

## CRISPR-Cas9 System: Opportunities and Concerns

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Currently, a new revolutionary genome-editing tool is opening new avenues for gene engineering. It is known as the clustered regularly interspaced short palindromic repeats (CRISPR)<sup>11</sup> and the CRISPR-associated (Cas) 9 system.

In general, the CRISPR-Cas system has been evolved in archaea and bacteria as part of their adaptive immune mechanisms. Mechanistic aspects of the system can be found in the literature. Among the 3 CRISPR-Cas system types that were found in these organisms, the type II system in *Streptococcus pyogenes* the most widely applied.

The type II (CRISPR-Cas9) system includes the RNA-guided Cas9 nuclease, which binds to specific DNA sequences (complementary to the RNA-guide sequence) and creates double-stranded breaks on the DNA. The dsDNA breaks can be repaired via homology-directed repair (HDR) or nonhomologous end-joining (NHEJ). Based on this principle, the Cas9 and the guide-RNA were modified in various ways to improve the efficiency and specificity of this system, to expand its potential for different applications. This system can be used for altering specific genetic loci through insertions, deletions, point mutations, and sequence inversions. More recently, the system was modified to act as a genome regulator, by tethering effector domains to the Cas9 or guide-RNA, and as a visualization tool by fusing with marker molecules. This multiplex capacity of engineering CRISPR-Cas9 enabled scientists to apply this system for genome modifications in a variety of organisms, like *Arabidopsis*, *Drosophila*, *Caenorhabditis elegans*,

zebrafish, mosquitoes, mice, primates, and humans. Lately, the CRISPR-Cas9 gene editing has been used in human embryos and generated several ethical questions and concerns.

In this Q&A, 5 experts from around the world discuss the capabilities of the CRISPR-Cas9 system in editing genomes and discuss the associated ethical concerns.

***The interest for using the CRISPR-Cas9 system to targeted genome editing is rapidly emerging. The efficiency of this tool has dramatically improved the last couple of years, by application of different modifications in the Cas9 or RNA-guide molecules. What is the importance of these new enhancements?***



**George M. Church:** Several modifications of Cas9 are quite impactful: (a) switching Cas9 from a nuclease to an activator, (b) making Cas9 less toxic in stem cells, (c) increasing HDR vs NHEJ, (d) increasing specificity to the point that single nucleotide differences can be discriminated routinely.

**Henry T. Greely:** Anything that makes the system faster, easier, cheaper, or more accurate increases the ways it will be used and the number of people who will use it. The democratization of the technology—by making it cheap

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<sup>11</sup> Nonstandard abbreviations: CRISPR, clustered regularly interspaced short palindromic repeats; Cas9, CRISPR-associated 9 nuclease; HDR, homology directed repair; NHEJ, non-homologous end-joining; TALEN, transcription activator-like effector nucleases.



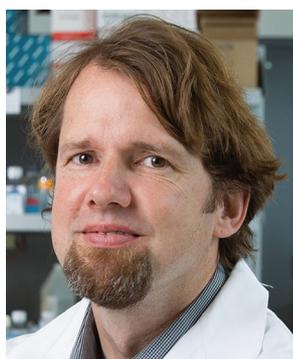
and easy enough for poorly funded amateurs—could have vast effects by making it harder for anyone to control the uses.



**Charis Thompson:** The importance of the CRISPR revolution is its relative ease of use and low startup cost and its relative high precision to effect targeted gene “editing.” The fact that nearly every academic and industry laboratory—and some civilian-run laboratories and garage spaces—can

participate in this work relatively easily changes everything: how fast it is being improved; how democratic participation is; and how quickly good and bad uses could be developed and spread.

