**THE FUTURE OF GENE EDITING: BUILDING A COMPETITIVE U.S. STRATEGY**

**Executive Summary**

It is not difficult to imagine a future in which the major military powers are all capable of deploying genetically enhanced super soldiers. The challenge is to imagine a future where the U.S. is not one of these powers. Foreign powers may not be the only threats either. Insurgents within the U.S., self-modified using kits like the ones that are already on the market in 2018, could threaten to destabilize the country from the inside. The seeds of this future are already being planted. With the regulatory framework we have now for human genomic modification, the U.S. is already falling behind on an international stage because it is locked into a place where it cannot proceed. Clinical trials in gene modification have reached more advanced phases elsewhere, particularly in China. The path to leveling the competition will require a system that has been developed with the specific challenges of gene modification in mind, as well as funding focused on improving the baseline of gene editing technology.

**Introduction**

The main focus worldwide is on using CRISPR for healthcare rather than enhancement, and to this point it is only practical to edit one gene at a time rather than making massive genome edits. However, there is still cause for concern that the U.S. is not keeping up with the global pace. Gene editing trials are progressing much more rapidly in other regions due to different regulatory standards. Since 2015, China has reportedly conducted nine studies on 86 total patients using CRISPR technology. The most recent trial involved injecting CRISPR into patients with aggressive forms of cancer, and results have not yet been publicized.1 Elsewhere, CRISPR Therapeutics has been approved to go ahead with a clinical trial in Europe aimed at combatting beta-thalassemia using CRISPR Cas-9.2 The same company was approved to begin clinical trials on a CRISPR approach to cure sickle cell anemia in 2018, but the trial has been placed on clinical hold by the FDA until further questions are answered.3 The U.S. is not keeping pace with international competitors, in part due to its regulatory system.

Under the current U.S. regulatory framework, an oversight body of a grant-bestowing institution may require a potential trial to be approved by National Institutes of Health Recombinant DNA Advisory Committee (RAC). Two conditions are required to request RAC review. The oversight body must believe the protocol would benefit significantly from review, and the protocol must involve a departure from previous studies: a new vector, genetic material, or delivery methodology, preclinical data obtained using a new model of unknown value, or association with possible toxicities that are not widely known.4 If the protocol is approved, the subsequent clinical trials and the resulting drug or technology are monitored by the FDA. Specifically, gene modification is regulated by the Office of Tissues and Advanced Therapies, a division of the Center for Biologics Evaluation and Research. The OTAT also regulates antivenins and recombinant therapeutic proteins, giving it a broad jurisdiction, rather than a specific focus on gene modification.5

In contrast, Chinese trials have to be approved by the Ministry of Health, but a proposal for a cancer treatment was approved in one afternoon. One member of the committee admitted that she did not really understand the science laid out in the 100-page proposal, but she approved it anyway.1 The ethics of the Chinese process are almost certainly incompatible with U.S. ethics, and this should not be taken as a suggestion to immediately adopt the less stringent restrictions of the Chinese regulatory system. However, if the U.S. is going to attempt to keep pace with Chinese developments, the system as it stands may need to be reevaluated.

Although it may not be a military issue at the deployment phase yet, DARPA and its Chinese equivalents, the Chinese Academy of Military Medical Sciences and the Third Military Medical University, already have some investment in human gene modification. Exact financial investment is not known for the Chinese organizations, but both have sponsored CRISPR-related clinical trials.6 DARPA, however, has chosen to focus more on allele expression with the PREPARE program because it is reversible and can in theory defend against pathogens, radiation, and toxins.7 This is acknowledged as a diversion from contemporary gene editing research, which could put the program at a disadvantage without the benefit of being able to draw on the research of other institutions. The U.S.’s readiness for international competition will therefore be significantly dependent on its ability to enable private sector innovation in the field of human gene editing.

