CHAPTER 24

Bioethics in Biotechnology

SUMMARY

With the advances in molecular biology and biotechnology, the ethics and morality of the research are under fire. Culture, religion, and ignorance are major players in the debates of modern genetic technology. Many questions arise when discussing bioethics, and as the field of biotechnology continues, the line between ethical and unethical behaviors will be more blurred. The focus in this chapter is on issues arising from scientific background discussed in earlier chapters. Many questions can be raised, such as who controls biotechnology, who has access to the information, who decides, and who pays the expense?

Ethics is defined as the moral value of human conduct or the knowledge that deals with moral principles, specifically referring to the principles that govern behavior. However, the term *ethics* has been used more so to define behavior as opposed to principles that govern the behavior. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research issued a report (Belmont Report) that was mostly concerned with research on human subjects. Nonetheless, the basic principles of the Belmont Report were autonomy, beneficence, and justice. In 2005, the United Nations issued a Universal Declaration on Bioethics and Human Rights that expanded on autonomy, beneficence, and justice. These principles expand autonomy to include consent, privacy, and confidentiality. They also include nondiscrimination; social responsibility; and protection of future generations, the environment, the biosphere, and biodiversity.

The precautionary principle places the burden of proof onto those individuals proposing a change when it is possible that change can cause harm to people or the environment. This principle is applied to biology in the fallowing ways: disease spreading by accident, the introduction of new pharmaceuticals, genetically modified organisms and the environment, and the creation of artificial life. GMO crops are not grown in most European countries because the precautionary principle has been applied despite the fact that these crops are disease and pest resistant, which lowers cost for farmers. Testing for safety of biotechnology products is also a concern.

Ownership of genetic information is also up for debate. Generally, in many nations, invention means ownership. In the United States, human gene sequences could be patented, although this has recently changed. "Natural" DNA sequences are protected by court rulings, but any DNA sequence that is manipulated can be patented. How much manipulation constitutes a patent is fuel for bioethics discussions.

Any new advance in technology, including the genetic revolution, usually creates large amounts of debate. The majority of the general public is uneducated on the subjects of cloning, gene therapy, and transgenic animals and plants. Fueled by fear and misinformation (accidental or deliberate) and unintended consequences, the debates often become heated. However, most novel technologies eventually become widely accepted and mainstream.

Many potential dangers are associated with recombinant DNA technology. However, any new technology can be abused just as easily as it can be used to help the population. For example, many questions are raised concerning health care. Technology has increased the life expectancy of the planet's population and decreased infant mortality. This, in turn, swamps health care, welfare, and pension systems. Not only are social systems overwhelmed, but also overpopulation increases the spread of novel infectious diseases. Due to societal concerns by scientists researching recombinant DNA technology, many programs were on hold until the National Institutes of Health (NIH) developed guidelines to govern that type of research. Realistic threats from biotechnology include germ and chemical warfare and also antibiotic and antiviral drug use and resistance. Other areas of concern include gene therapy, genetically modified plants and animals, human cloning and engineering, and organ replacement. The authors raise many questions on each point. For example, why is germ or chemical warfare more gruesome than traditional bombs, bullets, or even nuclear warheads? Should research in general be limited because of its potential misuse? Or, who should pay for expensive

treatments such as gene therapy? Is human cloning moral? And if so, should we clone humans to have spare parts that are specific to individuals?

Humans have selectively bred animals and crop plants for desirable characteristics for thousands of years. However, now it is possible to improve individual genes and also move blocks of genes from one organism to another. Many people wonder about the interference with nature regarding this technology. Scientists simply view these technologies as faster methods than traditional selective breeding with the same general outcome. There is no evidence that GMOs cause hazards to human health.

Genetically modified crops in the United States include soybeans, cotton, and corn. These crops have improved yields because they are resistant to drought, disease, and insect pests. "Terminator" technology was developed because the movement of transgenes from crops to weeds or other crops is possible. This is certainly an environmental issue, although the technology was produced for financial reasons, as the seeds of engineered crops are sterile and farmers are forced to buy new seeds each season. Sequestration of transgenic plants in the environment is difficult. Adhering to planting distances can minimize cross-fertilization between transgenic plants and non-GMO crops. However, some mixing has already occurred.