Like all technologies, historical patterns of inclusion and exclusion specific to given jurisdictions will tend to be reproduced in gene editing if individual nations and the international community do not explicitly make sure this doesn’t happen. Efforts to fix and cure individuals’ problems will go ahead because that is how science is already set up; the more difficult task is to get the social architecture in place to monitor health equity, eugenics, and environmental impact across time, place, and groups of people, and to have the necessary correctives feed back into the way the field develops.



**Gerold Schmitt-Ulms:** The main technological improvements to the CRISPR-Cas9 system in recent years are advances in specificity, efficacy, and range of applications. Improvements to specificity minimize unpredictable off-target effects, i.e., inadvertent genome editing of nonintended sites. Efficacy advancements save valuable resources required to achieve a particular outcome and are essential for certain

applications. Some of the most innovative CRISPR-Cas9 technology advances in recent years relate to the range of applications the technology can now be used for. Its core usage for gene knockout or precise gene editing purposes was augmented by the identification of Cpf1 endonucleases (see below). Novel applications that harness aspects of the system for other purposes are emerging at a rapid pace and include its use to affect the transcriptional control of preselected genes or visualize endogenous genomic loci in living cells.

**What are the major limitations of the CRISPR-Cas9 system?**

**George M. Church:** (a) Very few simultaneous changes per cell (up to 62 in one experiment in pigs, but usually <4 per cell), (b) inefficient HDR to NHEJ ratio, and (c) efficient delivery to all cells or to a precise subset.

**Henry T. Greely:** This isn’t really in my expertise but I’d suggest 2 things—the fact that it is not perfectly accurate makes its uses more worrisome and the uncertainty about who owns, or will own, the relevant intellectual property could affect research and applied uses, through delay or rushing or both.



**Françoise Baylis:** I can think of 2 major limitations with the CRISPR-Cas9 system: the first limitation is “the user,” and the second limitation is “user error.”

With respect to the first limitation, there is reason to expect that the science will seed fierce competition among research teams, for-profit companies, and nation states. This competition might be similar to that which characterized the 20th century’s space race and nuclear arms race. This is not to deny the possibility of wide-ranging collateral benefits for humankind resulting from such competition. It is to say that we should be wary of allowing scientific, corporate, and political elites to dominate the relevant policy and ethical deliberations.

With respect to the second limitation, we must be wary of the potential consequences of off-target effects, lack of specificity in targeting, incomplete targeting, and so on, all of which could have devastating effects on patients. Here it is worth remembering that we have no idea what most of the human genome *does*. How much is due to selfish genes making copies of themselves (transposable elements)? How much is

simply noise? How much is the result of retroviral infections in our distant past? Moreover, we are only just now beginning to investigate epigenetic influences over gene expression. We need to be mindful of these facts as we learn to exploit and optimize gene editing technology.

**Charis Thompson:** I am a social scientist (with some life science training) so this is not my area of expertise. From the side of civil society, however, we will be looking for improved nucleases to increase safety and efficacy. In particular, the improved nucleases hold promise for reducing off-target effects, which would improve the effectiveness of the target gene edit, and reduce unintended consequences. Greater accuracy will also improve our ability to characterize mechanism and to monitor efficacy and safety, including over multiple generations.

**Gerold Schmitt-Ulms:** Major limitations of initial CRISPR-Cas9 systems were the frequent occurrence of inadvertent off-target effects. Several technology improvements, including the availability of assays for genome-wide identification of off-targets and improved algorithms for selecting target sites, improved this shortcoming. However, the advent of Cas9 nickases, in which 1 of 2 endonuclease modules within the Cas9 protein is rendered inactive by point mutation, resulted in the most dramatic improvement. When combined with pairs of guide RNAs targeting nearby sites on opposite strands, the nickase approach greatly improved target site specificity. Taken together, these advances make limitations in the system's efficacy the most pressing bottleneck at this time. The latter can be further crudely subdivided into limitations related to its delivery to cells and limitations that relate to the rate of gene editing itself. The delivery problem is not unique to CRISPR-Cas9 systems but also poses a formidable challenge to the clinical use of transcript knockdown technologies. Similarly, limitations in the rate of CRISPR-Cas9-mediated gene editing are also encountered with other gene editing technologies, such as those based on transcription activator-like effector nucleases (TALEN). While these limitations are less pronounced with CRISPR-Cas9 systems than with alternative gene editing strategies, they still force a workflow that relies on relatively time-consuming downstream selection steps for the isolation of clones that have undergone the desired gene-editing step.

