The Interim Plus + + + + + +

Curriculum Learning Resource

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The potential benefits of modern biotechnology like CRISPR are enormous. But at the same time, many people in the field of research find it dark and foreboding because of dangerous ramifications that might flow from the misapplication of this novel technology. The topic merits close study because of its revolutionary impact on bioengineering techniques, thereby also unleashing a torrent of serious ethical considerations that must accompany the implementation of the technology.

This edition of The Interim Plus offers questions to guide reading and to stimulate thinking about the promise and the grave threat of CRISPR. In a future edition we shall delve into the implications of CRISPR in the field of human and animal genome editing and the ethical questions raised in those research fields.



Jennifer Doudna (left) and Emmanuelle Charpentier (right), Nobel Prize winners for CRISP (*Image courtesy euronews nobel-prize-in-chemistry-awarded-to-two-women-for-discovering-tool-for-rewriting-code-of-l.htm*)

Part A

What is CRISPR?

Here is an introductory article to the field of CRISPR technology. An explanation is provided and the table is set for some of the more controversial aspects of the technology. To obtain the full references for all the articles cited you are kindly urged to follow the link to the original article. The removal of the references has been done for the sake of making this learning resource manageable in reading time.

No time to waste—the ethical challenges created by CRISPR

CRISPR/Cas, being an efficient, simple, and cheap technology to edit the genome of any organism, raises many ethical and regulatory issues beyond the use to manipulate human germ line cells

Arthur L Caplan, Brendan Parent, Michael Shen, Carolyn Plunkett <u>Author Information</u> EMBO Rep (2015)16:1421-1426 <u>https://doi.org/10.15252/embr.201541337</u> <u>https://www.embopress.org/doi/full/10.15252/embr.201541337</u>

The term "CRISPR" has gained a lot of attention recently as a result of a debate among scientists about the possibility of genetically modifying the human germ line and the ethical implications of doing so. However, CRISPR is not just a method to edit the genomes of embryonic cells, as the public discussion might have implied; **it is a powerful, efficient, and reliable tool for editing genes in any organism**, and it has garnered significant attention and use among biologists for a variety of purposes. Thus, in addition to the discussion about human germ line editing, CRISPR raises or revives many other ethical issues, not all of which concern only humans, but also other species and the environment.

CRISPRs are short DNA sequences with unique spacer sequences that, along with CRISPR-associated (Cas) proteins, constitute an adaptive immune system in many bacteria and archaea against invading bacteriophages <u>1</u>. By using short RNA molecules as a template, **Cas makes highly sequence-specific cuts in DNA molecules that can be exploited to insert genes or to precisely modify the nucleotide sequence at the cut site.** CRISPRs were first identified in the 1980s, but it is only during the past few years that scientists realized their potential to edit the genomes of any organism, from microorganisms to plants to human cells and, most controversially, human embryos. The CRISPR/Cas system is not a breakthrough technology in the sense that it enables genome editing; biologists have been using transcription activator-like effector nucleases (TALENs) and zinc finger nucleases (ZFNs) to edit genomes for some time. However, those technologies are expensive, technically challenging, and time-consuming, as they require protein engineering to target specific DNA sequences. **CRISPR/Cas, in contrast, recognizes its target sequence via guide RNA molecules that can be cheaply and easily synthesized**. A standard molecular biology laboratory can now edit genes or whole genomes of many organisms, as CRISPR/Cas does not require sophisticated knowledge or expensive equipment.

This **has rekindled the ethical debate about modifying the human germ line**. Notwithstanding the talk about "designer babies," **CRISPR/Cas offers new possibilities to render humans immune to a range of diseases, or to repair fatal gene defects in a human embryo**. Prominent researchers have therefore called for a voluntary moratorium on germ line genome modification in humans until scientists and ethicists have jointly analyzed the implications of doing so. <u>2</u> The debate boils down to two sides in a "go/no-go" standoff. One group insists that research on human germ line editing should advance in order to reap the scientific and clinical benefits, while the other camp argues that editing the human germ line is too unsafe, or crosses an inviolable ethical line. <u>3</u>

However, rather than the use or not of CRISPR to edit human germ cells and embryos, there are more immediate ethical concerns that need to be addressed. CRISPR is already being used to modify insects, animals, plants, and microorganisms and to produce human therapeutics <u>4</u>. Since such work has been going on for years—or even decades—the CRISPR technology may not appear to create new ethical problems in these contexts. However, there is a danger that CRISPR's affordability and efficiency could run roughshod over long-standing and valid concerns about the generation and release of genetically modified organisms (GMOs). The recent characterization of a new type 2 CRISPR system from *Francisella novicida* demonstrates that the toolbox of genome editing technologies is ever-expanding <u>5</u>. Consequently, **there is an urgent need for effective, global regulations that govern the testing and environmental release of GMOs.**

Current **national and international regulations** provide inadequate guidance and oversight for these applications. As such, **they do not foster public trust in the safety of CRISPR-edited organisms or the regulatory agencies charged with monitoring them.** The concern is that public misunderstanding and mistrust of GMOs will hinder scientific progress and valid uses of CRISPR. Thinking through—and getting right—the regulations and research ethics for these applications of CRISPR might also help to create an ethical framework for human germ line editing.



In the USA, the regulation of genetically modified animals and insects is done by a number of regulatory agencies that comprise the Coordinated Framework for the Regulation of Biotechnology, which was created in 1986 to facilitate inter-agency regulation of biotechnology. Its scope and regulatory approach has not been revisited since 1992 <u>6</u>, but individual agencies within the Coordinated Framework—the Food and Drug Administration (FDA), the US Department of Agriculture (USDA), and the Environmental Protection Agency (EPA) have issued their own guidelines on particular applications......

The EU has a more centralized regulatory scheme in which the European Food Safety Agency (EFSA) conducts risk assessments, while final approval of a genetically modified animal or plant falls to the

Orange? Kiwi? Image courtesy (<u>https://discoveryeye.org/gmo-and-nutritional-content-of-food/</u>)

European Commission (EC). Analogous to the USA, human therapeutic applications are regulated and approved by the European Medicines Agency (EMA). Other countries with intense biomedical research programs likewise have their own regulatory and oversight schemes. Internationally, there is no unified guidance for the modification of non-human organisms other than the Biological and Chemical Weapons Convention, which seeks to prevent research into and development of biological weapons......