Animal testing is also up for debate, with approximately half of Americans not supporting it. Any new product for consumers is often tested on animals, although the need is waning. The NIH has retired most of their research chimpanzees. With advances in molecular biology, this means more testing on cell culture lines instead of whole animals. The production of transgenic animals also leads to many questions, ranging from the acceptance of prescientific breeding experiments to the use of transgenes to give animals novel properties. However, animals could be engineered for entertainment purposes as well, such as for "transgenic art" or for pets.

Theoretically, scientists could take DNA from an extinct species and perform nuclear transplantation to produce an embryo that could then be inserted into a surrogate female animal. In theory, this process may sound like something from the movies, but the reality is that DNA has a short half-life at 520 years and most sample DNA from extinct animals is much older than that. However, it might be possible to sequence the extinct animal's genome and rebuild it from scratch.

The potential also exists for altering the human germline. Prenatal genetic screening of the parents could be performed prior to conception, at which point the parents could make choices to have a child based on their propensity for certain genetic disorders. Postconception screening could detect genetic abnormalities in the fetus, at which point the parents would have to make a decision to abort or continue the pregnancy. Genetic screening is routinely used on newborns as well, primarily to detect genetic issues, such as phenylketonuria, which is treatable if discovered early. In addition to knowledge regarding any genetic disorders, in the future, parents may be able to select, or at least identify in a fetus, probable height, eye color, IQ, and beauty. The ethical questions raised in these situations center around abortion and the definitions of life and personhood.

Stem cell research also has been a hot topic in recent years. Stem cells are undifferentiated cells that have the ability to mature into any cell type. There are several types of stem cells. Embryonic stem cells are the most controversial because to acquire them, an embryo has to be destroyed. Federal grant money is available to researchers who obtain embryonic stem cells only from excess embryos created during *in vitro* fertilization—of course, with the permission of the parents. Induced pluripotent stem cells are somatic cells that have been chemically reverted into embryonic-like stem cells. Stem cells have great potential in regenerative medicine.

Gene enhancement could one day lead to gene doping or the creation of human cyborgs. Gene doping could provide a few extra copies of genes that would give athletes a competitive edge. Human cyborgs could provide limbs for amputees that are enhanced using current technology. A cyborg cockroach has already been developed.

Human cloning is also controversial. Aside from the technical issues surrounding human cloning, what if we could clone humans to harvest organs? The organs would be specific to an individual, which means he or she would be less likely to reject the organ. Or perhaps the manipulation is to produce humans that are transgenic through human genetic engineering. Some of the transgenes could confer resistance to certain diseases, more intelligence, or desired physical features such as blue eyes. In the future, it might be possible to insert foreign DNA, such as genes in a metabolic pathway for the biosynthesis of vitamin C or an essential amino acid.

As technology advances, more and more issues surface. To the general public, who are mostly ignorant of the science behind the technology, biotechnology results in unrest and fear. Over time, the fear dissipates and the technology becomes more widely accepted.

Case Study Caution Required for Handling Genome Editing Technology

Motoko Araki, Kumie Nojima, Tetsuya Ishii (2014). *Trends in Biotechnology* 32(5), 234–237.

With the advancing field of genetic engineering, the lines between natural and modified organisms are blurred. Regulation of genetic engineering in higher organisms should be discussed and established. In higher organisms, zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and the clustered regularly interspaced short palindromic repeat (CRISPR)/Cas system are used to edit genomes. Some countries have tried to regulate the use of ZFNs and TALENs. The fear is that genome editing may cause negative relationships with society as a whole, which could lead to the decline in agriculture and environmental applications.

The authors discuss the implications of genome editing on society, review the current state of genome editing regulation, and propose future directives for the biotechnology field.

How does gene editing differ from traditional methods of genetic engineering?