*Like Cas9, Cpf1 is another single RNA-guide nuclease of the type II CRISPR-Cas system. What is the importance of using improved nucleases with this system?*

**George M. Church:** We have not found Cpf1 to be an "improved nuclease" (yet). In contrast, the 4 modifica-

tions to the Cas9 system listed in question 1 have been significant improvements.

**Gerold Schmitt-Ulms:** The discovery of the CRISPR-Cpf1 technology is promising for several reasons. Whereas Cas9 requires 2 RNA molecules to direct it to its DNA cut sites, Cpf1 requires only one guide RNA and is a smaller protein, which facilitates getting the system into cells. Most importantly, however, Cpf1 generates staggered cuts (as opposed to blunt ends by Cas9), which make it an attractive endonuclease for achieving true gene edits in nondividing cells in which the cell-autonomous homology-directed repair mechanism is not working effectively. The recent discovery of C2c2, a naturally occurring RNA-guided enzyme that targets RNAs, adds yet another exciting capability to the tool box of molecular biologists.

*Experiments in humans are currently restricted. However, gene-editing of some sort in human cells has been applied in research for decades. The use of the CRISPR-Cas9 system in human embryos by a Chinese group started a debate regarding the application of this technology to humans. Also, a UK investigator was recently approved to use this system for modifying embryonic stem cells. What is your opinion on this issue?*

**George M. Church:** Ironically, the first paper from Prashant Mali, Luhan Yang, and coworkers (Science 2013;339:823–6) on using CRISPR in nonbacterial cells used human stem cells, which were probably more capable of producing viable human embryos than were the triploid cells used in the study reported from Junjiu Huang (China) (Protein Cell 2015;6:363–72). Also, the mitochondrial germ-line engineering (from Shoukhrat Mitalipov's laboratory in Oregon) involved human embryos and was aimed at therapy. The UK embryo work (from Kathy Niakan's lab) was aimed at basic biology, not gene therapy. So it is odd that the Chinese and UK experiments are discussed as if they were more problematic than the Oregon and Harvard experiments. All 4 of these experiments are legal in most countries, including US, UK, and China. Gene editing is not just used in human cells or embryos, but also in approved clinical trials (human adults and children).

**Henry T. Greely:** I'm in favor of any well-conducted research with CRISPR-Cas9 (or similar systems) that does not use it to change living people or human cells that are intended to become living people (gametes, embryos, or fetuses). I'm in favor of well-conducted and regulated research to use these techniques to modify the somatic cells of people to treat disease, as well as clinical use if and when proven safe and effective. I think we need to

talk more as societies about possible uses in living people not to treat disease but for “enhancement,” bearing in mind that we don’t have a clue how to make superbabies or how to do even minor enhancements. I am against using it to make inherited changes unless or until that technique is proven, by high standards, to be both safe and effective, at which point my reaction is similar to my reaction to somatic cell uses in existing people.

**Françoise Baylis:** Ethical concerns about germline gene editing can usefully be clustered into 2 categories: concerns about any and all research involving human embryos and concerns specific to gene editing involving human embryos. In the first category there are concerns about the moral status of the developing human embryo, as well as concerns about the source of the embryos used for research purposes—for example, whether proper consents were obtained, and whether women egg providers were exploited.