Other applications in animals, however, pose novel ethical concerns. In particular, CRISPR could be used to replace expensive TALENs, ZFNs, and other methods of genetic modification to improve food for human consumption. For example, **CRISPR could be used to increase the muscle mass of animals, render farmed animals less susceptible to disease, enhance nutritional content, or create hornless cattle that are easier to handle 4**. Research groups and private biotech companies are currently assessing whether such genome edits are feasible and safe. So far, no genetically modified animal has ever been approved for human consumption; the approval of genetically modified salmon for human consumption has been pending at the FDA for years. But it is

not clear what criteria the FDA—or any other agency involved—uses for assessing the safety of genetically edited animals for human consumption. These regulatory processes must be more transparent and accountable.

There is another, potentially much more **dangerous and controversial, application of CRISPR, namely to potentially eradicate disease by eradicating disease vectors and invasive species** <u>8</u>. This involves research with the *Aedes aegypti* mosquito, which transmits dengue fever, and certain subspecies of the *Anopheles* mosquito that carry the *Plasmodium* parasite. Researchers at academic centers and private biotech firms are exploring socalled gene drives to block disease transmission by editing the female mosquito so as to render it incapable of carrying the disease. Others aim to induce sterility in male mosquitos to prevent reproduction, or limit the lifespan of their offspring. Such **methods could effectively destroy an entire species and could have significant environmental consequences**.

Gene drive is a powerful tool that makes it more likely that the edited trait will be passed on to offspring through sexual reproduction. When genetically modified organisms are introduced into the environment and mate with wild-type organisms, their offspring generally have a 50% chance of inheriting the modified genes (Fig 1). The introduction of a few edited mosquitos or animals is therefore unlikely to have much of an effect. However, gene drive actively copies a mutation made by CRISPR on one chromosome to its partner chromosome and thereby ensures that all offspring and subsequent generations will inherit the edited genome. Over



Figure1. Gene drives can be used to alter population-wide traits. Image courtesy (https://www.embopress.org/doi/full/10.15252/embr.201541337)

generations, this would lead to a noticeable effect: for example, in lowering transmission rates of dengue fever or malaria. The use of gene drives, though, also poses a much larger risk to the environment, as they have the potential to decimate an entire species, eliminate a food source for other species, or promote the proliferation of invasive pests.

A gene drive is preferentially inherited by all offspring and would quickly spread itself in the target population. The endonuclease cuts the homologous wild-type chromosome; repairing the break using homologous recombination therefore copies the gene drive onto the wild-type chromosome. Gene-drive technology could be used to eradicate diseases, such as malaria or dengue fever, by targeting wild populations of disease-transmitting mosquitoes but could have unanticipated secondary effects on other species. Figure adapted from <u>9</u>.

Scientists have already called for strict biosafety measures and public review when it comes to introducing edited animals and insects into the environment <u>9</u>. Yet, **many questions remain unanswered**: Can off-target effects of CRISPR—unanticipated mutations leading to undesirable phenotypes—be controlled? What are the effects on animals or humans who eat genetically edited insects or animals? Will wiping out an entire species—albeit invasive, or disease-bearing, such as mosquitos or ticks—upset the ecological balance? Will edited organisms be able to survive in natural environments, and if so, for how long? Addressing these questions requires far more



regulatory oversight than currently exists anywhere in the world.

Editing the genomes of crops and trees is not new, and debates over the pros and cons of genetically modified (GM) plants have gone on for decades in the USA and Europe, and, more recently, globally. Agriculturally important plants have been genetically manipulated to make these less susceptible to disease and pests, more productive, and more resilient to changing climates. What makes CRISPR different from other methods of agricultural genetic engineering is that it no longer requires the insertion of foreign DNA into the plant genome using a virus, bacterial plasmid, or other vector system. Various commentators have therefore called for changes in the regulation of GM plants because CRISPR- or TALEN-edited organisms would no longer classify as transgenic organisms in *sensu* strictu.

In the USA, the Coordinated Framework under the purview of the USDA, the FDA, and the EPA provides guidance on agricultural applications of genome editing, but their regulations only cover "plant pests"—animals, bacteria, fungi, or parasitic plants that can directly or indirectly damage crop plants or parts thereof. This stipulation enters the regulatory process when parts of pest DNA are inserted into a host organism, or when certain viral vectors are used. The plant pest regulations also govern edits to insects that are detrimental to crops, plants, and trees, whereas

Canadian regulation flowchart image courtesy <u>https://inspection.canada.ca/plant-varieties/plants-with-novel-</u> traits/general-public/eng/1337380923340/1337384231869

applications of CRISPR that do not use pests or pest parts to induce genetic edits fall outside current regulations. Since the regulations frame the insertion of DNA as genetic material from a "donor organism," it is also unclear whether the regulations cover copies of pest DNA that are synthesized in the laboratory.

The Animal and Plant Health Inspection Service (APHIS), an arm of the USDA, reviews applications for research on GM crops. APHIS has indicated that products resulting from CRISPR/Cas **that only** *delete* **a gene, in most cases, would not be regulated because no new genetic material is integrated into the recipient genome.** Substitutions and insertions of genes would be reviewed on a case-by-case basis to determine whether the inserted trait counts as a pest. In recent years, APHIS has seen an increase in requests for non-regulation status by academic centers and biotech companies asking them to affirm that their products do not fall under current regulations, and so do not warrant review for safety and efficacy by federal agencies. The current trend toward deregulation will promote research into a variety of applications of CRISPR, but the wide implementation of those edits without enforceable oversight could be detrimental to ecosystems, biodiversity, and human health.

In contrast to the USA, the European Union (EU) has much stricter regulatory regime for genetically modified crops in agriculture. It requires an extensive risk assessment by EFSA before the EC decides to grant or withhold approval for use in the EU. EU regulation currently considers all genetically modified crops or animals as transgenic—whether this includes the insertion of foreign DNA or direct genome editing—and therefore subject to regulation and risk assessment. However, there is ongoing debate arguing that CRISPR- or TALEN-edited plants without any foreign DNA should not be subjected to the same regulatory regime and risk assessment as transgenics. Since the EU is the largest market for agricultural products in the world, other countries are now waiting to see whether the EC will change its definition of transgenic and its regulations before they move on with marketing edited crop plants.

