"'Editing': A Productive Metaphor for Regulating CRISPR"

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Summary. The metaphor of "gene editing" has been employed widely in popular discussions of CRISPR technology. The editing metaphor obscures the physical mechanism of action in CRISPR techniques, and understates the present frequency of off-target effects. However, the editing metaphor may be a useful means to think about approaches to regulating the future use of CRISPR. Conceiving of CRISPR as an information technology recalls the highly computational, information-oriented context of genomic research in which CRISPR has emerged. More importantly, the editing metaphor, while currently inaccurate, anticipates a future moment when CRISPR technology will be ubiquitous and extremely reliable. Contemporary deliberations about the regulation of CRISPR should keep in mind that the technology may become more powerful—and more susceptible to misuse—as the overall state of genomic science advances and applications of CRISPR become less expensive and more refined.

O'Keefe et al.'s (2015) study of popular media identifies two predominant metaphors in descriptions of CRISPR-based genetic technologies: editing and targeting.[2] The authors view the editing metaphor as troublesome—it does not accurately reflect the physical mechanism underlying CRISPR techniques, and substantially understates the risk of error and consequent possibility of harm. This is certainly true: the ease implied in the editing metaphor anticipates extensive future refinement of CRISPR technologies, and naïve use of the metaphor may tend to frustrate rather than promote public understanding. However, I argue that the editing metaphor, though reductive, can be a useful means for ethicists to think about the regulatory challenges posed by CRISPR, especially its possible applications to humans.

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[2] In the interest of brevity, I will use the term "CRISPR" to refer to CRISPR/Cas9 and related techniques.

Regulation is a metaphorical practice. It is relatively rare for a regulatory framework to be created *de novo*. In most cases, regulation involves drawing an analogy between something new in science and something that is already regulated, thereby extending an existing framework. Effective regulation of science must also be imaginative: the framework must prospectively address future applications and governance issues as well as present uses. The editing metaphor used in popular media implicitly treats CRISPR like an information technology. In two respects, accepting this imaginative leap is useful for regulation. First, the technology has developed during a period when genetic research has turned toward informational and computational research approaches. Second, CRISPR technology is very flexible, and could become reliable, inexpensive, and widely diffused.

The range of possible uses and users greatly heightens the possibility of accidental or malign misapplication, which is a strong reason to consider restrictions on the diffusion of CRISPR as well as regulation of specific uses. Though the technology physically modifies cells rather than manipulating symbolic representations, it is productive to think about CRISPR by analogy to dual use computing technologies; these technologies possess similar forms of flexibility, and are regulated in a manner fundamentally distinct from biological dual use research of concern. (Though the targeting metaphor evokes potential misuse more vividly, it is also potentially distorting: launching a missile is an inherently destructive act, while substituting a gene sequence is not.) I am not definitely proposing the classification of CRISPR as a dual use technology, but suggest that the analogy may foster broader thought about possible regulatory approaches.

Although CRISPR is employed in the modification of gene sequences in living cells, it arises in a research context that is increasingly oriented toward genes as information; this

development includes approaches such as genome-wide association studies, as well as entire fields such as bioinformatics. The practical scope of application for CRISPR techniques is proportional to scientific knowledge about the function and sequence of specific genes, and the acquisition of such knowledge will generally involve research on digitized sequences. I have argued elsewhere that the traditional biomedical model of regulation is poorly adapted to this context (Merriman and Molina 2015), and a licensing model drawn from intellectual property would be a valuable complement to existing approaches to human subjects protection (Merriman 2014). This informational orientation to human genetics research may be gaining in currency: recently proposed changes to the Common Rule would substantially tighten the regulation of biospecimens, including digitized gene sequences, and there is even the possibility that these will come to be regulated as personally identifiable information (PII) (Department of Homeland Security et al. 2015). To the extent that the editing metaphor can remind ethicists of this informational backdrop, and CRISPR's indirect reliance upon computationally-informed efforts to identify specific genes, its application is not wholly misguided.

More significantly, the editing metaphor calls attention to important possibilities for CRISPR technology itself: with continued refinement, it may become a cheap, widespread, and very reliable means of performing an extremely broad set of genetic modifications. This is a matter of concern, first, because not all possible applications are beneficent (Charo and Greeley 2015). This concern is heightened because the technique is flexible, and in addition to probable improvements and cost reductions in the technology over time, its applicability will grow with the general state of scientific knowledge about gene functions. It is therefore worthwhile to consider to think about CRISPR-based genetic modification techniques within the framework of dual use technology. Reflecting on the regulation of dual use computing technologies, which are

similarly flexible in their application, may provide a useful complement to ongoing bioethical discussions about dual use research of concern, particularly because CRISPR may soon be cheap enough to be employed in biohacking as well as well-regulated laboratory settings.

Sankar and Cho (2015) present a refreshing exploration of social responsibility in genetic engineering. They consider CRISPR-based gene drives as well as the controversy over gain-of-function studies of H5N1 influenza. Their core point is well-taken: genetics researchers are obliged to think about possible misapplications and unintended consequences of their work in a way that goes beyond mere adherence to guidelines. However, it is worth reflecting on key differences between the two cases examined. The influenza controversy arose from concerns that gain-of-function research could lead to weaponization of the influenza virus, and contributed to an NIH funding pause on gain-of-function research in 2014. However, the techniques employed in this research were already part of the store of tacit knowledge of genetics researchers; indeed, the researchers induced the initial virus mutations using a commercially available kit (Herfst et al. 2012: 1538). At issue was the possible hazard of the specific application, not the general acceptability of using mutagenesis in research.

This is rather different from a broadly applicable technology such as CRISPR-based genetic modification, or even a broad class of applications of that tool such as gene drives or human germline modification. A framework for thinking about ethical scientific practice on a case-by-case basis is certainly useful. Yet this approach also has notable limitations. The influenza controversy exposed the relative underdevelopment of the scientific and legal framework for regulating dual use research of concern, as well as the shortcomings of defining a general ethical approach on a case-by-case.

By contrast, there are well-established though imperfect bodies that regulate the export and circulation of dual use technologies, most notably the 41-state Wassenaar Arrangement. Among other things, this body regulates computing technologies such as cryptographic and network penetration software. These can be readily put to a very wide range of uses, some of them bad, and a very large number of individuals and groups possess the technical proficiency to use them. This approach has an obvious virtue: it can definitely limit the acquisition as well as specific application of potentially dangerous technologies, and firmly defines certain applications as illegitimate. It also has obvious problems: export restrictions deter appropriate uses of technology, scientists have a limited role in restriction decisions, and Wassenaar member states are not always trustworthy stewards of dual use technologies. However, these are arguments in favor of greater scientific participation in decisions about restricting access to technologies, not an argument against restriction as such (Dubov 2014).

CRISPR technology may dramatically expand the practical power of genetic science. This has the potential to include irresponsible or malign uses, as well as benevolent ones. The technology itself cannot be designed to tell the difference: in principle, it can be used to substitute any gene sequence, hence the salience of the neutral metaphor of "editing." Careful thought about how to make responsible use of the technology is certainly required. However, it may also be the case that responsibility demands strong limitations on access to the technology, particularly in these relatively early stages of its development (see Schweber 2000). Enforceable restrictions on the number of users, as exist for many computing technologies, may simplify the ethical task of defining responsible and beneficent uses.

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