Traditional genetic engineering techniques require the use of lengthy protocols to introduce random mutations such as through exposure to chemicals. Newer methods allow mutations to be directed instead of random. Genetically modified organisms are traditionally produced through labor-intensive processes involving genomic DNA extraction, vector construction, and then transfer to an appropriate cell culture line. This process is followed up with significant screening techniques to ensure the desired DNA sequence was obtained. Gene editing allows a gene within a genome to be directly edited through the action of enzymes that create double-stranded breaks in target regions and induce repair.

What are the advantages and disadvantages of using gene editing in higher organisms?

The advantage of using gene editing over traditional methods is that small genetic changes can be made in the organism without leaving behind genetic artifacts, such as antibiotic resistance genes. The disadvantages of gene editing include the screening process, off-target mutagenesis, monoallelic changes in diploid organisms leaving heterozygous cells, and mosaicism.

What types of regulations are employed on genetically modified organisms?

The regulations governing genetically modified organisms are one of two varieties: product-based and process-based regulation. Product-based regulation aims to regulate the final outcome of the process. Health and environmental risks are assessed prior to the release of the genetically modified product. Process-based regulation assesses the health and environmental risks associated with the procedures involved in the production of genetically modified organisms.

Describe the positions and response from various countries on the regulation of ZFNs in the genetic engineering process.

The authors detailed the regulation of ZFNs in the process of genetic engineering. Overwhelmingly, most countries do not regulate the use of ZFNs, and furthermore, some declare that organisms produced using ZFNs are not genetically modified. For example, Australia and New Zealand concluded that while plants produced using ZFN-3 technology are genetically modified, ZFN-1 and ZFN-2 are also used in traditional mutagenic techniques and should not be regulated. New Zealand further concluded in 2013 that plants modified with ZFN-1 are not GMOs. The USA determined that plants developed with ZFN-3 without exogenous DNA are not regulated. The EU and Argentina agree that ZFN-3 modifications should be regulated, but there is some leniency in Argentina to ZFN-1 and ZFN-2.

The regulation of genetically modified plants seems to predominantly center around ZFN-3. ZFN-1 and ZFN-2 can also be used to produce genetic modifications. What are some reasons for the exclusion of ZFN-1 or ZFN-2 from a regulatory scope?

The exclusion of ZFN-1 or ZFN-2 from regulation has more to do with the type of regulation adopted by the agency. For example, ZFN-1 is regulated partially within the scope of process-based technology. Depending on which regulation scheme the country uses, ZFN-1 may not be regulated by that country's agency. ZFN-2 regulation again depends on the country and the classification of the short repair template.

What implications for society need to be considered when producing genetically modified organisms and regulation schemes?

The authors caution against advancing genome editing technology without care or regulation, citing societal issues and repercussions in agriculture and environment. Genetically engineered organisms are more difficult to characterize than nonmodified, natural organisms. These organisms may need more careful assessment before being released into the environment. In terms of agriculture, these organisms should be assessed for any toxicity or allergens in the product and labeled accordingly. The environmental effects may lead to a gain of function and a threat to the local ecosystems if released without extensive assessment.

One of the major concerns that authors have regarding this technology is the introduction of undetected off-target sites. How do they propose dealing with this possibility?

The authors encourage proceeding with caution and establishing assessment methods to evaluate the genomes of modified organisms. They propose using whole genome sequencing to ensure that no unintended off-target mutations were introduced while gene editing. Additionally, they encourage the development of new, faster sequencing techniques to aid in the identification of potential off-target mutations.

Regulation schemes need to advance in pace with the advances in genetic engineering and genome editing. These are powerful tools, and researchers must use caution and discretion when using them and also with regards to the final product. Ideally, these regulations should come from international efforts and constructive dialogue to ensure responsible use of these technologies with regards to health and the environment.

