

# CRISPR: What Potential? What Peril? Who Decides?

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The human genome contains around 6.2 billion nucleotides, usually referred to using the letters A, C, G and T. By contrast, the Bible has only about 3.5 million letters in it. Imagine how difficult it was to edit the entire Bible before the age of computers and word processing. Now imagine editing a book almost one thousand times larger and one can get the sense of the enormity of the challenge of reading and correcting the human genome.

Today, however, we can easily download a copy of the Bible, search for specific words or phrases, cut and paste any part, or rewrite what we want. Applying this kind of editing technology to the human genome is what is behind the current excitement about

the scientific breakthrough called CRISPR—which stands for Clustered Regularly Interspaced Short Palindromic Repeat. This name comes from the genetic structure that was discovered in many bacteria and archaea which allows these organisms to build up a collection of genetic sequences acquired from the viruses that attack them. These stored sequences are then used as a kind of immunity defense when the organism is attacked again by the same viruses. This defense works by matching up the stored sequences with the attacking virus's genetic sequence which signals the Cas9 protein (CRISPR-associated protein 9), or similar proteins, to chop up the invading viral genome. This combination of adaptable, yet relatively

precise, target sequence recognition and ability to cut DNA is what was so exciting to genetic researchers. [see figure on page 6]

While researchers have been using much more limited genetic editing technologies since the 1970s (e.g., restriction endonucleases), they have constantly worked to develop technologies that would allow them to target accurately any DNA segment in the human genome (or even multiple targets), edit it as desired (add, delete, substitute any number of nucleotides), and do all this at a relatively reasonable cost. The CRISPR-Cas9 breakthrough represents the first opportunity to achieve this kind of genome editing in bacteria, plants, animals and humans.

While CRISPR technology has these significant benefits, it also has some troubling limitations. Especially in its potential application to humans, there is concern regarding off-target effects, i.e., the constant challenge for genetic therapies of genetic changes that are made at sites in the DNA that are not being targeted that may disrupt normal cell functioning.

In response to this challenge, research is being done to reduce off-target effects through improved design of the guide

RNAs used for targeting, and to develop Cas9 variants or find alternative proteins to cut the DNA. In addition, the delivery of the components of the CRISPR-Cas9 system into cells can be difficult due to their relatively large size. Research has already generated several alternatives to the Cas9 protein that include smaller and more accurate DNA cutting systems, and even an enzyme, C2C2, that cuts RNA instead of DNA.

Still, CRISPR remains the most affordable and versatile genome editing technique widely available. That is why the CRISPR/Cas9 system has been the target of huge investment, wide publicity, and an ongoing major patent fight between the Broad Institute of MIT and Harvard and the University of California at Berkeley. Though this patent case has slowed somewhat the use and development of this exciting new technology, application of CRISPR-Cas9 has already moved into the realm of clinical trials.<sup>1</sup>

China has initiated the first clinical trial using the CRISPR-Cas9 system. CRISPR is being used to knockout the PD-1 gene from patients' T cells to stimulate the patients' immune systems to more

aggressively attack their metastatic non-small cell lung cancer.<sup>2</sup> T cells are a type of white blood cell that scans for cellular abnormalities or infections. In addition, three more clinical trials are lined up in China to begin recruiting patients that will employ CRISPR to knock out PD-1 in the T cells of patients with bladder, prostate and renal cancers.

In the U.S., the University of Pennsylvania is poised to lead a clinical trial that will similarly target T cells from patients with several types of cancers. The 18 patients chosen will have their T cells removed and three CRISPR interventions done on them to facilitate T cells targeting the tumor and to prevent the tumor from disabling the T cells. After being checked for accurate CRISPR editing, the T cells will be infused back into the patients. This trial is being designed primarily to demonstrate safety rather than effectiveness, and it will take place in Pennsylvania as well as in California and Texas.<sup>3</sup> Now that the door is open, it is safe to say that many more clinical trials targeting a wide array of genetic diseases will soon be proposed—if the current trials do not disclose some unexpected harm to patients from the CRISPR treatment.