In the second category there are myriad concerns about the introduction of heritable modifications should any of the manipulated embryos be used in reproduction. There are concerns about the risk of errors and (unintended) consequences, not only for the resulting child(ren) but also for humankind. In the latter context there are concerns about the risk of exacerbating problems of racism, sexism, health inequality, and so on, as a direct consequence of who will and who will not have access to the technology. In addition, there are wide-ranging objections to this research grounded in the belief that we should not be tinkering with the “*patrimoine génétique*” (which is a reference to the human genome as the heritage of humanity). The worry here is that some among us will boldly go where no one has gone before in selecting modifications for the population at large, thereby possibly irretrievably altering the human species.

**Charis Thompson:** My opinion is that the current consensus in the UK is right. That is, I agree that appropriately consented and procured human embryos [exited from reproductive projects in assisted reproductive therapy (ART) clinics] can be gene edited to learn about basic biology, to improve gene editing procedures and mechanisms, and to understand failures of pregnancy (cf Kathy Niakan’s research), but edited human embryos should not at this point be implanted in any woman’s womb with the intention of establishing a pregnancy. More evidence that gene editing is accurate and safe and efficacious needs to be accumulated before implantation.

Should the needed evidence build up, however, I would not be averse to using gene editing for reproductive purposes if the correct social architecture was in place to monitor and counteract tendencies to become selecting and/or inequitable. I call this position CRISPR:

(Currently restrict implantation; someday permit reproduction). People with disabilities and those who tend to be medically disenfranchised (low income, migrant, non-citizens, racialized others, etc.) should lead the conversation in what kinds of selecting and access and uses are acceptable. The disability justice slogan, “Nothing about us without us” should be the guiding philosophy.

**Gerold Schmitt-Ulms:** I am in favor of transparent research to explore the strengths and limitations of CRISPR-Cas9 and related systems in human cells, including in nonviable human embryos (e.g., with major chromosomal anomalies). These experiments will not only help us better understand the risks associated with the use of this technology but will also generate insights into the function of proteins and their role in early human development. The widespread fear that these experiments are the precursor to inevitable future uses of the technology in human genome engineering seems overblown. The ability to combine in vitro fertilization with the selection of embryos devoid of a particular disease-causing mutation to overcome inherited monogenic diseases already exists. It is difficult to see how undertaking CRISPR-Cas9 genome edits in reproductive cells (also known as germ-line editing), an inherently more invasive technology, could supersede this safer approach. A more realistic scenario might be that lessons learned from CRISPR-Cas9 experimentation with human cells prompt the use of this technology in the correction of disease-causing mutations in somatic cells. If such an application were to become a reality, it would need to be preceded by a rigorous safety evaluation in combination with a global ethics debate involving stakeholders from all facets of society and not just the scientific community.

*If the CRISPR-Cas9 system becomes 100% safe and effective, what are the potential ways of utilizing this technology to correct human heritable diseases?*

**George M. Church:** Parents who are carriers of serious genetic diseases (like Tay-Sachs) could use gene editing of sperm or egg producing cells, rather than putting embryos at risk of abortion (or nonimplantation in in vitro fertilization).

**Henry T. Greely:** First, you could, at least in many cases, edit the somatic cells of people (or, even when shown safe and effective, fetuses and embryos) to prevent the disease. If this does not become sufficiently safe and easy, germline modification may not be attractive. Second, you could modify the germline, either by modifying a “future person’s” entire body by making modifications in the gametes or embryos that becomes the person, or by modifying a living person’s eggs and sperm so the disease alleles will not be passed on. Frankly, there are very, very

few times that genome editing would be needed to avoid passing on a genetic disease; using preimplantation genetic diagnosis, a procedure with which we have more than 25 years of experience, to select embryos that do not carry the disease-causing genes will almost always be sufficient. (For more on embryo selection, see my new book, *The End of Sex*.)

**Françoise Baylis:** As worded, there are at least 3 significant problems with this question. First, nothing is 100% safe and effective and this is not the standard for moving from clinical research to clinical practice. In effect, a particularly interesting and challenging question is how much safety and how much effectiveness should be required before patients are offered innovative technological interventions?

