GENETIC TECHNOLOGIES

Synthetic "Life," Ethics, National Security, and Public Discourse

Synthetic biology draws notice to the need for balanced and informed discussion about benefits and risks in the life sciences.

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The work by Gibson and colleagues in this issue of *Science* (*1*) showcases technological achievement, highlights the promises of science, and raises questions about the nature of life. The ensuing discussion has featured a number of concerns about biosecurity and ethics—some real, some imagined.

"Synthetic genomics" refers to the laboratory synthesis and assembly of genomes and their expression to produce viruses or cellular life forms, whereas "synthetic biology" refers more broadly to the creation of synthetic biological systems that are programmable, self-referential, and modular. The design of synthetic genomes has been largely based on the sequence of known, naturally occurring genomes. Until now, because of the challenges of synthesizing and assembling large pieces of nucleic acid accurately and of choreographing genome replication and expression properly, only viral genomes have been synthesized and expressed. However, the associated skills (i.e., to read, write, and assemble DNA) have advanced considerably over the past several decades (*2*). This rapidly changing landscape also includes other (non–synthesis-based) genetic engineering techniques for generating, expressing, and screening novel genetic diversity, such as directed molecular evolution and DNA shuffling. What has lagged behind most noticeably is a predictive understanding of function and of the emergent properties of cells based on genome sequence and, hence, the insight necessary to design truly novel forms of life.

The kinds of individuals participating in the life sciences revolution have also expanded to include nonprofessional scientists and those trained in disciplines well outside the traditional mainstream (*3*). The public sees a growing population of operators with various interests in manipulating and controlling life, but less well articulated rationales.

In the midst of revolution, and especially over this past decade, awareness of risk in the life sciences has become heightened, in part because of the growing and more widely disseminated capabilities mentioned above and in part because of a less-stable global political and social landscape (*4*). The greatest challenge in addressing biosecurity and ethical concerns has been, and will be, to design effective oversight mechanisms that avoid undue harm to the overwhelmingly beneficial life sciences enterprise.

The U.S. National Science Advisory Board for Biosecurity (NSABB) has proposed a definition for dual-use research of concern and a framework for overseeing this research, including approaches for outreach, education, and risk communication (*5*). The NSABB criterion is purposefully broad and defines dual-use research of concern as "research that, based on current understanding, can be reasonably anticipated to provide knowledge, products, or technologies that could be directly misapplied by others to pose a threat to public health, agriculture, plants, animals, the environment, or materiel" [(*5*), page 1, footnote 1]. In addition, NSABB and other organizations have offered recommendations for managing some of the risks associated with synthetic genomics, prompting preliminary governmental response (*6*). [For example, the U.S. government is developing guidance to producers of synthetic genomic products regarding the screening of orders for sequences of "select agents and toxins" (*7*)]. A major unresolved problem is the increasingly dangerous reliance on microbial threat lists, and another is the arbitrariness of microbial taxonomy based on sequence homologies (*8*). Microbial genetic diversity discovered in nature, as well as generated in the laboratory, increasingly blurs these taxonomic boundaries. Lists of named agents create an illusion of having defined the spectrum of potential threats.

From a security perspective, Gibson *et al*. do not cause particular concern. Although synthetic genomics poses potential risks and will increasingly do so in the future, the methods and findings here are probably of limited applicability and generalizability (e.g., limited to genomic transplantation of cell-wall deficient organisms), and may be difficult to apply to other kinds of organisms. In addition, the work does not provide new guidance or instruction that aids in the creation of an organism with new worrisome attributes. In 1999, Cho *et al*. (*9*) identified ethical issues associated with efforts to create synthetic genomes and synthetic life, including the problems with reductionist approaches and a genetic definition of life. Cho *et al*. argued that further discourse in this area should be informed by perspectives from theology, philosophy, the social sciences, and the general public. They also proposed that fears of "playing God" were inconsistent with major Western religious traditions, but that scientists should take their role as stewards and the dangers of hubris seriously. It was noteworthy in the recent discussions of Gibson *et al*. that the Vatican response was fairly positive, noting that it was "important research" that had not created life, but had "replaced one of its motors" (*10*).