Trends in Biotechnology May 2014, Vol. 32, No. 5

Caution required for handling genome editing technology

Motoko Araki[1], Kumie Nojima[2], and Tetsuya Ishii[1]

[1] Office of Health and Safety, Hokkaido University, Sapporo 060-0808, Japan
[2] Molecular Imaging Center, National Institute of Radiological Sciences, Chiba 263-8555, Japan

Genome-editing technology, although a robust tool for genetic engineering, is creating indistinct regulatory boundaries between naturally occurring and modified organisms. However, researchers must act with caution in research and development to avoid misleading society. Furthermore, appropriate regulations should be proactively discussed and established for handling genome-editing technology.

Current conditions

Precise genetic engineering can be achieved in higher organisms through genome editing with nucleases such as zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and the clustered regularly interspaced short palindromic repeat (CRISPR)/Cas system [1]. Although genome editing has received significant attention owing to its potential applications in plant and/or animal breeding, it has also raised regulatory issues. The artificial nucleases may generate novel organisms that are extremely similar or identical to naturally occurring organisms. Currently, some countries have attempted to establish regulations for handling ZFNs and TALENs, but not yet the CRISPR/Cas system. By contrast, some researchers advocate that organisms modified using genome editing do not fall under the genetically modified organism (GMO) regulations. Yet caution is needed because inappropriate use of genome editing may cause societal problems and loss of opportunities for agricultural and environmental applications. Here we briefly review regulatory responses, scrutinize societal implications, and propose a future direction for the biotechnology of genome editing.

Technical aspects

The genetic material in an organism can be modified using various mutagenesis techniques. Older techniques, such as chemical mutagenesis, produce entirely random mutations, whereas newer techniques, such as those of genetic engineering, can produce site-specific mutations. A GMO is an organism modified using such genetic engineering techniques. The most common type of genetic engineering begins with extracellular DNA manipulation to construct a vector harboring a specific DNA sequence or gene that is intended for transfer. The vector is transduced into cells or directly into an organism using physical, chemical, or biological methods. The modified cells, such as protoplasts, callus cells, or embryonic stem cells, are used to generate a GMO that harbors the exogenous DNA sequence. When the sequence is derived from an unrelated organism, the process is referred to as transgenesis. When DNA sequences are transferred between closely related organisms, the process is called cisgenesis, particularly in the genetic engineering of plants. Both transgenesis and cisgenesis can be labor intensive and require time-consuming screens to identify GMOs, especially when dealing with higher organisms. Building on the concept of transgenesis and cisgenesis, genome editing is an advanced genetic engineering technology that can directly modify a gene within a genome. This modification is achieved by enzymes that cause double-stranded breaks (DSBs) in target sequences and induce DNA repair through non-homologous end-joining (NHEJ) or homology-directed repair (HDR) (Box 1). The repair systems can subsequently facilitate the efficient creation of the desired mutation even in the genomes of higher organisms. Genome editing causes genetic modifications in which one or a few bases are removed, an amino acid substitution of a protein occurs, or a mutation is completely repaired in the resultant organism genome without leaving marked genetic vestiges following the modifications.

Despite the advantages of genome editing, there are still some technical issues. Obtaining a GMO that has an intentional mutation from among arising variants, albeit less laborious than conventional transgenesis or cisgenesis, continues to require screening. The technology may also cause off-target mutagenesis after attaining the desired modification in a target sequence [1]. The nucleases may fail to induce a biallelic modification in diploid organisms, thereby resulting in an organism with a monoallelic modification [2]. Furthermore, the microinjection of the nuclease mRNAs into zygotes may induce not only germline modifications but also mosaic modifications in which wild-type cells, including germline cells, and genetically modified (GM) cells coexist in the resultant organisms [3]. Therefore, the research done using genome editing must be well controlled, and the resultant organisms require meticulous screening and characterization.

Responses by regulatory agencies

In the Cartagena Protocol on Biosafety, a 'living modified organism' (the technical legal term that is close to GMO) is stipulated as 'any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology' [4]. The use of nucleases such as ZFNs may be outside the scope of current GMO

Corresponding authors: Ishii, T. (tishii@general.hokudai.ac.jp, tetsuya.ishii0302@gmail.com).

