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Dual-Use in Synthetic Biology:
Balancing Intellectual Freedom with Regulations on Research

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Introduction

In recent years, scientific research in genetics and cellular mechanisms has led to a new approach to the study of biology—one that encourages researchers to be innovators and agents of change rather than simply observers. This burgeoning field—called synthetic biology—focuses on the creation of medical technologies and artificially engineered life by manipulating the natural order of living entities. In other words, synthetic biology is geared towards changing the existing forms of life (usually on a genetic basis) to develop insights regarding health and medicine. Although this field is producing groundbreaking discoveries, research in synthetic biology is being partially tempered by a new brand of ethics. Because synthetic biology relies on the ability to change current living entities, it inevitably raises ethical concerns regarding the potential consequences of engineered life.

Common ethical dilemmas surrounding synthetic biology include the idea of "playing God" when manipulating life or using a reductionist perspective to lower the "dignity" of life so as to treat genetic information as a mere toolkit (Heavey, 2013). The strongest ethical concern deals with the possibility of adversely impacting human health, degrading the environment, or facilitating the practice of bioterrorism. These potential misapplications of synthetic biology are collectively referred to as dual-use research of concern (DURC) (Cho & Relman, 2010; Edwards, 2014). Especially due to the horrific attack during 9/11 and the subsequent rise in the potential for bioterrorism, dual-use has become an increasingly important ethical issue in determining when to permit synthetic biology research. However, in the process of conducting ethical examinations of research, we must ensure that the rights of scientists and research institutions are not infringed upon. Furthermore, we must consider the potential benefits of synthetic biology research in the face of possible harms due to dual-use. In this paper, I assert that synthetic biology research should be treated largely with a policy of openness and acceptance—but at the same time, should be subject to reasonable regulations and ethical examinations by appropriate governing bodies. This practice will allow synthetic biology to flourish while also regulating the research to prevent dual use harms.

Basics of Dual-Research of Concern (DURC)

One of the landmark events that spurred the development of new ethical concerns regarding dual-use was the creation of a synthetic genome that could replicate itself in bacterial cells (Garrett, 2013; PCSBI, 2010). Conducted by the J. Craig Venter Institute, this research project caused much controversy over synthetic biology, as possible mistakes could have led to an outbreak of bacterial cells that harm human health or degrade the environment. Additionally, if the methodology of this research project were easily reproducible, terrorist organizations might be able to use Venter's publications for bioweaponry. Thus, in response to the creation of this synthetic genome, a new brand of ethics regarding dual-use was born.

The U.S. National Science Advisory Board for Biosecurity (NSABB) defines dual-use as "research that … can be reasonably anticipated to provide knowledge, products, or technologies that could pose a threat to public health, agriculture, plants, animals, the environment, or materiel" (Cho & Relman, 2010). This definition is quite broad by design, as many of the potential consequences of synthetic biology are unknown—simply because the field is still in its infancy. However, it is relatively clear among ethicists that research in synthetic biology is moving faster than the development of germane ethical examinations/regulations (Biller-Adorno et al., 2013; Edwards, 2014; Heavey, 2015). This "lag time" increases the possibility of harms due to dual-use being realized before appropriate policies are promulgated. As such, a central issue in synthetic biology is reconciling ethical policies with current research—but this act of reconciliation sparks questions about the extent of re-

strictions that should be put in place to avoid harms due to dual-use while not stifling scientific research.

Value of Openness in Synthetic Biology

Throughout the history of scientific research, it has been well-established that discovery and innovation are best promoted using a policy of openness, in which information and methodologies are widely shared and reproduced (Cho & Relman, 2010; PCSBI, 2010; Smith, 2013). This principle holds for the field of synthetic biology as well, as it is a branch of science research like any other. Therefore, in order to maximize the utility of synthetic biology research, it is necessary to keep the field as open and unrestricted as possible. This approach is often referred to as a laissez-faire policy regarding synthetic biology (Smith, 2013). When continuing this utilitarian mode of analysis, however, we reach a stumbling block: the quantification of the possible harms of dual-use. Ethicists have found it difficult to estimate the potential harms, largely because dual-use is intrinsically a speculative enterprise. In other words, quantifying the harms due to dual-use would be relatively inaccurate, as it is possible that very few or very many of the harms will actually materialize. Furthermore, the potential harms themselves are difficult to estimate, as they can range from being almost innocuous to being catastrophic (Edwards, 2014; Smith, 2013). For example, disease outbreaks due to safety breaches in research labs could be trivial if the disease is weak or if there are vaccines/cures for distribution, whereas the outbreaks could be devastating if there are no protective measures in place. Thus, the range of possibilities is too broad for sufficiently accurate quantifications of the risks of dual-use.