Finally, Cho *et al*. discussed the need for new models of intellectual property to ensure that both commercial and public interests were protected. Gibson *et al*. have not raised new issues regarding patenting, but current intellectual property structures remain a potential barrier to synthetic biology research and development (*11*).

Most commentators on the implications of synthetic genomics and synthetic biology have agreed that few, if any, new ethical issues are raised (*12*–*19*). Some, however, have reemphasized the larger questions raised about humans as creators and definers of life (*13*), the intrinsic value of synthetic biology independent of consequences, nonphysical harms (such as fair distribution of benefits), and the appropriate relationship between humans and the natural world (*17*). Molecular biologists have characterized the importance of the work by Gibson *et al*. in technological terms, whereas social scientists have portrayed it in more philosophical terms.

Although synthesis and assembly of an intact bacterial genome is a noteworthy achievement, it represents the net result of many incremental, technical advances over the past several decades and is primarily a matter of scale. Of perhaps greater technological significance is the manipulation and transplantation of an intact bacterial genome into a heterologous cell. However, the authors

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also demonstrate the ability of their synthetic construct to direct its own sustained replication, as well as the operation and replication of its new cellular "home." This achievement lends the work a different type of importance, with largely symbolic value in the near term, but more practical and possibly strategic importance in the long term.

In general, our current ability to predict and design novel organisms with virulence (or other relevant phenotypes) de novo (aside from simple toxin gene cassette insertions, and so on) is fairly primitive. This paper does not address or provide new solutions to this major challenge. Instead, it presents what is largely a resynthesis of a naturally occurring genome. Nevertheless, because this work clearly lies on a trajectory leading to more substantial risk in the future and because the subject is rife with potentially misleading terms and ethically charged concepts, communication of risks and benefits and careful education of the public are critical.

The work has drawn attention to synthetic biology and its implications at the highest levels of the U.S. government (*20*, *21*), even though there is little public awareness of the state of the science and technology, potential applications, and risks. This event provides a great opportunity for the scientific community to engage in public discourse, as well as to educate its own members about the importance of articulating the responsibilities of investigators, publishers, and industry (*19*).

Synthetic genomics and synthetic biology may necessitate a new model for addressing ethical and policy issues because of the complexity of the biological systems being mimicked and manipulated. The complex interactions of biological parts and their evolution will likely lead to unpredictable, emergent behavior in engineered organisms and ecosystems (*16*). Even addition of a single gene, e.g., encoding a well-characterized fungal toxin, to a heterologous fungal host species led to unexpected virulence and host range in infected plants (*22*). More complex combinations will be less predictable and may require different conceptual frameworks for oversight than "as safe as" regulatory standards (*16*), as well as creative thinking about engineered fail-safe designs and more comprehensive bioassays.

Much of the concern about synthetic biology has been focused on illegitimate users of technology. However, the ease of access to research tools and concepts increases the likelihood of unintentional effects by well-meaning institutionally based scientists or amateur biologists. Because these fields are fast-moving, complex, and accessible, ethical and policy considerations must be integrated as far upstream as possible in and before the design phases of research to be effective. One question that will need to be addressed is, "To what degree and in what ways should a genome differ from previously known genomes before perceptions of security and ethical risks deserve special notice?"

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Risks and benefits need to be evaluated broadly (i.e., not only in terms of safety and security but in terms of environmental, social, and economic risks and benefits) and as part of the planning of research questions and designs. Identifying and addressing an expanded notion of risk and benefit might require expertise beyond genomics, for example, in environmental or social sciences. A realistic assessment of likely benefits is important because it highlights potential issues of distributive justice and fairness, especially with growing skepticism about the practical application of genomics to date, and the tendency toward hype (*23*, *24*). It is perhaps even more important, however, to communicate the intentions of the scientist and to minimize potential financial and other conflicts of interest. In the absence of clear communication about the rationale for synthetic genomics and synthetic biology research, the scientific community leaves itself vulnerable to growing mistrust by the lay public. Use of reductionist terms such as "programming life" or "artificial life" are questionable scientifically and ethically because they vastly overstate our current ability to control biological processes at the organismal level.

By taking the lead in public discourse, scientists can maintain public legitimacy (*15*). During this period of scarce public resources and other competing needs, and as the motives of scientists are increasingly questioned, it behooves us to take action.

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