Second, safety and effectiveness are not the only relevant criteria. A new intervention could be “safe enough” and “effective enough,” but trivial in the grand scheme of things and, as a result, not worth the investment of time, talent, and resources. Persons seriously contemplating the use of germ line gene editing to correct a heritable disease will need to carefully consider the nature of the health condition they aim to correct, as well as the availability of alternative, safer treatment options.

Third, there is no agreement on which, if any, human heritable diseases should be corrected. Consider, for example, debates around ableism or overpopulation alongside debates about available, safer options for promoting the birth of so-called healthy children.

**Charis Thompson:** I think that we should move slowly and focus on monogenic and oligogenic diseases for which there is not already a good somatic treatment first. We should also stand by a principle I have called the cure–care parity principle, so that we invest equally in improving care and accommodations and access and don’t focus all our attention on some fictive idea of all being cured from what ails us.

We must also make sure that we empower those best placed to talk about what things are diseases and what things are only diseases seen from a narrow and a historical point of view. No one has the right to say whether or not someone else’s life is intrinsically worth living. We know from prenatal screening that weeding out difference happens all too easily; today people abort for much more minor deviations than in the past.

**Geroald Schmitt-Ulms:** Due to the inherent complexity of natural systems, a technology of this nature can never be completely safe. But risk–benefit considerations may indicate its use in certain cases provided there are no ethical concerns. Two major uses of this technology to address inherited diseases can be identified: genome editing of reproductive human cells (also known as germ-

line editing) or the correction of mutations in somatic cells. The first application refers to correcting the heritable disease in a manner that would eradicate the risk to subsequent generations and would be undertaken at the earliest possible embryonic stage. A somatic correction would most likely be directed to a subpopulation of cells that are both accessible and critical for the manifestation of the most severe disease symptoms but would not impact inheritability of the disorder.

***Do you believe that this system or alternatives will ever be used to improve the human race in terms of appearance and intellectual capacity, etc. (eugenics)?***

**George M. Church:** Cosmetics and coffee have been in wide use for decades to affect appearance and cognitive features, but would we rank these as major improvements in the human race? Truly major biological augmentations include global elimination of smallpox and reduction in childbirth-associated deaths. We will probably improve cognition via drugs aimed at reducing cognitive decline in our increasingly aged population. This may not involve gene editing but could nevertheless impact many generations. The context of eugenics has changed completely since the time (up until the 1970s) that many countries, including the US and Sweden, forced sterilizations. In contrast, gene therapy is about giving people more choices.

**Henry T. Greely:** Clearly yes, in one sense. Avoiding certain genetic diseases will improve appearance and intellectual capacity. But assuming you mean apart from treating diseases, I suspect some people will eventually use methods for genetic enhancement—after we figure out what genetic variations actually “enhance” us, something we know almost nothing about. My own guess is that embryo selection will be used much more rapidly and commonly than genomic editing, but in the long run both are likely to be used. Whether that would deserve the term “eugenics” depends in part on what you think that word means—any selection, or government-enforced selection? (Or, as happened in the past but is highly unlikely in the future, in part because of CRISPR-Cas9, government-enforced sterilization.)

**Françoise Baylis:** While there are some “disease genes” we might all agree should be eradicated, I don’t think we know (or can know) what will improve the human species. Traits that seem important and useful to us today may prove to be irrelevant and perhaps even disadvantageous in the not too distant future. Regardless, at least some among us remain enthralled by the prospect of human enhancement.

I have argued elsewhere, and continue to believe, that human genetic enhancements are inevitable. This perspective is informed by a particular view of human

nature having to do with capitalism, heedless liberalism, a drive for knowledge, a desire to outperform, and a fair amount of hubris allowing us to believe that “the future is ours for the shaping.” This claim about the inevitability of genetic enhancements is descriptive, not normative, and aims to motivate careful reflection on the ways in which we can use our intellect, our energy, and our financial resources in pursuit of the common good.