The clinical trials I have described above all fall within the category of gene therapies that target somatic cells from one patient at a time. This type of genetic intervention has had broad support among researchers, ethicists and health policy makers for about 30 years. This broad support falls apart when genetic interventions that would potentially be passed from one generation to the next are considered. Such germline genome editing raises concerns regarding both the safety of such interventions (i.e., mistakes that would be passed on to future generations) and the normality or sanctity of human nature (i.e., germline genetic changes that would change who we are as human beings). The discussion of germline genome editing in plants, animals, and especially humans, is complex and contentious, and, hence, cannot be reviewed in this brief article.<sup>4</sup> These developments raise serious issues of safety and the appropriateness of changing the genomes of living organisms, especially humans. I will cite two uses of CRISPR that I find particularly troublesome.

- 1) Human Germline Engineering. If one desires to use CRISPR to alter *all* the cells of a human being, including sperm and eggs, then one

might argue that logistically the best time to do that would be the embryo stage of development, as there are relatively few cells wherein one would have to change the DNA to affect the entire human being. This may have been the reasoning behind the research done on non-viable human embryos by researchers in China who published an article in 2015, describing their attempts to use CRISPR to modify the genes that cause beta-thalassemia.<sup>5</sup> Since it was rather surprising to many that such an experiment had been both approved and published, it set off worldwide ethical debate. There were responses both in scientific journals and international meetings that the potential impacts of CRISPR and other genome-editing technologies were of such magnitude that extensive public engagement would need to take place before applications such as human germline interventions could occur. Despite these appeals for broad public engagement, additional human embryo research projects have since been approved in the UK, Sweden, and again in China. Though these

projects either involve nonviable embryos, or a promise not to implant the altered embryos in a woman's uterus, they clearly are oriented towards human embryo genome editing for reproductive purposes. Hence, regardless of one's position on the moral status of human embryos, or human germline engineering, this research has gone forward without the kind of global public dialogue that was proclaimed to be necessary.

## 2) Do-It-Yourself CRISPR editing.

The other use of CRISPR that requires public review is the Do It Yourself CRISPR movement. For \$150, anyone can purchase a home CRISPR kit from a company called The Open Discovery Institute (The ODIN) in Calif. The company has already sold thousands of kits, mostly to people who are curious about science and CRISPR, enabling them to experiment at home. The company's founder and CEO, Josiah Zayner, and other like-minded "biohackers," believe science should be available to everyone. But is this

true for CRISPR? After all, considering the potential CRISPR has for harm as well as benefit, should it be so available to the public? It is already too late for CRISPR, but the public will need to weigh in on how to balance public safety (regulation) vs public access (innovation).<sup>6</sup>

CRISPR-Cas9 has made genome editing available to all. It has dramatically raised the stakes of the ethical issues going forward—especially the need for robust public engagement.

What role should we, and our institutions, play regarding this rapidly developing biotechnology?

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<sup>1</sup> Dermot Martin, “Who Owns CRISPR?” <http://www.labnews.co.uk/features/owns-crispr-17-01-2017/>

<sup>2</sup> NCT02793856 “PD-1 Knockout Engineered T Cells for Metastatic Non-small Cell Lung Cancer in Sichuan, China,” [www.clinicaltrials.gov](http://www.clinicaltrials.gov)

<sup>3</sup> “First CRISPR Clinical Trial Gets Green Light from U.S. Panel,” Sara Reardon, *Nature*, 22 June 2016, doi:10.1038/nature.2016.20137

<sup>4</sup> For a general review of the ethics of genetic interventions see,

<https://www.chausa.org/publications/health-progress/article/september-october-1999/ethical-issues-in-genetics>. For a more indepth analysis of the role of religion and philosophy in assessing human genome editing see, Kevin FitzGerald, S.J., “The Need for a Dynamic and Integrative Vision of the Human for the Ethics of Genetics,” in *Genetics, Theology, and Ethics*, ed. Lisa Cahill, The Crossroad Publishing Co., 2005.

<sup>5</sup> “CRISPR/Cas9-mediated Gene Editing in Human Triprenuclear Zygotes,” Liang et al, *Protein & Cell*, May 2015, Volume 6, Issue 5, pp 363–372.

<sup>6</sup> “CRISPR for the Masses,” Rachael Moeller Gorman, <http://www.biotechniques.com/news/CRISPR-for-the-Masses/biotechniques-365397.html?autnID=344253#.WIEs1IWcE2w>