A common solution to this ethical dilemma is to combine the utilitarian value of openness with a deontological argument regarding intellectual freedom (PCSBI, 2010). The idea of intellectual freedom stems from the fundamental belief that we, as people, have the right to think about and investigate any issues that we want. In the case of dual-use, intellectual freedom is more specifically defined as the right of scientists and research institutions to pursue any scientific investigations that they wish. However, both of these definitions have a relevant caveat: the pursued investigations as a result of intellectual freedom must not produce unethical consequences. In other words, in the case of dual-use, while practicing intellectual freedom and potentially increasing utility, scientists and research institutions must ensure that they are not harming human health, degrading the environment, or increasing the likelihood of bioterrorism. This idea of intellectual freedom was used by the Presidential Commission for the Study of Bioethical Issues (PCSBI) when analyzing the ethical nature of the synthetic genome created by the J. Craig Venter Institute (PCSBI, 2010). The PCSBI employed the concept of intellectual freedom to introduce the useful corollary of regulatory parsimony, which suggests that synthetic biology should be subject to "only as much oversight as is truly necessary to ensure justice, fairness, security, and safety while pursuing the public good" (PCSBI, 2010).

It is clear from the PCSBI's concept of regulatory parsimony that synthetic biology is most effective when in an environment of openness. To excessively restrict synthetic biology research would be to take away the right of scientists and research institutions to intellectual freedom. Thus, the value of openness in synthetic biology is both scientifically supported and ethically valid. However, ethicists and the PCSBI promote intellectual freedom and regulatory parsimony with the assumption that there will be necessary restrictions in place to prevent the harms of dual-use. This balanced approach attempts to grant as much openness as possible while still adding necessary regulations to preclude the risks of synthetic biology research from being realized.

Ethical Basis of Regulations and Policy Implications

Before discussing the regulatory policies that would be ethical to implement in synthetic biology research, it is worth investigating why regulation is ethical in the first place. It has already been established that intellectual freedom is a right that scientists and research institutions should possess. Without a significant amount of independence and self-motivation, progress in research would be greatly hampered (Cho & Relman, 2010; PCSBI, 2010; Smith, 2013). However, scientists and research institutions must not use their freedom to purposefully or inadvertently contribute to unethical consequences regarding dual-use. It is within reason to

consider that labs in the United States and around the world can make mistakes (or do intentional harm) that hurts human health, degrades the environment, or promotes bioterrorism. In all of these cases, it would be unethical to allow such research because the consequences can be harmful to our society. Thus, we have an ethical issue to balance—by allowing sufficient intellectual freedom without losing regulatory control (PCSBI, 2010).

In finding an appropriate balance, it is useful to consider the weights of the two sides: intellectual freedom for effective research versus regulation for the prevention of harms due to dual-use. The former (i.e., intellectual freedom) is a constantly applicable right; that is, scientists and research institutions would be definitively reduced in capacity if intellectual freedom were limited. On the other hand, the latter (i.e., regulation to prevent harmful consequences) is largely based on speculation. Regulations would be put in place to prevent potential harms due to dual-use, but there is no definiteness that is associated with those harms. (In other words, the harms may or may not actually be realized.) Therefore, the ethical balance tips in favor of intellectual freedom, and in crafting appropriate policies, we must consider this difference in weight of the two sides.