The US Coordinated Framework for the Regulation of Biotechnology was created to facilitate a unified approach to biotech regulation, but it is no longer adequate in the age of CRISPR <u>6</u>. Even the EU's stricter regulatory regime is not suitable to address all possible risks—in particular with gene drive—as it is designed to regulate transgenic organisms. Moreover, given that CRISPR is cheap, easy to use, and does not require sophisticated equipment or expert knowhow, it has become a popular technology worldwide, which will eventually require international standards for testing genetically edited organisms, releasing them into the environment, and assigning liability for damage. Regulations should set clear requirements for testing the safety and efficacy of edited organisms in carefully controlled environments or contained settings that simulate their natural environments <u>8</u>. Gene drives in particular should be approved only if the safety and efficacy of desired edits have been rigorously tested. Finally, edited organisms should only be released in typical environments, whether on a farm or in a wild habitat, after public consultation and appropriate consent of potentially affected populations.

Regulations should also require the development of methods to halt the effects of edited insects or animals should they prove harmful to other organisms, the environment, or humans. Such reversal, immunization, and suppression drives would neutralize the effects of already-released gene drives by introducing new genes into the population to counter unwanted effects from previous generations <u>9</u>. However, these safety mechanisms are limited by the same facts that limit all gene drives. As the species must reproduce through multiple generations for the desired trait to proliferate, the negative environmental impacts caused by the original gene-drive population cannot be immediately halted by a counter gene drive. Furthermore, natural mutations cannot be prevented in the wild and might eliminate an engineered trait—whether the original gene-drive edit or the counter edit—anytime after introduction <u>9</u>.

One approach to address this problem would be so-called terminator genes or self-limiting genes that limit the lifespan of edited organisms or make engineered organisms more fragile or easy to kill. In addition, edited insects and animals should also be tagged to be able to assign responsibility and liability for damages. It would also enable researchers to better track the flow of gene edits through a population of insects or animals. These are not merely theoretical scenarios. A private biotech company is developing GE mosquitos in Florida with the aim of

lowering the incidence of dengue fever by suppressing the population of *A. aegypti* mosquitos. To date, the FDA has not approved the trial; environmental review and the public comment period are pending. Some Florida

residents strongly oppose the release of the GE mosquitos, citing human safety and environmental concerns. They do have a point, as GE organisms will not always move and behave in predictable ways; GE mosquitos, for instance, even if released on an isolated island, might end up many miles away and have unanticipated effects on the environment such as crossbreeding with related species. Without clear safety and testing guidelines, and public engagement and discussion, the public's trust in the safety of GE insects and animals will follow the same path as GM food. Im



Image courtesy https://www.bbc.com/news/world-us-canada-53856776

CRISPR is now being applied in many academic and industry laboratories around the globe. International **treaties and policies are therefore required to govern the release of GE organisms into the environment.** The WHO's "Guidance framework for testing of genetically modified mosquitos" for instance suggests updating the Cartagena Protocol on Biosafety <u>10</u>. Article 17 of the Protocol obligates parties to notify an International Biosafety Clearinghouse and affected nations of releases that may lead to movements of modified organisms with adverse affects on biological diversity or human health. However, **the document does not specify who will enforce the treaty, what prior testing ought to have been conducted, what the limits on organism viability should be, what methods should be used to assess effects, or how to estimate damages or mitigate harms.** The treaty's effectiveness is further limited by voluntary participation. Some significant players in the field of genetic engineering, including the USA and South Korea, are not parties to the Cartagena Protocol.

CRISPR is also an enormously powerful tool for synthetic biology to generate microorganisms for a broad range of applications, from the production of pharmaceuticals, biofuels, or chemicals to the remediation of pollution or disease diagnostics and treatment. Gene editing allows synthetic biologists to design and edit whole genomes of bacteria and viruses with new properties, but it raises the same concerns about accidental or



deliberate release of GE microorganisms into the environment.

Image courtesy https://slideplayer.com/slide/13570710/

In the USA, the regulation of genetically modified microorganisms is under the purview of various agencies: the FDA, the EPA, and the National Institutes of Health (NIH), but they lack sufficient control and monitoring capacity. **The NIH has guidelines for the use of recombinant DNA technology, of which CRISPR is one, that require notification and containment procedures based on the organism's pathogenicity, virulence, communicability, and environmental stability. However, research not funded by the NIH is not subject**

to these guidelines. The EPA requires notification of new chemical production, which covers some commercial applications of synthetic biology, but the agency relies on voluntary reports and does not perform proactive audits and does not monitor smaller scale operations. The FDA requires that drugs and biologics be proven safe and effective before entering the market, which covers synthetic biology-based human therapeutics, but it does not require specific containment methods to prevent accidental release or design controls such as terminator genes.

Only the NIH's guidance was designed specifically to address genetically modified microorganisms, yet it is also the agency with the least regulatory authority. As CRISPR becomes the primary method of genetic engineering, it would behoove these agencies to require that researchers demonstrate sufficient control

mechanisms as a condition of using the CRISPR editing system.

There is yet another aspect of the genetic editing of microorganisms to consider, as CRISPR could also be used to synthesize and manipulate pathogens, including smallpox, the Spanish flu virus, avian H5N1 flu virus, and SARS. It is not unreasonable to think that, in the wrong hands, CRISPR could be used to make dangerous pathogens even more potent.



Image courtesy https://ici.radio-canada.ca/ohdio/premiere/emissions/les-annees-lumiere/segments/reportage/166977/nanotechnologies-

The use of technology to increase the pathogenicity of bacterial or viral disease agents falls under the purview of the Biological and Toxin Weapons Convention (BWC), an international treaty designed to prevent the creation and storage of biological weapons. However, the BWC covers state actors—at least those who have signed it—but it was not designed to address private companies or individuals. Moreover, as the tools needed to design and manipulate pathogenic organisms and the exact genetic sequences and instructions to do so become more readily available, the effectiveness of the BWC to prevent the misuse of biological tools and knowledge is increasingly limited.