**Charis Thompson:** Yes, I think that people are already thinking about this. It is all the more urgent to build the social architecture in proactively, so that the social innovation is just as important as the scientific innovation. Luckily, many kinds of intelligence are valued and necessary, and many kinds of looks are, too. We have to make sure that we stop tiny segments of the population imposing their ideas on the rest of us by making social monitoring and assessment and correction an intrinsic and nonvoluntary part of the research infrastructure.

There are very important conversations to be held and monitoring to be ongoing about, for example, which military uses of gene editing for certain kinds of physical and intellectual abilities need what kind of lay scrutiny. Similarly, pure majoritarianism does not work in this realm; protection of minority rights is central and essential. The latter is a poorly attended-to part of democracy; moving forward, it should be central.

**Gerold Schmitt-Ulms:** I am categorically opposed to the use of this technology in humans for the pursuit of non-medical objectives, and I am not aware of any reasonable person who would advocate it. However, I am less confident that it won't eventually be tried. Similar to ongoing global efforts to minimize the risk of nuclear wars, the abuse of CRISPR-Cas9-related technologies for eugenics needs to carry a sufficiently high penalty to discourage it. As with the ongoing threat of a nuclear catastrophe, this challenge will not go away. It is the collective responsibility of the global society to monitor and prevent the abuse of this technology for applications that lack moral foundation.

*The CRISPR-Cas9 system is capable of altering the genome of any organism in this planet. Scientists have used it for various research purposes and it is also capable of improving food quality and production, resulting in the increase of diversity among species. Could you highlight your environmental concerns?*

**George M. Church:** Since 2014, I have been drawing attention to the concern about the need for safety strategies for gene drives and for surveillance for people not employing such strategies. Increased diversity is often associated with healthy ecosystems, but each intentional release of new organisms into the wild (whether by “nat-

ural” random mutation, by transgenics, or by nontransgenic editing) should be carefully assessed first.

**Henry T. Greely:** Modified organisms might harm the environment, whether through an accidental escape from the laboratory or intentional release. Think of your least favorite invasive species—kudzu, Dutch elm disease, the starling in the US, the rabbit in Australia. Genomic engineering could produce more. Even worse, terrorists (or criminals) could use this to make pathogens for biowarfare or extortion. I'm excited about the nonhuman uses but they need to be known in advance, regulated, and followed after release.

**Françoise Baylis:** As Branden Allenby and Daniel Sarewitz explain, in their recent writings on the technohuman condition, we are part of a very complex networked system, the boundaries of which are difficult to determine. Try as we might, the ecosystem we inhabit is not subject to our understanding or control (viz. exponential population growth, finite space, limited resources, climate change). We act, however, as if this complex networked system was merely “complicated, messy, less predictable or understandable” than it might otherwise be. In addressing the complexity, messiness, and unpredictability, we erroneously assume a certain order and take comfort in the use of tools we have engineered to achieve clearly defined goals. This orientation explains, in part, intentional actions with unintended consequences, such as the introduction of rabbits and poisonous toads in Australia, mongoose in the Hawaiian Islands, purple loosestrife in New Zealand, and kudzu in the US.

All of this to say that we err in presuming an ordered determined world where we can simply take over the evolutionary story. Ours is a very complex networked system and we forget this at our peril. We need considerably more humility in contemplating whether to put our oar in waters that are not merely opaque and turbulent, but unfathomable.

**Charis Thompson:** My sense is that the environment is generally quite capacious and can tolerate gene tinkering because it is the way of “natural” evolution, but we are on the cusp of several tipping points (extinction, fresh water depletion, catastrophic climate change) so even small environmental destabilizations should be treated very carefully. Diversity per se is not necessarily a good thing itself, if it comes without the benefits of coevolution, including ecological niche, a degree of immunity, and intergenerational survival.