0167-7799/$ – see front matter
 http://dx.doi.org/10.1016/j.tibtech.2014.03.005

Box 1. Genome editing technology and GMO regulations

DNA repair pathways used in genome editing [1]

- Non-homologous end-joining (NHEJ) is a DNA double-strand break (DSB) repair pathway that ligates or joins two broken ends together without a homologous template for repair, thus leading to the introduction of small insertions and deletions at the site of the DSB.
- Homology-directed repair (HDR) is a template-dependent pathway for DSB repair, using a homology-containing donor template along with a site-specific nuclease, enabling the insertion of single or multiple transgenes in addition to single-nucleotide substitutions.

Zinc finger nuclease (ZFN) technologies used in plant breeding techniques [11]

- ZFN-1: NHEJ is used to introduce site-specific random mutations (substitutions, deletions and insertions) involving one or a few base pairs.
- ZFN-2: HDR with a short repair template is used to generate site-specific desired mutations and the copying of the repair template.
- ZFN-3: HDR with a large stretch of DNA is used to cause site-specific transgenesis (targeted gene addition or replacement).

Legislation and guidelines relevant to the section 'Responses by regulatory agencies'

- Argentina: the National Biosafety Framework (Developed under the United Nations Environment Program – Global Environment Facility Biosafety Project).
- Australia: the Gene Technology Act 2000.
- EU: the Regulation (EC) 1829/2003 on Genetically Modified Food and Feed.
- New Zealand: the Hazardous Substances and New Organisms Act 1998.
- USA: 7 CFR Part 340 – Introduction of organisms and products altered or produced through genetic engineering which are plant pests or which there is reason to believe are plant pests.

regulations, including the Cartagena Protocol, because these regulations largely depend on the existence of an exogenous DNA sequence in the resultant organisms. At present, some countries have attempted to establish regulations for the agricultural use of three types of ZFN (Box 1) and TALEN. The major issue is whether plants modified using genome editing fall under existing GMO regulations. However, there are two types of GMO regulations: product-based and process-based approaches [5]. For instance, the USA has adopted product-based regulations under which health and environmental risks associated with a GMO are assessed according to the final product. By contrast, in the EU, GMOs are subject to process-based regulations involving a detailed procedure based on a scientific assessment of the risks to human health and the environment. The differences in these GMO regulatory approaches may be reflected in the regulations of genome editing technology.

Argentina

In 2011, a preliminary view of the regulatory criteria for new plant technologies, including genome editing, was expressed in a regulatory workshop [6]. Although plants developed using ZFN-3 would fall under their product and process-based regulations, ZFN-1 might not be regulated under the Argentinian regulatory framework (Box 1). Moreover, it was stated that ZFN-2 would be regulated on a case-by-case basis if its use entails the introduction of coding sequences.

Australia and New Zealand

In 2012, the Food Standards Australia New Zealand GMO workshop concluded that plants generated using ZFN-3 should be regulated as GMOs [7]. By contrast, they concluded that ZFN-1 and ZFN-2 should not be regulated owing to their similarity to traditional mutagenic techniques. Against this backdrop, the Australian Office of the Gene Technology Regulator stated in a 2011 review of the current act that the product-based regulatory oversight of new organisms generated using tools such as ZFNs requires improvement [8] (Box 1). In 2013, the New Zealand Environmental Protection Authority (EPA) committee declared that plants modified with ZFN-1 and TALENs are not GMOs under the act (Box 1), despite repeated statements from New Zealand EPA staff that the resultant organisms are GMOs [9]. The Sustainability Council, an independent council that undertakes research into genetic engineering issues, believes that the New Zealand EPA misinterpreted the act and is currently appealing the decision in the High Court [10].

EU

In 2010, the EU carried out a study of the new plant breeding techniques (NBTs), in which genetic and epigenetic changes in the plant genome as well as the possibility of detection of these changes were evaluated [11] (Box 1). In 2012, the European Food Safety Authority (EFSA) GMO panel issued a scientific report concluding that 'breeding' with ZFN-3 might minimize the hazards from food and feed products derived from plants with the induced disruption of a gene because ZFN-3 facilitates DNA insertion into a predefined region of the genome, unlike traditional transgenesis or cisgenesis [12]. Additionally, they stated that ZFN-3 may be assessed under the European Community regulations (Box 1). At present, the EFSA expresses no opinions regarding regulations on ZFN-1 and ZFN-2.