In light of the higher weight of intellectual freedom, we must ensure that all applicable policies provide sufficient but not excessively stringent regulations on synthetic biology research. A felicitous starting point would be to advocate self-regulation of research by the scientists and institutions themselves (Smith, 2013). This policy can be implemented both informally and formally. In the former case, scientists would simply be subject to their own ethical decision-making and would hopefully use common sense and ethical judgment to choose proper research projects and ample safety measures. This practice is sometimes referred to as upstream engagement, in which scientists are required to consider safety and security threats due to dual-use while, not after, they conduct their research (Edwards, 2014). In the latter case, research institutions would subject their scientists to an ethical review before they embark upon a research project. This would be the first official "line of defense" against any unethical research practices. Both of these aspects of self-regulation are ethically valuable because they limit any reduction in intellectual freedom.

At the same time, since self-regulation has a relatively high risk of bias and corruption, it is necessary for an external governing body to conduct sufficient ethical reviews of synthetic biology research. This aspect of policy is more controversial, as it is difficult to draw boundaries between external regulations that are ethically justified and those that are excessive. However, most ethicists agree on the point that current ethical reviews for synthetic biology research are lacking in rigor (Biller-Adorno et al., 2013; Edwards, 2014; Heavey, 2015). Because the field of synthetic biology is developing so quickly, it is difficult—but necessary—for ethical reviews to maintain the same rate of development. The PCSBI has suggested that research institutions be subject to the NIH Guidelines for Recombinant DNA Research and undergo ethical examinations facilitated by the Federal Bureau of Investigation (FBI) and the Department of Homeland Security (PCSBI, 2010). With regard to international research efforts in synthetic biology, ethicists have suggested using the World Health Organization (WHO) to construct a body of regulations modeled after the Codex Alimentarius, which regulates food safety. Some ethicists have also encouraged researchers to engineer suicide genes in their synthetic biology projects, which would enable the engineered life to be relatively easily killed if deemed uncontrollable (Garrett, 2013). Yet another compelling suggestion is for all research publications to include an ethical assessment—thus ensuring that all scientists and institutions are undergoing proper ethical examinations (Heavey, 2015). All of these suggestions merely brush the surface of a large, developing field in policy regarding synthetic biology. At this point, ethicists and policymakers are fighting an uphill battle, as more regulation is almost certainly necessary to deal with the possible harms due to dual-use. However, in order to encourage progress in synthetic biology, it is critical to ensure that these regulations do not become excessively stringent on the intellectual freedom of scientists and research institutions.

A Glimpse of the Future in Synthetic Biology

As aforementioned, the field of synthetic biology is often touted to be pivotal in the coming years of development in medical technologies and scientific

innovations. One of the main reasons for the excitement about this field is that scientists are using nature's building blocks of life as the foundation for our own innovations. Nature has been priming its creations for millions of years, so using these naturally primed tools will significantly boost our ability to innovate. For example, scientists have learned that bacteria have Clustered Regularly Interspaced Palindromic Repeats or a CRISPR-Cas system, which functions in bacterial immune response. By synthetically controlling the CRISPR-Cas system using small molecules, scientists have been able to learn about DNA repair mechanisms and genome editing (Yu et al., 2015). Another example of cutting-edge research in this field deals with the synthetic modification of histones and nucleosomes, which are related to chromatin structure and gene expression. By changing the structure of histones and the positioning of nucleosomes, scientists have been able to affect gene silencing and other features of transcription (Keung et al., 2015). Both of these research projects have a wide breadth of applicability, ranging from cancers to stem cell use to neurodegenerative diseases.

This well-defined importance of synthetic biology makes it even more vital to balance the intellectual freedom of scientists and research institutions with the necessary regulations to prevent the harms of dual-use. By doing so, we will not only be ethically justified in giving more weight to intellectual freedom but also be scientifically shrewd in considering the potential benefits of this research. One final note of encouragement is that "the dual-use dilemma that first hit chemistry a century ago, and then hit physics a generation later, is now emerging with special force in contemporary biology" (Garrett, 2013). Thus, the general issue of dual-use is not completely unprecedented and can be resolved over time with proper ethical judgment. With a resolution that provides an appropriate balance of intellectual freedom and regulations, the field of synthetic biology will be primed

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