Using Genetics to Identify Critical Regulators of Immune Dysfunction Driving Cardiovascular Disease and Metabolic Abnormalities in the Polygenic Autoimmune Disease Systemic Lupus Erythematosus
(Technical Paper)

Social Perspectives of Genetic Engineering for Medical Purposes
(STS Paper)

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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:

In 1990 the Human Genome Project was funded with the goal of sequencing the entire human genome in 15 years and was completed two years ahead of schedule. While in its early days there were many critics, in hindsight, the project's overwhelming success made it clear that the benefits greatly outweighed the cost (Chial, 2008). With technological advancements in genetics, we now know so much more about the human genome and molecular biology. As a result, biomedical research and medicine is heavily relying on genetic information to understand and ultimately treat all types of medical conditions. While many medical professionals are determined to fully master and manipulate the human genome, social restrictions remain a large obstacle to genetic engineering. As such, my STS topic is focused on the societal constraints and implications with respect to FDA approval of gene therapies, with an emphasis on human genetic modification.

Determining the critical genetic players in disease has become a major focus of biomedical research as it provides insight into the relevant pathophysiological mechanisms and potential areas for targeted drug intervention. Systemic lupus erythematosus (SLE) is estimated to affect nearly 1.5 million people in the United States alone (Genetics Home Reference, 2019). Additionally, premature heart disease is a major cause of morbidity and mortality in SLE (Liu & Kaplan, 2018). Unfortunately, the standard drugs for SLE are not effective in prevention or treatment of cardiovascular disease (CVD) in these patients. Identification of critical genetic pathways of CVD in SLE can provide insight into optimal drug targets for improved outcomes. For my technical project, I will be investigating the shared pathways underlying SLE CVD in hopes of identifying existing drugs that can be repurposed in SLE to prevent or treat CVD.

Technical Topic:

Systemic lupus erythematosus (SLE) is a highly heterogeneous autoimmune syndrome characterized by inflammation, immune disfunction, and greatly contributes to the development of cardiovascular disease (CVD). Compared to the general population, patients with SLE have a twofold to tenfold increased risk of CVD. The relative risk for women with SLE between the ages of 35 and 45 is increased 50-fold and the chance of having a fatal heart attack has been reported to be three times greater in SLE patients (Leonard et. al, 2018). Additionally, many SLE patients who have had a heart attack are relatively young, suggesting an increased risk with SLE rather than chance occurrences (Zeller & Appenzeller, 2008).

The therapeutic challenge presented by SLE is largely due to the extensive heterogeneity of the disease. In general, SLE is associated with hyperactivity of the immune system. Standard-of-care treatments for SLE include glucocorticoids, non-steroidal anti-inflammatory drugs, antimalarials, and immunosuppressive drugs (Nasonov et. al, 2015). These drugs only treat symptoms and control the progression of the disease. Recently, belimumab has been approved for treatment of SLE as well. Belimumab was not only the first new drug approved for SLE in decades, it also is the first biological agent used for treating SLE (Aringer et. al, 2011). Despite the moderate effectiveness, the approval of belimumab is revolutionary as it marks a shift in treatments for SLE away from superficial, symptom-focused medicine.

While SLE deaths related to infections and active disease has decreased, CVD-related death rates have not improved and the standardized mortality ratio due to CVD has slightly increased (Björnådal et. al, 2004). Treatment options remain limited as statins have little effect on cardiovascular outcomes in SLE populations despite their effective preventative role in non-SLE patients. Recent studies exploring the association between SLE and premature CVD

demonstrate that alterations of specific immune functions play a pivotal role in the increased cardiovascular morbidity and mortality observed in SLE patients (Liu et. al, 2008). Nonetheless, additional studies are needed to identify critical pathways in SLE CVD pathogenesis that can be used as novel points of therapeutic intervention.

Genetic predispositions are important risk factors for both SLE and CVD. The lack of a correlation between severity of SLE and development of CVD in SLE (Ciccacci, 2018) supports the hypothesis of the presence of genetic predispositions in SLE patients for developing CVD. Although Genome-Wide Association Studies (GWAS) have mapped specific genetic variations to both autoimmune and cardiovascular diseases, these results have failed to impact clinical practice. Understanding the functional mechanisms of causal genetic variants underlying SLE and CVD may provide information to identify shared molecular pathways and therapeutic targets relevant to disease mechanisms.

Working with AMPEL BioSolutions, I will be investigating the shared pathways underlying SLE CVD with a focus on identifying novel therapeutic options. I will first map genetic mutations associated with both CVD and SLE to causal genes using web-based tools and public databases. Using a comprehensive bioinformatics approach, I will build protein-protein interaction networks for the SLE and CVD predicted genes. These molecular pathways will be used to determine critical genetic players and potential targets contributing to disease. Next I will match therapeutic targets discovered in critical pathways in SLE CVD pathogenesis to existing drugs, which will then be scored using the Combined Lupus Treatment Scoring (CoLTs) system. As such, the ultimate goal of this project is to identify drugs that can be repurposed to prevent or treat CVD in SLE. This method of repurposing available drugs can greatly expedite and inexpensively bring effective therapeutic options to the market.

STS Topic:

Sickle cell anemia was discovered over 100 years ago, yet still there exists no cure and most sickle cell patients do not live to see age 50. This disease affects millions of people worldwide and is caused by a single mutation in the HBB gene. The mutated gene results in atypical hemoglobin and distorts red blood cells into a sickle shape (Genetics Home Reference). CRISPR-Cas9, a gene editing technology, has been utilized in patients of life-threatening conditions with no standard treatment and continues to show its great potential. Additionally, there have been significant developments in gene editing technology to introduce genetic variants that initiate cell death in cancerous cell lines. Ethical concerns with gene therapies, however, continue to hinder effective treatments and cures of many fatal conditions.