USA

In 2012, the US Department of Agriculture informed a private enterprise that a GM plant developed using ZFNs with no exogenous DNA insertion would fall outside the regulations [APHIS responded to an inquiry from Dow AgroSciences regarding the regulatory status of organisms modified using their zinc finger technology (EXZACT). March 8, 2012. http://www.aphis.usda.gov/biotechnology/downloads/reg_loi/APHIS_response_DOW_ZFN_IPK1_030812.pdf] (Box 1). This seems to indicate a possible exemption for ZFN-1 in the product-based regulations.

Blurring of regulatory boundaries

ZFN-1 and ZFN-2 seem to blur the current boundaries of product- and process-based regulations (Figure 1). However, on closer examination, the positions of ZFN-1 and ZFN-2 differ significantly in the product-based versus the process-based regulations. ZFN-1 is outside the scope of product-based regulations but partly within the scope of process-based regulations. This implies that the regulatory position of ZFN-1 depends on whether a country adopts product-based or process-based regulations. By contrast, ZFN-2 has both regulated and unregulated positions, although the existence or use of a short repair template varies its classification by different countries (Figure 1).

Although the regulatory response to genome editing is complicated, the current regulatory landscape suggests

some directions. By definition, the use of ZFN-3 is regarded as a conventional transgenesis and/or cisgenesis. In the product-based regulations, an efficient assessment method should be required to verify that a product generated using ZFN-1 is outside the regulatory scope. Further scientific and regulatory efforts are needed to minimize the frequency of case-by-case responses to ZFN-1 use under process-based regulations and ZFN-2 under both types of regulation.

In both regulatory systems, it is more important to confirm the actual mutations caused by genome editing and whether the mutations cause a functional change that can affect human health or the environment. To explain it differently, the emergence of genome editing technology may provide an important opportunity to form a new global consensus for future regulations in the field of genetic engineering.

Societal implications

Although the current regulations are out of step with progress in the field, the efficiency and effectiveness of genome editing in higher organisms does not authorize researchers to advance the application of this technology without caution. The careless use of genome editing would raise social issues and/or repercussions in agricultural and environmental applications. In conventional genetic engineering, the detection of exogenous DNA facilitates the characterization of the resultant organisms. Conversely, some organisms modified with genome editing seem to be almost identical to naturally occurring organisms, implying difficulty in genetically characterizing these organisms. However, such organisms require scientific scrutiny prior to being released into the market and/or into the environment.

Agricultural use

If genome editing results in unforeseen immunogenicity or toxicity in agricultural products, the consequences of widespread consumption of such products will be problematic. Although persuasive evidence of the safety of GM crops is available [13], careful food-risk assessments would also be required for the agricultural use of genome-editing technologies. At a minimum, the sudden discovery of an unintentional mutation in agricultural products would jeopardize the reliability of food labeling in various markets.

Environmental use

Some genetic mutations may cause a loss of function in modified organisms, probably resulting in their extinction in the environment even if they are released. However, other mutations might lead to a gain of function [14]. If organisms modified with genome editing in which a gain of function unintentionally arises are released without rigorous risk assessments, they may rapidly affect the local ecosystem by seriously threatening native species. Even if they do not pose a serious threat to native species, the released organisms may negatively affect the environment owing to crossbreeding. Notably, a plant with a new trait that occurred in the wild owing to the crossbreeding of wild-type canola with herbicide-resistant GM canola was recently discovered in the USA [15].