**Gerold Schmitt-Ulms:** Humans have continually altered the environment ever since they abandoned their hunter-gatherer lifestyle. Over time we have learned to

improve harvest yields by techniques ranging from careful selection to genetic manipulation. CRISPR-Cas9–related genome engineering could profoundly accelerate our ability to shape the natural world around us. I am highly critical of such an interventionist approach that sets free gene-manipulated organisms at this time because of our rudimentary understanding of the complex biological interplay of the environment. Currently, a compelling argument cannot be made that genetically modified crops are essential for human survival. Instead, I would argue that existing food shortages are not the consequence of a fundamental scarcity of foods but a result of unequal distribution. However, I am not fundamentalist in this matter and, just as I am supportive of responsible research that explores the use of CRISPR-Cas9–related technologies to improve human health, I am also supportive of efforts to understand how food sources could be improved through genetic manipulation. Undertaken responsibly, this research may teach us lessons that could become essential for human survival in the future.

**What do you think will be the most useful clinical/societal application of this or a similar system in the future?**

**George M. Church:** (a) Reducing risk to embryos and abortions—spontaneous and induced (see question 5), (b) gene drives for malaria (see question 9), and (c) increasing safety of xenotransplantation.

**Henry T. Greely:** It should greatly improve our ability to manipulate life, to feed and to provide energy for humans while preserving and even restoring or otherwise improving the environment. It should help make classic gene therapy, which has been 5 years in the future for the past 35 years but now really is close, better. And it may be useful in surprising ways to help stop infectious diseases (change mosquitoes to stop malaria) or make better use of our microbiomes for our own health and comfort.

**Françoise Baylis:** The most useful clinical application of CRISPR-Cas9 or a similar system will be for the somatic cell treatment of single-gene defects that result in conditions that are lethal within the first weeks to years of life. This is a very small set of conditions.

I can't even begin to imagine the most useful societal application of CRISPR-Cas9 or a similar system given my beliefs about the complexity of the world in which we live, and my concerns about the hubris motivating those who embrace volitional evolution.

More generally, in thinking about possible clinical and societal benefits, it is worth thinking about useful preclinical applications of CRISPR-Cas9 or a similar system. Gene editing technology does not have to be used to directly correct a gene abnormality in a human. It can be

used in cell-based and preclinical animal models (like zebrafish) to replicate specific human mutations to better understand the biology and to test therapeutics. This could lead to less controversial, less risky, and more effective therapeutic interventions.

**Charis Thompson:** I think CRISPR is most useful for the basic biology it is revealing; I have no doubt that all kinds of clinical and societal dimensions of this will unfold in the years to come. I think the second most important is in drug discovery, including moving slowly but surely from animal models toward in vitro humanized organoid dish models. Finally, I think there is the potential to rid us of some of the more debilitating diseases that are currently fatal. It is vital, however, that the voices of those living with the diseases or traits or differences in question be central in any decision-making apparatus about which conditions to use gene editing for.

**Gerold Schmitt-Ulms:** The most useful application of this technology for human health and society will be in translational research. Amongst a myriad of potential applications, the ability to model critical aspects of diseases in eukaryotic cells or model organisms stands out. This unprecedented access to disease models will help us dissect the complex molecular interactions underlying diseases and, in turn, will greatly support ongoing efforts to derive selective diagnostics and treatments for them.

A profound long-term benefit of this technology may emerge from the manipulation of eukaryotic pathogens or the vector organisms transmitting them with a view to selectively disarm or ameliorate their human pathogenicity. The list of diseases this general concept could be applied to is long, and it includes prevalent diseases in the tropics and temperate regions, including malaria, leishmaniasis, dengue fever, and Lyme disease. However, this potential application raises profound ethical questions and technical challenges. Before releasing genetically engineered organisms into the wild, it will be critical to verify that the engineered genetic element designed to spread in a population does not cause undesired disturbances to the ecosystem of the respective pathogen or vector. Compared to other pathogen eradication strategies that have been applied in the past, including vaccination programs or the wide-spread use of pesticides, this approach may eventually not only become more effective but may also prove to be more enduring and to cause less ecological damage.