One way to achieve some control would be to regulate the tools of synthetic biology, notably DNA synthesis. Many companies that offer DNA primers, molecules, or even whole-genome synthesis already monitor orders for specific sequences from pathogenic organisms. While this is an important move by industry to prevent misuse, it does not include all companies; moreover, an increasing number of companies are expanding their customer base beyond academia and industry to private individuals. One possibility to address this problem is to take the industry's voluntary commitment further and **create an international clearinghouse with which genetic**



image courtesy https://www.medicalnewstoday.com/articles/322334

sequence producers and sellers must register. It would require all registered companies to monitor their orders and make sure that those who order biological material that could be misused have appropriate credentials, containment facilities, and training.

Much of the discussion about the risks of CRISPR technology has focused on using it to edit the human germ line. Yet, **CRISPR has many potential therapeutic applications beyond this specific use, ranging from cancer immunotherapy to treating infectious diseases, to creating stem cell models of disease.** These applications constitute genetic editing of human somatic cells and the changes made are therefore not heritable. In cancer immunotherapy, current research focuses on adoptive cell therapies, wherein T cells are harvested from patients, modified *ex vivo* to increase their potential to destroy tumor cells, expanded in number, and infused back into patients. One particularly promising approach involves chimeric antigen receptor T (CAR-T) cells, which are engineered to express receptors with the specificity of monoclonal antibodies on their surface. CAR-T therapeutics have proven to be particularly effective in trials against acute lymphoblastic leukemia in both adults and children. As researchers work to elucidate the mechanism by which these therapies achieve a robust response in order to optimize these cells to survive and carry out their effector function *in vivo*, CRISPR is becoming an attractive option to edit the properties of CAR-T cells. Another therapeutic application of CRISPR might help to cure latent infections with HIV or herpes viruses by targeting and "cutting out" viral DNA in infected human cells.

With the rapid application of CRISPR/Cas in clinical research, it is important to consider the ethical implications of such advances. Pertinent issues include accessibility and cost, the need for controlled clinical trials with adequate review, and policies for compassionate use. Many cell-based therapies come at a considerable cost, particularly patient-specific immunotherapies and stem cell treatments. Adding customized gene editing on top of that will further push the price of such treatments well out of the reach of those with average means and insurance, to say nothing of those who are uninsured, destitute, or rely on national health services to decide what is to be made available to patients. It also raises the issue of educating patients to secure informed consent for research trials and clinical use. CRISPR/Cas can be a tricky concept to explain, especially concerning its subtleties and potential for off-target genome editing.

As excitement over CRISPR grows, so will demand from patients. Balancing requests from patients desperate for novel treatments with the need for rigorous clinical trials is already a challenge for regulators and will not become easier with the advent of CRISPR. USA, European, and corporate policies provide some guidance on when and how to allow compassionate use or expanded access to experimental treatments, but these may have to be adapted to address gene editing. Moreover, and as we have seen with stem cell therapies, there are always those willing to

promote misinformation or exaggerate in order to profit from desperate patients and their families. Ensuring that CRISPR/Cas does not become touted as a panacea for all genetic illness is crucial for proper application and dissemination of the technology.

There are specific regulatory challenges and ethical issues pertinent to the various applications of CRISPR technology to edit both somatic and germ line human cells. Far more worrisome, however, is the emerging application of CRISPR to non-human organisms. The ability to design first-generation organisms with desired



Image courtesy https://www.alamy.com/stock-photo/genes-and-blood.html

characteristics might encourage development without sufficient containment mechanisms, or result in the premature environmental release of those organisms and loss of control over their spread. In addition, CRISPR

could be co-opted for nefarious purposes, such as bioterrorism or biowarfare. **The ease and efficiency of CRISPR raises the concern that anyone with the appropriate equipment could engineer a vaccine-resistant flu virus or invasive species in a crude laboratory.** While the new technology has sparked important debate about whether to proceed with human germ line engineering, the risks of the applications described here should serve as a call for discussing domestic and international regulation and guidelines for CRISPR's use.

Sidebar A: Further reading

On using CRISPR/Cas to edit the human germ line:

Baltimore D, Berg P, Botchan M, Carroll D, Charo RA, Church G, Corn JE, Daley GQ, Doudna JA, Fenner M, Greely HT, Jinek M, Martin GS, Penhoet E, Puck J, Sternberg SH, Weissman JS & Yamamoto KR (2015) Biotechnology. A prudent path forward for genomic engineering and germline gene modification. *Science* 348: 36–38

Liang P, Xu Y, Zhang X, Ding C, Huang R, Zhang Z, Lv J, Xie X, Chen Y, Li Y, Sun Y, Bai Y, Songyang Z, Ma W, Zhou C & Huang J (2015) CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes. *Protein Cell* 6: 363–372

On editing plants and animals, in particular mosquitos

Alvarez L (2015) A mosquito solution (more mosquitoes) raises heat in Florida Keys. *The New York Times* 19 Feb. Available at: <u>http://www.nytimes.com/2015/02/20/us/battle-rises-in-florida-keys-over-fighting-mosquitoes-with-mosquitoes.html</u>

Harris AF, Nimmo D, McKemey AR, Kelly N, Scaife S, Donnelly CA, Beech C, Petrie WD & Alphey L (2011) Field performance of engineered male mosquitoes. *Nat Biotechnol* 29: 1034–1037

Camacho A, Van Deynze A, Chi-Ham C & Bennett AB (2014) Genetically engineered crops that fly under the US regulatory radar. *Nat Biotechnol* 32: 1087–1091

Wang S, Zhang S, Wang W, Xiong X, Meng F & Cui X (2015) Efficient targeted mutagenesis in potato by the CRISPR/Cas9 system. *Plant Cell Rep*

Podevin N, DEevos Y, Davies HV, Nielsen KM (2012) Transgenic or not? No simple answer. *EMBO Rep* 13: 1057–1061

Paarlberg R (2010) GMO foods and crops: Africa's choice. Nat Biotechnol 27: 609-613

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7129066/ Bioethical issues in genome editing by

CRISPR-Cas9 technology. This is another excellent introductory abstract on the theme and thesis of genome editing please consult this Turkish source. It deals with the CRISPR technology but also its various applications and the ethical issues that they raise: RNA editing; industrial uses; military applications; military research; DNA replacement; ecological imbalance; chimeric animals. etc.

Turk J Biol. 2020; 44(2): 110–120.