In order to achieve a better relationship between biotechnology and society, researchers must act with caution and establish a scientifically valid assessment method for evaluating organisms that have been modified with genome editing. In particular, with regard to off-target effects, whole-genome sequencing is available to ensure that no off-target mutations develop after genome editing. If the sequencing is time-consuming, researchers must develop a novel, efficient method based on genetic or epigenetic vestiges that are associated with genome-editing technology. For instance, in a recent report on a primate that was modified via CRISPR/Cas-mediated gene targeting, the potential off-target sites were defined and comprehensively investigated in the primate genome [16]. Such an approach

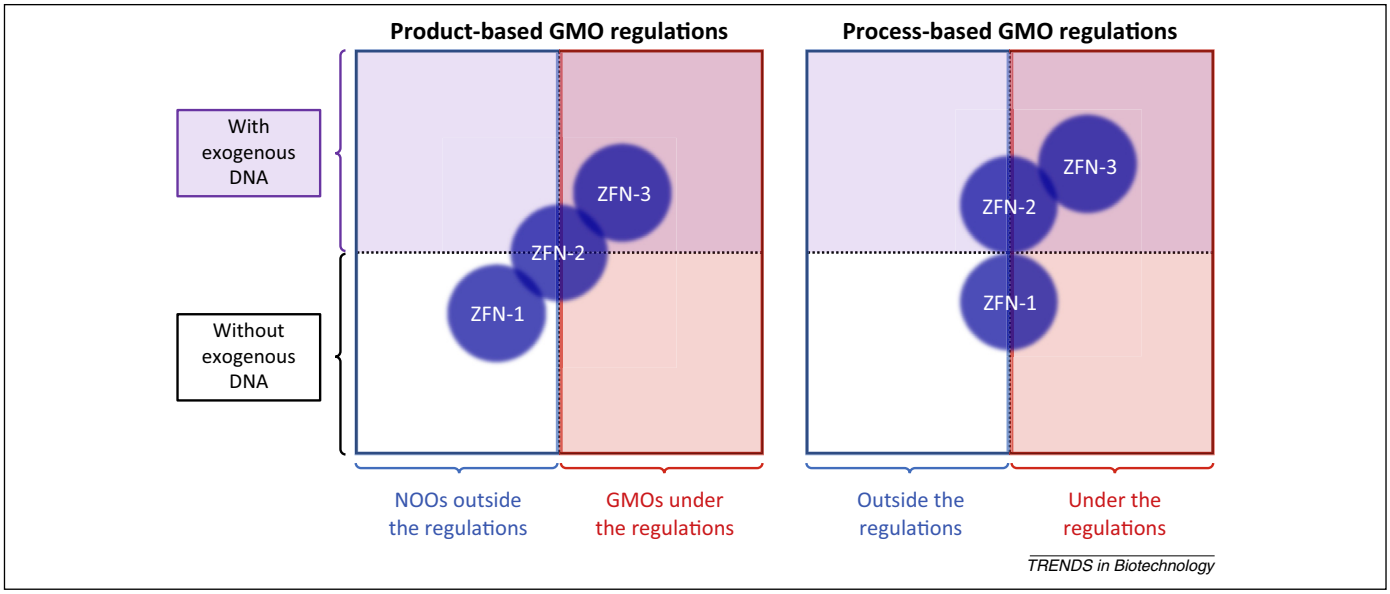

Figure 1. The presumed treatment of organisms modified with genome editing technology under genetically modified organism (GMO) regulations. The positions of zinc finger nuclease-1 (ZFN-1; site-specific random mutations involving one or a few base pairs without exogenous DNA), ZFN-2 (mutations and gene repair with short exogenous DNA), and ZFN-3 (transgenesis with long exogeneous DNA) (Box 1) are mapped in the product-based or the process-based regulations for GMOs or naturally occurring organisms (NOOs). In this analysis, the form of genome editing enzymes is presumed to be protein or RNA, not DNA.

can be effective if a scientific and regulatory consensus is reached.

Concluding remarks

Although genome editing demonstrates efficient and effective genetic engineering, this new biotechnology is creating indistinct boundaries in the existing GMO regulations. Under the present conditions, researchers should act with more caution in research and development using genome-editing technology compared to traditional genetic engineering technology in the interest of scientific accountability. Most importantly, international harmony is required on this issue, as we experienced a constructive discussion at the Asilomar Conference in 1975 in which researchers, layers, and physicians successfully drew up voluntary guidelines [17,18]. In order to harness the potential of genome editing for future science and broad applications, researchers, private enterprises, and regulators should proactively discuss and establish appropriate regulations based on a scientific assessment.

