widespread accessibility. In doing so, we can successfully apply those practices with CRISPR to cut down costs. Vaccines, for example, are a perfect example of a revolutionary form of medical treatment that is now affordable and accessible by individuals from all corners of the world. Without insurance coverage, the retail price of vaccines ranges on average around $50, with the vast majority being less than $20 and a few outliers of more than $100 – prices that are drastically cheaper than the costs of CRISPR (CDC, 2019).

According to a study examining the complexity and cost of vaccine manufacturing, the cost of products is driven by production-related economics. It states that "achieving large scale production and long product life cycles help manufacturers produce at low cost and recover their investments in vaccine research and development." Furthermore, stringent regulatory requirements such as WHO prequalification, local and federal NRA licensure, and quality control requirements play significant roles in driving down costs of vaccines (Plotkin, 2017). The following flowchart illustrates these factors that contribute to lower costs, as depicted in Figure 2:

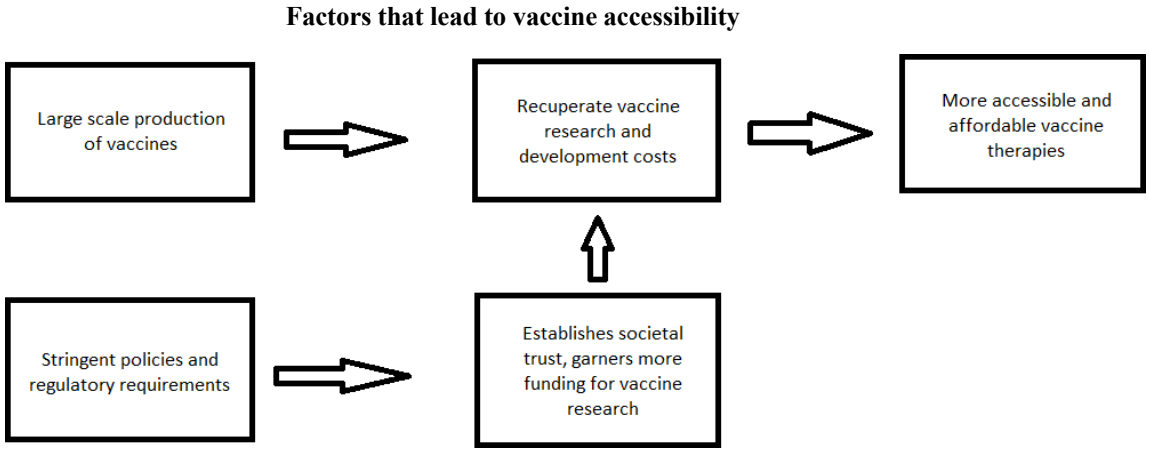

Figure 2: The flowchart above illustrates the various factors that lead to higher accessibility of vaccines, where large-scale production, stringent regulations, increased societal trust leads to more affordable therapies (created by author).

It is important to note that a like-for-like comparison cannot be made between CRISPR and vaccines. Due to CRISPR research being still in its infancy, large-scale production of these therapies is not a currently viable option. Developing CRISPR itself involves much higher complexity than vaccine development, and the market size for CRISPR therapies is far smaller than that of vaccines. That being said, however, a thorough understanding of the sociotechnical framework that allows for the increased accessibility for vaccines and related treatments is crucial for these same factors to be incorporated for CRISPR in the near future.

Conclusion

The anticipated deliverables of the technical work include an improved treatment for cystic fibrosis, a currently incurable genetically inherited disease. This treatment would utilize CRISPR-Cas9 technology, a revolutionary advancement in biotechnology that can perform precision edits on the human genome, to rectify erroneous segments of a patient's DNA. The deliverable of my STS research aims to understand the historical precedence of currently affordable treatments and how these factors could be incorporated with CRISPR treatments. If

completed successfully and appropriately implemented, these deliverables would provide a better therapeutic alternative for patients suffering from cystic fibrosis – an alternative that could potentially cure the condition instead of merely reducing symptoms. These therapies would also be accessible by a much larger percentage of the population with limited barriers arising from socioeconomic status. The technical and STS deliverables are essential components of a comprehensive approach towards tackling cystic fibrosis; taken together, these deliverables represent a combination of both scientific innovation and societal responsibility by offering tangible technical solutions while also promoting equity and accessibility for all.

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