**Could this technology favor the rich people, to increase their advantage over the poor?**

**George M. Church:** Yes or it could be used to greatly help the poor. It is up to all of us to work hard toward the latter. Examples: (a) CRISPR-gene-drives are probably

far less expensive than vaccines and classical (small-molecule) antibiotics, which have not been ideally effective for malaria, dengue, and nematode diseases—which afflict millions of the poorest people in the world. (b) Genome sequencing has come down in price 3-million-fold and continues to drop—providing preventative medicine that can be much more affordable than reactive medicine or no medicine. (c) For people who can only afford bare minimal foods, agricultural advances like golden rice could save millions of lives.

**Henry T. Greely:** It could if we let it, which makes it no different from any other useful technology. Vigilance will be needed, not of the technology but of the society.

**Françoise Baylis:** The challenge in answering this question is whether to think about this intranationally or internationally. If somatic gene editing ever becomes a safe and effective therapeutic intervention for one or more discrete conditions, there is reason to believe that it will only be available in high- and some middle-income countries. I cannot imagine this as a priority in countries that struggle to provide their population with access to basic healthcare.

In response to this concern some will argue that, as with other technologies, in time, somatic gene editing will be affordable for the masses. This is hard for me to imagine, however. In a country like the US that does not have a universal healthcare system, I can't see the masses having access to this kind of personalized medicine. As well, I expect the same will be true for countries with universal healthcare. Public health needs will always be a priority over personalized medicine.

As such, somatic gene editing does not raise new health equity issues, but rather exacerbates existing social injustice both inter- and intranationally. In a world that joyfully embraces capitalism it is hard to know how best to address this issue. In all aspects of life, the rich have an advantage over the poor as they can purchase what others can only dream of, and frequently they do so with impunity (oblivious to the harmful consequences of their actions).

**Charis Thompson:** Yes, especially in countries without universal healthcare but with biomedical investment (most notably the US, but also many other countries), this technology is likely to fall into existing patterns of discrimination and inequity, unless we explicitly prevent it from doing so (see above). The crucial elements are to have the right people opt in—starting with those with the condition in question and those without vast resources at the table—and to make sure that monitoring is comprehensive and that these social monitoring bodies have real teeth, being able to intervene and correct the path that individual, biomedicalizing (or industry or military) research is going.

**Gerold Schmitt-Ulms:** It is a sad truism that technological advancements generally tend to benefit wealthier segments of societies first. This technology will be no exception, and it is to be expected that access to certain CRISPR-Cas9 applications will first become available in places that have a well-functioning healthcare system.

Individual benefits of this nature may manifest through genome editing of somatic cells in several specific diseases. For example, if one could restore the wild-type allele coding for the cystic fibrosis transmembrane conductance regulator protein in a small percentage of lung epithelial cells of individuals afflicted with cystic fibrosis, a pronounced benefit for their lung functions would be expected. Similarly, in certain immunodeficiency diseases or leukemias caused by mutated hematopoietic stem cells, CRISPR-Cas9 might be employed to restore the wild-type gene sequence underlying the disease.

Fortunately, the 2 areas in which this technology may have the most pronounced impact, (i) its ability to greatly accelerate our understanding of the biological world around us, including how to diagnose and treat diseases, and (ii) the possibility it offers for subtly changing our environment to disarm pathogens or the vectors that transmit them, are of such a nature that they may eventually benefit all. Thus, compared to the challenges posed by the potential abuse of this technology, unequal opportunities to access this technology for specific personalized medical applications may be a relatively small concern.

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