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Questions for classroom discussion

- 1. In one sentence describe/define CRISPR?
- 2. How is the CRISPR/Cas a "revolutionary" and advantageous technology?
- 3. What is "gene drive" and what problems does it pose?
- 4. What complication does CRISPR bring for agricultural bio-engineering?
- 5. What are "terminator genes"? Why and how would they be also dangerous?
- 6. Explain the special dangers in releasing genetically modified organisms into the environment?
- 7. Define the terms *germ line* and *somatic cell line*.
- 8. What are the main arguments in favour of or against the application of CRISPR technology?
- 9. Why is there a need for global regulations of CRISPR application? What significant differences are there between American and EU approaches regarding regulations of GMOs?
- 10. How do the American and European (EU) approaches differ in their efforts to regulate genetic editing of animals and insects and plants?
- 11. There is a delicate balance in nature with everything being interconnected. If one believes that everything has a purpose in nature then should we be altering things in such a way that an entire species is destroyed?
- 12. What risks does the application of CRISPR pose when applied in the animal and insect world?
- 13. How is the affordability and ubiquitous nature of CRISPR technology a weakness?
- 14. What is the Cartagena Protocol? What is it intended to do? What are its limitations or weaknesses?
- 15. What are some of the problems associated with regulatory bodies, either setting them up or giving them adequate control over research and approval of findings?
- 16. What are the real concerns with the application of CRISPR technology on agriculture, animals, insects, and pathogens?
- 17. Given the potential of CRISPR is it possible that the Covid-19 virus was created in a lab using CRISPR technology?
- 18. What is the Biological and Toxin Weapons Convention and what is it supposed to achieve?
- 19. What are other practical suggestions for controlling the application of CRISPR?
- 20. Summarize the pros and cons of the application of CRISPR specifically for therapuetic purposes
- 21. CRISPR is a tricky field, so what are some of the major ethical considerations for CRISPR use in clinical research?
- 22. The author concludes with some sober cautions: that CRISPR/Cas does not become touted as a panacea for all genetic illnesses and that CRISPR technology is not applied dangerously to non-human organisms. Can these problems be avoided? Why or why not?

Part B

The introductory articles and questions framed in **Part A** are a useful start in understanding the wide ramifications of this new biotechnology. There are other aspects that need exploring. The articles that follow are repetitious to some extent, covering some of the same general concerns, but they will help expand knowledge of the technology itself and the serious issues associated with its application in the different fields of science and medicine.

A host of questions arise. The following are some of the key questions that must be answered. There is no guarantee that all nations will act in the best interests of their people or for the greater universal good of mankind. Sometimes we have heard the expression, "If it can be done, it will be done sooner or later". But is that the kind of spirit that we want governing such serious matters as determining the future course of human genome editing? As

Dr. James Rusthoven asked in a webinar on this topic, "Can we choose to say no to a particular vision of progress"? How can we frame the issues? Who should frame the issues? [eventbrite sign-ups for the webinars:Part I: *What could CRISPR-Cas9 mean for human flourishing*? (Wednesday, March 31 at 4 pm EST) Part II: *Who will determine the course of human genome editing*? (Wednesday, April 28 at 4 pm ET)]

Control

CRISPR technology is only at the very early stages. It is not perfect and its consequences are not known. Concerns and questions abound and there must be bodies established to study and consider the impact of such interfaces. The government no doubt has a role to play, primarily to help set parameters for research in the fields making use of CRISPR techniques and the application of same. Perhaps ethical and research commissions need to be set up, ones that would include a broad spectrum of society, not just scientists, but also ethicists,

theologians, industry leaders, bankers, professors and ordinary citizens. To some extent CRISPR concept of gene modification is not new nor totally radical. The fact is that human beings have been designing, tinkering and changing plants, vegetables and animals to some degree over the centuries. Genetically modified plants have been developed to protect them from drought or to make them resistant to plant diseases. For example, the development of Marquis wheat in Canada in the 19th century that expanded the wheat growing area of the Canadian prairies. But all these new possibilities call for caution and wisdom. Who will control the use of the technology for the various purposes or application? Will control be exercised on a national basis or an international basis? Will it be done by governments enacting laws or merely by governments establishing regulations and desirable protocols, but leaving it to the scientists themselves to effectively stop any unethical uses? Can scientists be trusted with this power and responsibility? One Chinese scientist took a chance to be first in his field and in November 2018 he cut out a gene, CCR5, from two girls whose father carried the HIV virus.



So to prevent that line of human beings to be subject to that HIV possibility **He Jiankui** used the CRISPR technique to delete an "undesirable or dangerous gene". He was universally condemned for acting prematurely, without anyone's permission, altering the inheritable traits of the twin girls. The Chinese government banned him for life from working in this field of genetics. Does this kind of move necessitate a one-world-government to prevent unscrupulous scientists and states from going rogue with the technology??

Ethics

Societies will face very deep and troubling options if CRISPR is implemented without adequate parameters and clear rules being in place beforehand. Who controls the research processes currently? Who is funding the research? It is important to know exactly what motivates these scientists and entrepreneurs. What do these research people and entrepreneurs believe about the nature of the universe, the nature of man, the destiny of the human race, existence of God? How will their belief system affect their approach to these ethical issues? Will it change the human view of suffering? Will it reinforce or further strengthen the atheistic attitude that heaven can be built on earth and therefore thus more firmly implant a materialistic philosophy in the minds of people? Human temptations and motivations are such that some may well argue that it would be unethical not to use tech tools to get rid of a disease right from the beginning. In any case, who will decide what is ethical and unethical? Professional associations? Panels of ethicists? Who will choose the panel members whether at the national or international levels? And if established regulatory boundaries are crossed, who will enforce the rules or how would they be enforced? What sort of punishment would be meted out and by whom, what agency, what government, what international body?

The Promise of CRISPR and Artificial Intelligence

The case in favour of CRISPR could include such things as curing some of the 10,000 single cell diseases for 95%



of which there is presently no cure, and improving the quality of life for millions of people. Others point to the strengthening of human memory and extending life expectancy and to the science fiction possibility of rejuvenating lost species like carrier pigeons, mammoths, and dinosaurs. Admittedly, it might work to develop immunity to certain diseases to prevent aging and thus even permit extended space travel because the aging process is slowed down or prolonged for centuries. As well, biotechnology wedded to artificial intelligence (AI) may be a wonderful combination for liberating human beings from the drudgery of certain types of work. What would happen to the nature of work, to the number and types of jobs if CRISPR technology was used in conjunction with AI? Would the meaning of life change as a result? Would there still be the mystery and purpose of life to be discovered?