With many severe and terminal conditions resulting from genetic variants and abnormalities, there is great interest in using gene editing technologies to cure genetic disorders (Genetics Home Reference, 2019). There are a wide range of ethical concerns related to human genetic modification, especially with respect to editing the germline. Many people are primarily concerned with potential abuse of the technology for improving human traits such as intelligence or appearance (Genetics Home Reference, 2019). Others are entirely opposed to gene editing and argue that it is impossible to achieve informed consent considering individuals affected by the genetic modifications are embryos and future generations (National Human Genome Research Institute, 2017).

Geneticists appreciate the magnitude and organization of the human genome, thus separate medical genetic therapies from genetic enhancement: the transfer of genetic material to modify nonpathological human traits (National Human Genome Research Institute, 2017). Similarly, with the extensive understanding of many human genes, geneticists and molecular

biologists are very confident in their ability to predict the effects of specific modifications. While many people directly associate identity and individuality with one's entire, unique genome, others do not, especially with respect to distinct, disease-causing mutations. These people have a very different perception of genetic therapies; rather than viewing gene editing as "playing god," it is seen as the simplest approach to preventing or treating almost any medical condition directly at the source.

An important aspect when considering societal implications with respect to gene editing is the different and contrasting perspectives of relevant populations. One of four components of Social Construction of Technology (SCOT) is the concept of relevant social groups (Klein and Kleinman, 2002). SCOT characterizes the way in which society shapes technology. It embodies the ongoing cycle of technological design and consumer feedback, which continues until all relevant groups come to a consensus on the interpretation and use of a technology. In reality, reaching a true consensus with respect to human genetic modification is nearly impossible due to underlying principles behind the contradicting perspectives.

On one hand, there are the millions of individuals afflicted by diseases that currently can only be cured or treated by genetic therapies and technologies. On the other hand, there are countless individuals that are against gene editing for a number of personal beliefs. The real dilemma occurs when you consider individuals that fall into both categories. FDA approval of human genetic modification for treatment of specific diseases has the potential to be tremendously detrimental to the population that falls into both relevant groups, as the market for alternative treatments may not be large enough to incentivize the necessary research.

A popular critique of SCOT is its failure to consider the way in which technology shapes society. Technological Determinism is the theory that technologies introduced into society

greatly influence the society. It advocates that technological change drives social change and more intense interpretations of technological determinism suggest that technological development can even act as an autonomous force independent of social constraints (Smith, 1994). In the case of gene therapy, it is clear that the use technological development is heavily influenced by societal constraints. In fact, all of medical research and clinical practice is significantly regulated by bioethical principles.

A third concept, Technological Momentum, describes the shift in power from society to technology as it is integrated into society (Hughes 1994). While SCOT is more applicable to the current status of gene editing, the standardization of gene therapies will increase the acceptance of gene editing. As the social resistance towards gene editing decreases, the technology will become engrained into society and gain momentum. Additionally, a technology this powerful has the potential to greatly influence society. Many hypothesize that standardization of medical gene therapies will in turn result in an increase of gene editing for human enhancement. Thus, it is imperative to also consider the technological momentum and determinism associated with gene editing.

Research Question and Methods:

To determine the societal concerns on genetic engineering and the implications of such technologies on society, I will employ policy analysis, documentary research methods, and historical case studies. This includes evaluating current bioethical standards, relevant case studies, and international use and results of similar technologies. Similarly, I will analyze the change in perspectives on medical practices and bioethics over time with the emergence of previous ground-breaking technologies. Additionally, given the nature of my topic, I will also

utilize wicked problem framing. Wicked problems are characterized by social complexity rather than technical complexity and have no correct solution due to diversity amongst stakeholders (Rittel and Webber, 1973). The controversy around gene therapies and human genetic modification is the epitome of a wicked problem. Ultimately, this process will ensure an objective evaluation of the problem at hand, the challenges and concerns that must be addressed, and potential solutions to the problem.

I will start by identifying the specific concerns about the medicinal use of genetic engineering to ensure my research considers all perspectives. I will then research and hypothesize the impacts of such technologies on society. Next, I will use current bioethical standards and case studies to evaluate the validity and significance of such concerns. I will also access the experience of other countries with the approved use of genetic engineering to see how these technologies have impacted society. Lastly, I will examine shifts in medical standards and bioethics in our society for insight on why and how such dramatic shifts occurred. Using these resources, I will employ the wicked problem framing approach to analyze the system and determine potential solutions. Ultimately, this process will ensure an objective evaluation of the problem at hand, the challenges and concerns that must be addressed, and potential solutions to the problem.

Conclusion:

The genetic mechanisms of disease are extremely useful in developing treatments. Specifically, identification of critical genetic players in CVD in SLE will provide insight into the increase in risks as well as potential areas of targeted drug intervention. Ultimately, customized drug recommendations by specific genetic markers identified in my technical project have the

potential to decrease morbidity and mortality in SLE patients. However, as genetic engineering involves difficult bioethical concerns, it is important to thoroughly evaluate the relevant societal perspectives and implications. As such, my STS research will provide a deeper understanding of the societal concerns about genetic engineering and can offer insight into potential solutions to the controversy as well as important considerations and restrictions for the use of the genetic therapies.

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