**Primary Recommendation**

The primary recommendation of this paper is to create a separate division of the FDA specifically for the regulation of gene modification. Gene modification is going to fundamentally alter humanity in a way other drugs do not, and the current regulatory system, with gene editing overseen by a small sub-office of a subdivision, does not reflect that. The pharmaceutical regulatory system as it stands renders it difficult to get even standard drugs approved. Reports have placed the average cost to bring a new pharmaceutical to market at $2.6 billion, taking an average of 12 years.8, 9 For gene editing products specifically, the prime example is the AquAdvantage salmon by AquaBounty. The salmon, which was engineered using a growth hormone gene from the Pacific Chinook salmon to enable faster growth, was not approved by the FDA until 20 years after the initial application, reportedly almost bankrupting the company.10 After six years of attempting to regulate the Oxitec mosquito, engineered to reduce the population of disease-carrying insects, the FDA transferred regulatory jurisdiction to the EPA.11 These timelines do not encourage innovation. The University of Guelph, a Canadian institution, engineered a pig that produced more environmentally friendly waste products. The pigs had been bred since 1995, and the research team was looking to reach U.S. markets and therefore seeking FDA approval.12 Its FDA application was retracted in 2012 because Ontario Pork, the primary investor, was concerned about the slow approval process for the AquAdvantage salmon and decided to stop supporting the project, fearing a similar result.13

Although no human gene editing trials have yet advanced far enough to predict the approval timeline, effects of delays are already becoming evident. CRISPR Therapeutics stock dropped 19% after the clinical hold was placed, and other gene editing stocks also took abrupt downturns.3 The long approval times of the current regulatory system potentially serve as a barrier to innovation, particularly for smaller companies. A regulatory division with a framework that has been established specifically for human genetic editing would not suffer from the delays that come from trying to regulate a new type of product in a system meant for conventional pharmaceuticals. Removing jurisdiction from the FDA entirely would cause definition-based disputes, but in order to be competitive internationally, steps must be taken to streamline the regulatory process.

**Secondary Recommendation**

The second recommendation of this paper is to invest greater NIH funding in developing the technologies of gene modification. The most recent NIH initiative with this focus is the Somatic Cell Editing program, launched in January 2018. The goal is to award $190 million to researchers over the next 6 years.14 This works out to approximately $31.6 million a year. The average annual NIH investment is $37.3 billion, making the yearly investment in gene editing approximately .085% of annual NIH funding.15 This is a very small percentage, especially when both international competition and the future state of humanity itself stand to be impacted by gene editing technologies. Currently, millions of dollars of NIH funding go into research on heritable diseases. For example, $47 million was spent in 2017 on research for Huntington’s disease, which is caused by a defect in a single gene.16, 17 With improved gene editing techniques, Huntington’s disease could be eliminated, allowing for a redistribution of funding. While eradicating cancer requires much more than the modification of a single gene, gene modification still provides a potential cure, meaning that a greater investment in gene editing could save both lives and money in the long run.

Although gene editing itself has become less expensive due to breakthroughs like CRISPR, developing and testing a new therapeutic is still expensive. While many scientists are working on using CRISPR in their labs to work on therapies for specific diseases, this funding increase would be dedicated to improving gene editing techniques themselves in order to improve the standard toolkit for disease research. CRISPR represents a breakthrough in terms of affordability and ease of use, but reaching the next breakthrough will take dedicated resources.

**Conclusion**

The U.S. is falling behind in gene editing trials, but it is not so far behind that it cannot remain competitive by modifying its policies. The one option it does not have is to stay out of the international debate around gene editing. Susan Hennessey said of AI, a technology with similar ethical issues, “Whenever large companies choose not to participate […] you forfeit the ability to actually shape those technologies, and I think it is an accurate prediction that this doesn’t mean those systems aren’t going to be built, it means they aren’t going to be built by you. You are giving up the ability to bake in some of your values.” 18 As with AI, if the U.S. chooses to limit technological development of human gene editing, it will have very little ability to influence the ethical bearing of the technology on an international stage. Caution is important while developing a new technology, but it must also be balanced with innovation. A focused structure and increased funding are two steps towards enabling these values.

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