Image courtesy <u>https://www.amazon.ca/Extinction-Science-Bringing-Lost-Species/dp/1467794902</u>

Some envision CRISPR and AI functioning together in a synchronous fashion so human beings can produce works and processes, skills and techniques, that rival human creativity, even in fields as diverse as playing complex challenging games like chess, painting of landscapes or portraits, writing novels and short stories in different literary genres, or inventing new recreational games. Others are enthused by the

prospect of bold new vistas for man's future through the application of CRISPR technology, in effect, making it possible for enhanced human life to be exported to extraterrestial locations like the moon and Mars and beyond our solar system. To spur such out-reaching ventures, huge prizes (like the X Prize) are offered to motivate innovation in thinking and scientific discoveries that solve practical problems. One science entrepreneur and avid promoter of AI and CRISPR, Peter Diamantis, seems to have the boundless optimism of Dr. Pangloss (from Voltaire' *Candide*) – believing that we live in the best possible world, that it is an exciting time to be alive and that we should take advantage of these opportunities to change ourselves and our environment. His advice is that one should not complain and bitch about a problem, but rather work on a solution. He suggests that solar power, for example, could be a tremendous source of our energy needs, and climate change could be mitigated by planting one trillion trees, an action he believes could rebalance the carbon on earth. In the minds of such entrepreneurs CRISPR offers enormous business opportunities for investors, for pharmaceutical companies, for start-ups companies in biotechnology.

Social Inequality

The proponents for developing and using CRISPR make it all sound begnin, as long as there is transparency and adequate controls. But not everone shares this boundless optimism. These skeptics recognize that in the hands of unscrupulous people, CRISPR could become a means by which Governments control the size and categories of people within their areas of jusridiction, or, worse, reduce them to a sort of occupational slavery. Will there be more inequality in the world and within individual states because of CRISPR? Can the research end up creating pronounced inequality among human beings of the future, the human enhanced by gene-editing and the human being conceived the natural way and allowed to simply develop according to the random chances of nature, nurture and the environment? And could it be utilized to screen out total groups of human beings who evidence an "undesirable trait" and thereby be killed while still in the womb as some countries are doing at present (Norway, Denmark with respect to Down Syndrome)? Put another way, do we want designer babies, human beings made to order with certain traits and thus produce inequalities before birth, by design – blond or dark hair, fair or swarthy complexion, muscular or soft, etc. There are people who out of vanity or for other unjustified reasons already are asking for or demanding a CRISPR baby. How does one prevent that when in vitro babies are allowed? Unchecked genetic engineering could radically change everything forever. We need to have a broad look at and appreciation of creation. Are we willing to upset the balance of human life and the created world? The procreation

of human beings is not an industrial production process. We should not change the nature of the natural world. Political parties and governments need to be approached and questioned about these things. They must be educated and be held accountable.

Fundamental principles and beliefs

It is such an overwhelming topic that the very core of human existence seems to be under attack or at least under new, radical reconsideration. Will CRISPR technology influence the evolution of the human race itself? Are scientists just trifling with secondary traits, not with what truly makes up the human person? The fact is that

modification to somatic cells impacts only one individual, but germ line manipulation impacts the whole human race because those DNA changes, whether additions or deletions, become inheritable. Because of these reasons many argue for extreme caution in researchers dabbling with germ lines in any way. Deep philosophical and religious questions also pop up. It will inevitably change the way we make babies and why human beings are created. Will procreation in vitro become the normal way to generate new life rather than through intimate, natural sexual intercourse? Will this become another source of inequality - origin or source of conception? And what about the human soul?



Image courtesy https://art-twerks.com/ai-program-art-painting/

Vaccines and other benefits

Vaccines have been developed fo the prevention and control of various diseases. The latest claim is that vaccines have been developed for COVID -19. CRISPR reduces the time needed to get certain research done - maybe this accounts for the quick turnaround of vaccine development for Covid-19. However, there are medical personnel and scientists who controversially do not accept the term vaccine for what has been injected into millions of human beings in an effort to stop the COVID-19 pandemic. Some experts believe that through the "vaccines" they are injecting something that does not belong in the human being.

Questions for discussion

1. From a considerations of the issues above, what are the most important questions that society faces when dealing with this CRISPR technonolgy?

2. What are the most serious caveats in the pursuit of biogenetic research in your opinion?

3. Are scientists guilty of hubris, the kind of optimism expressed in this praise of Nietzchean philosophy? https://www.zacharyfruhling.com/philosophy-blog/2001-a-space-odyssey-a-thoroughly-nietzschean-film

While the emergence of consciousness carried a certain evolutionary advantage, the mistake that Western philosophers have made, from Socrates and Plato onward, and culminating in the Enlightenment philosophers' views about the nature of human reason, is to view human consciousness as what Nietzsche pejoratively calls "the kernel of man," mistakenly believing that consciousness and modern humanity are the pinnacle of the evolutionary process, when in reality consciousness is latecoming in the history of the natural world and a quirk of natural evolution, still in the process of developing. In other words, modern humans, consciousness and all, are still in the process of evolving and developing, both biologically and culturally, and it's a mistake to view our current human achievements, either psychological or technological, as the peak of human potential or cultural evolution.

Valuable Sources

https://theconversation.com/heres-how-we-could-build-a-colony-on-an-alien-world-54923

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https://www.bbc.com/news/world-55905354 The myth and reality of the super soldier

https://www.youtube.com/watch?v=YO9sACtHN28 Why is the U.S. Military Creating an Army of Cyborgs?

Part C

The next two articles offer opinions on the ethical debate regarding CRISPR technology. They appeared in the October 2020 edition of *Chemistry World*.