Acknowledgments

This article does not necessarily reflect the views of our organizations. The authors take full responsibility for their opinions.

References

1 Gaj, T. *et al.* (2013) ZFN, TALEN, and CRISPR/Cas-based methods for genome engineering. *Trends Biotechnol.* 31, 397–405
2 Yang, H. *et al.* (2013) One-step generation of mice carrying reporter and conditional alleles by CRISPR/Cas-mediated genome engineering. *Cell* 154, 1370–1379
3 Ma, S. *et al.* (2012) Highly efficient and specific genome editing in silkworm using custom TALENs. *PLoS ONE* 7, e45035
4 The Convention on Biological Diversity. *Text of the Cartagena Protocol on Biosafety*, United Nations Environment Programme (http://bch.cbd.int/protocol/text/)
5 Davison, J. (2010) GM plants: science, politics and EC regulations. *Plant Sci.* 178, 94–98
6 Burachik, M. (2011) Regulatory Framework for biotechnology-derived crops with specific focus on new plant breeding techniques in Argentina. In *Comparative Regulatory Approaches for New Plant Breeding Techniques, European Commission workshop, 12–13 September 2011 Seville, Spain*. (http://ipts.jrc.ec.europa.eu/presentations/documents/05Argentina.pdf)
7 Food Standards Australia New Zealand (2013) *New Plant Bleeding Techniques*, Food Standards Australia New Zealand (http://www.foodstandards.gov.au/publications/Pages/New-plant-breeding-techniques-workshop-report.aspx)
8 The Australian Office of the Gene Technology Regulator (2011) *2011 Review of the Gene Technology Act 2000*, Australian Department of Health (http://www.health.gov.au/internet/main/publishing.nsf/Content/1314E9D6ECC17EBDCA257BF0001C6BF6/)
9 The McGuinness Institute (2013) *An Overview of Genetic Modification in New Zealand 1973–2013: The First Forty Years*, Auckland Council (http://www.aucklandcouncil.govt.nz/EN/planspoliciesprojects/plansstrategies/unitaryplan/Documents/Section32report/Appendices/Appendix%203.49.16.pdf)
10 The Sustainability Council of New Zealand (2013) *The GM Foods Designed To Escape Regulation*, The Sustainability Council of New Zealand (http://www.sustainabilitynz.org/new-gm-foods-designed-to-escape-regulation/)
11 Lusser, M. *et al.* (2011) *New Plant Breeding Techniques: State-Of-The-Art and Prospects for Commercial Development*, Institute for Prospective Technical Studies (http://ipts.jrc.ec.europa.eu/publications/pub.cfm?id=4100)
12 EFSA Panel on Genetically Modified Organisms (2012) Scientific opinion addressing the safety assessment of plants developed using zinc finger nuclease 3 and other site-directed nucleases with similar function. *EFSA J.* 10, 2943
13 EFSA GMO Panel Working Group on Animal Feeding Trials (2008) Safety and nutritional assessment of GM plants and derived food and feed: the role of animal feeding trials. *Food Chem. Toxicol.* 46, S2–S70
14 Prasad, K.V. *et al.* (2012) A gain-of-function polymorphism controlling complex traits and fitness in nature. *Science* 337, 1081–1084
15 Gilbert, N. (2010) GM crop escapes into the American wild. *Nature* http://dx.doi.org/10.1038/news.2010.393 2010
16 Niu, Y. *et al.* (2014) Generation of gene-modified cynomolgus monkey via Cas9/RNA-mediated gene targeting in one-cell embryos. *Cell* 156, 836–843
17 Gottweis, H. (2005) Regulating genomics in the 21st century: from logos to pathos? *Trends Biotechnol.* 23, 118–121
18 Sharp, R.R. *et al.* (2004) Shaping science policy in the age of genomics. *Nat. Rev. Genet.* 5, 311–316