The ethical debate around CRISPR

by Philip Ball, 9 October 2020

The gene editing technique deserves its Nobel Prize, but we should continue to interrogate how it is used. Folk belief has it that Alfred Nobel founded his prizes out of guilt for having built his fortune on the destructive power of dynamite. It seems more likely that it was a case of image management:



source: © Lee Woodgate/Ikon Images

Nobel was disturbed to find himself commemorated as a 'merchant of death' in 1888 when a French journalist mistook the death of Alfred's brother for his. Resolving to improve his legacy, he declared that most of his estate should be invested in a fund to support 'prizes to those who, during the preceding year, shall have conferred the greatest benefit to mankind.' It's not clear that Nobel felt genuinely bad about his explosives business, however. Rather like Fritz Haber (the 1918 chemistry laureate) working on gas warfare, he seemed to believe that the more terrible the weaponry available to generals and leaders, the more they might recoil from armed conflict



at all. (It seems we routinely underestimate what Sigmund Freud dubbed our death instinct.) All the same, Nobel personifies the notorious Janus nature of scientific advance. The phrase 'dual use' doesn't do it justice, though: many important discoveries have complex social implications and applications not readily categorised as merely good or bad. The work awarded this year's Nobel prize in chemistry illustrates this more emphatically than ever. The Crispr technique for precise editing of genomes – enabling specific genes or DNA sequences to be accurately targeted and snipped out or replaced – was always a shoo-in for a Nobel, given how profoundly it has changed the science and technologies of gene editing since its introduction around 2012. It was merely a question of 'when?' – and more problematically, 'who?' No one doubts that this year's laureates, Jennifer Doudna and Emmanuelle Charpentier, deserve recognition; the question was who else (if anyone) should be included.

Yet that's a minor controversy compared with the matter of how Crispr should and might be used. The Nobel citation alludes only very briefly to the fact that 'the power of the Crispr-Cas9 technology also raises serious ethical and societal issues.' (Cas9 is the main DNA-cleaving enzyme used in the method.) But a capability for making precise changes to the human genome raises all kinds of difficult questions about how far we should go with it. Should genome engineering be restricted to the avoidance of genetic disease, or might it be justified for genetic enhancement? How can we distinguish one from the other? Where are the limits on the possible or permissible – giving us infrared vision, say, or tolerance to extreme cold, or the ability to photosynthesise?

What would such uses mean for the status of people with existing genetic diseases or impairments, if these are 'edited out' of future generations? Can we hope to ensure equitable access to these powerful techniques, or would they widen the divide between haves and have-nots? Should we use Crispr on the human germline, so that modifications are inherited by future generations?

The last issue has become particularly explosive since the revelation that Crispr was used in 2018 by Chinese biologist He Jiankui to modify twin embryos used for IVF, resulting in the birth of two girls allegedly containing alleles that would confer protection from infection by HIV. It wasn't just that He bypassed ethical regulations, nor even that he chose to use germline editing for pre-emptive protection. It was also that he did the job rather poorly and without any clear evidence that the procedure was safe.

Quite aside from the ethical questions about inheritable modifications, Crispr may be risky at this point because it is not necessarily as accurate as it is sometimes portrayed. It can and does lead to off-target modifications, the health consequences of which are unknown and unpredictable. So far the twin girls born from He's procedure seem to have normal health, but it is still early days. He's actions were almost universally condemned by the biological community – including Doudna, who said that genome editing of embryos should be countenanced at all only where a 'clear unmet medical need exists'.

He has now been given a three-year jail sentence and a fine of Yuan3 million (£345,000) for 'illegal medical practices'. Nonetheless, his demonstration that Crispr germline editing need not be obviously catastrophic has opened the floodgates. Other researchers are now petitioning to use it for reproductive purposes. Many, however,

advise a global moratorium until the social, medical and ethical issues have been properly considered. Doudna favours clear regulation instead, and as the Nobel citation states, the World Health Organization has established a committee to make recommendations about what form that might take.

Many scientists and bioethicists share Doudna's view that human genome editing is both inevitable and justified – and some feel that its medical potential should not be unduly delayed. One of the most libertarian is biologist George Church of Harvard University in the US, who stresses that Crispr is just one of several ways of doing it. Ultimately he advocates rewriting rather than (somewhat messy) editing, and explained to me last summer his goal of rewriting the entire human genome from scratch, raising the prospect of much more extensive but also more accurate modification – for example, to make our DNA unrecognisable to pathogenic viruses. Such vaulting ambition might now look more attractive than it did a year ago. The real lesson of Nobel's own work is that science is not divorced from society and that its goals and implications are neither neutral nor Manichean. In that respect, Crispr is a fitting choice indeed.

Questions for discussion

1. How does the background to the origins of the Nobel Prize illustrate what the author refers to as the "Janus nature of scientific advance"?

2. What factors make CRISPR such a risky technology at this time?

- 3. What would re-writing the entire human genome from scratch entail? Why attempt to do that?
- 4. Is this another case of human hubris?

https://www.chemistryworld.com/opinion/the-ethical-debate-around-crispr/4012573.article

https://chemistry.berkeley.edu/news/crispr-not-just-gene-editing Crispr, not just for gene editing, Let's watch how Crispr evolves into a platform technology by Jennifer Newton, 30 october 2020

Part D

The following excerpt is from an excellent abstract paper dealing with the moral considerations associated with the application of the CRISPR technology. Again for the sake of brevity only the headlkines of the apper are presneted and the concluding paragraphs. To read the paper in its entirety please go to https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6286228/. A very useful feature of this abstract is the comprehensive table provided by the authors summarizing the pros and cons of CRISPR technology, that is its abstract is the same frequencies.

benefits and its serious risks.

CRISPR ethics: moral considerations for applications of a powerful tool

<u>By Carolyn Brokowski</u>¹ and <u>Mazhar</u> Adli^{2,#}

II. CRISPR systems and their uses

III. CRISPR ethics and science: Uncomfortable bedfellows

IV. Ethical concerns



DNA. Source: © Science Photo Library

To what extent should CRISPR experimentation be permitted in basic and pre-clinical biomedical research?

To what extent should CRISPR use be permitted in translational and clinical medicine? To what extent should CRISPR use be permitted for non-therapeutic purposes? Who should have access to CRISPR technology and/or its products? Limiting human genome editing? Somatic vs. germline editing Should international regulations governing CRISPR use be crafted and promulgated?

V. Conclusions and future directions

CRISPR technology continues to mature, and existing systems are being engineered to contain innovative capabilities; excitingly new CRISPR systems with novel functions are still being discovered. The potential benefits of such revolutionary tools are endless. However like any powerful tool, there are also potential associated risks raising moral concerns. To make truly informed decisions about areas of ethical controversy, well-controlled, reproducible experimentation and clinical trials research are warranted. Currently, this is difficult because many international laws discourage or ban such research and/or inhibit its funding for certain types of investigation. Thus, widespread data about benefits and risks are unavailable. It is critical, however, for countries to examine their reasoning behind these prohibitions to ensure that they are not simply arising out of fear and without reasonable justification.

Going forward, many support establishing an organization that will decide how best to address the aforementioned ethical complexities. Recently, a group of European scientists founded the Association for Responsible Research and Innovation in Genome Editing (ARRIGE) to examine, and provide guidance about, the ethical use of genome editing^{169,170}. Furthermore, Janasoff and Hurlbut recently advocated for the development of an international, interdisciplinary "global observatory for gene editing"¹⁷¹. Briefly, they argued that deliberations about moral issues in gene editing should not be dominated by the scientific community, but instead should include a "network of scholars and organizations similar to those established for human rights and climate change. The network would be dedicated to gathering information from dispersed sources, bringing to the fore perspectives that are often overlooked, and promoting exchange across disciplinary and cultural divides"¹⁹⁸.

As the technology evolves, so will discussions about ethical and legal frameworks circumscribing its uses. The above-mentioned platforms present interesting ideas for furthering debates and potential resolutions. The research and ethical guidelines from national and international organizations, where diverse disciplines of society contribute, will be critical for federal funding agencies and

IRBs to enforce and regulate, to minimize the potentials risks and maximize the potential benefits of CRISPR technology. However, it is likely that the enforcement of ethical research laws and guidelines ultimately will be assumed by legal systems, principal investigators, and institutional review boards.

Table 1

Risk/Benefit Considerations in CRISPR Technology

	Benefit(s)	Risk(s)/Harm(s)
Basic and pre-clinical research	 new model organisms and cell lines 	 experimentation involving human embryos is controversial and illegal in some countries

	Benefit(s)	Risk(s)/Harm(s)
	 increased gene-editing efficiency 	potential for privacy and confidentiality breaches
	3. high throughput screens	
	4. novel drug targets	
	5. access to totipotent cells	
	6. identification of novel	
	signaling, regulatory, and developmental pathways	
	7. development of novel gene-	
	editing approaches (base	
	8. knowledge advancement	
Translational and clinical	1. immunotherapy	1. serious injury, disability, and/or
medicine	2. organoids	death to research participant(s) and/or offspring
	3. novel drug targets	2. blurry distinction between
	4. artificial intelligence	therapeutic and enhancement
	5. modification of pathological	applications, leading to potential subtle or obvious exacerbation of
	genes	inequalities
	6. nover therapeutics and fertility applications	3. misapplications
	7. procreative liberty	4. eugenics
	 ability to "fix" single base changes 	5. potential for inequitable access and exacerbation of inequalities

	Benefit(s)	Risk(s)/Harm(s)
	9. knowledge advancement10. potential for equitable access	
Non-therapeuticapplications	 enhancement to augment select faulty or human characteristics fortification of crops and livestock successful control of pests, invasive species, and reservoirs (gene drives) disease/infection control (e.g., malaria, dengue fever, Lyme and Chagas disease, schistosomiasis) ecosystem alteration to protect endangered species (gene drives) safety crop cultivation knowledge advancement 	 eugenics exacerbation of racism and inequality theoretical risk for damage to ecosystems theoretical risk of misuse
Access to CRISPRtechnology	 inexpensive (technology itself) widely available 	 price gouging prohibitively expensive applications

	Benefit(s)	Risk(s)/Harm(s)
	 profit, economic growth innovation 	
Regulations for clinicalresearch involvinghuman subjects	 established framework in some countries to manage research risk legal mechanisms for redress already exist, depending on location 	 lack of appropriate supervisory infrastructure, oversight, and/or regulatory framework in many nations unclear how to supervise the research even in some countries with regulatory oversight over regulation might hinder progress
National and internationalregulations, law, and policy	 prevention against misuses of technology safeguard against potential unethical conditions 	 potential to encroach on societal autonomy limit discovery and progress difficult enforcement lack of uniformity

Acknowledgments

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Footnotes

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MA and CB conceptualized the study and wrote the manuscript.

Questions for reflection and discussion in class.

1.In your opinion, what are the four greatest potential benefits of CRISPR technology? Explain why you would choose those four?

2. Which four risks or potential harms would you fear the most? Why?

3.Is this topic one that ought to be studied in a science class or ina religion or philosophy class? How might the approach differ and how might there be common ground?



AI created painting of Napoleon



mutant soldier of the future?



Gene-edited fish



bringing vanished species back to life

Reminder of the Father Ted Colleton Scholarship and Essay Contest deadline for submissions of application and essays is December 1, 2021.

FATHER TED COLLETON SCHOLARSHIP





Niagara Region Right to Life is once again pleased to offer The Father Ted Colleton Scholarship essay contest as part of its mandate to reach out to society in an educational format. In particular, Niagara Region Right to Life wishes to help educate and inform the younger generation about the preciousness and possibilities of human life from conception to natural death and how certain threats affect those possibilities in its beginnings.

All students in grade 11 or 12, attending a Canadian high school (or being home schooled in Canada) are invited to participate.

Three prizes of \$2000 (1st), \$1500 (2nd) and \$1000 (3rd) respectively will be awarded. Candidates are required to submit a personal profile, a letter of recommendation and a 1200 word essay on the theme outlined below:

Describe how one could help build a *culture of life* (one that uncompromisingly respects and cherishes the dignity of all human life from conception to natural death). Your suggestions may range from a plan to protect the conscience rights of both current health professionals and of those contemplating medical studies - to more effective regulations regarding biomedical research, or from new peaceful public activism - to more effective strategies in the various fields of communication. This is an open-ended, non-exhaustive list.

SUBMIT DOCUMENTS VIA EMAIL BY DECEMBER 1, 2021

Email:dirocco@theinterim.com

Or leave a message for Dan Di Rocco at (416) 204-1687