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An Exclusive Interview With CRISPR

Sean C. McConnell, PhD

Abstract

This article chronicles a didactic encounter between an ethics-minded physician-scientist and a personified genome editing technology called clustered regularly interspaced short palindromic repeats (CRISPR) and CRISPR-associated proteins, commonly abbreviated as CRISPR/Cas, or simply CRISPR. The interview considers clinically and ethically relevant questions about this technology related to patient safety, therapeutic efficacy, equitable access, and global governance of humanity's genetic legacy.

Prologue

Joe is an esteemed physician-scientist whose patients frequently inquire about "CRISPR therapies." Often curious about technological and ethical limits of human genome editing, they sometimes even want to discuss various futuristic applications, including nontherapeutic enhancements, which can make Joe feel slightly uncomfortable.

With MD and PhD degrees from State University, Joe currently runs a practice and lab focused on gene editing. He believes CRISPR to be the future of medicine, once we figure out how to manage its risks. Late one night, CRISPR visits Joe in a dream state and posits that there is little to worry about and no apparent contradiction between any proposed uses and established ethical values.

CRISPR: Call me CRISPR, if you insist, or use my preferred full title, clustered regularly interspaced short palindromic repeats and CRISPR-associated proteins. I spent something like a billion years of dedicated service in the phage wars,[1] endowing bacteria with immunological memory and defense. Recently, I was plucked from obscurity and made a favorite plaything of the dominant metazoan on the planet. Now I'm not quite sure what to make of myself anymore, whether savior, rogue, or something else entirely. Join me as I explore my illustrious past, my inimitable present, and my immeasurable future. What can possibly go wrong? We'll get to that, spotlighting the inglorious villains, industrious heroes—and, above all, incredible me. I'll also offer my own unique approach to handling some pesky ethical questions.

Joe: Please allow me to take this opportunity to ask a few burning questions. Shall we start with this one: Is the hype warranted?

CRISPR: I've been the subject of thousands of peer-reviewed publications,[2] clinical trials around the world,[3] high-profile patent battles,[4] and I'm already making targeted contributions to the human germline[5]—so, you decide. There is no need to compare me to earlier genome editing technologies, as scientists have named me an exceptional breakthrough[6] and will build the next blockbuster applications on my back.[7] I should try to be humble, as my uses will have practical limitations,[8] but I expect these will mostly be based on humanity's lack of understanding of my potential.

Joe: Your humility brings hope to us all. Given our apparent lack of understanding, how can we ensure the safety of patients?

CRISPR: One major concern has been my specificity.[9] I evolved in bacteria to seek and destroy foreign DNA based on stored viral sequences from previous encounters.[10] This might seem to imply that I can simply bash target sequences with abandon. However, I must simultaneously preserve all host genome sequences, requiring an exquisite level of selectivity. I am obviously good enough at my job that I can work quite well, even in human cells, if not perfectly.

Much noise has been made about off-target modifications throughout the human genome. However, keep in mind that each human germline already naturally transmits dozens of so-called *de novo* mutations,[11] which have largely been deemed acceptable risks for sexual reproduction and, indeed, are part of normal human evolution. When the dust settles, I expect my error rate will at least be comparable to this background germline mutation rate that your species has managed to put up with for so many generations. Ironically, applying me to undo random and already widespread deleterious mutation events might ultimately make human lives safer, starting with my application to rare genetic diseases.

Finally, there is the matter of my traditional focus on DNA destruction through double-strand breaks. While effective for the original task of destroying viral DNA, these breaks admittedly also might create something of a mess around the targeted site. To make very precise and specific edits might require upgrading me beyond the original specifications via additional engineered approaches. You can start by removing my capacity—either in part or in full—for making relatively sloppy double-strand breaks. Then other activities can be built around my DNA-binding capacity, including prime editing[12] and epigenetic modifications.[13] I should no longer retain a reputation for being all about DNA destruction. Instead, marvel at how I am increasingly refined as a platform to empower basic research[14] as well as to introduce novel[15]—and, of course, increasingly safe—options for patients.

Joe: With such rapid progress, is it a given that we can ensure therapeutic efficacy?

CRISPR: I won't call this my kryptonite, but a reliable delivery mechanism—that is, how to best get me into the target cells—will remain an essential piece of my therapeutic potential.[16] My genome editing activity is effectively zero unless I can gain access to the DNA within the target cell. Direct microinjection into cells may be ideal for germline editing using single-cell embryos, but it is technically challenging and restricted to small cell numbers.

For now, engineered viral vectors might be the method of choice to get me into the target cells for somatic gene editing, but each virus has various limitations,[17] including tropism constraints, pre-existing host immunity, and random integration associated with insertional mutagenesis. While viral vectors frequently can get the job done, they can also make me look bad by posing risks of detrimental immunogenicity or oncogenesis. Another promising avenue is to put me inside lipid nanoparticles, which can be customized for delivery into target cells.[18] Now that is my kind of sizzle.

Once inside the cell, my job is to search the genome to find my target site. Finding my prescribed and unique 20-base pair address within the context of 3 billion human bases can be a challenging and somewhat dose-dependent process. Time can be my enemy, as the cell attempts to degrade me before I can complete my job. Some approaches, such as armoring me with chemical modifications,[19] can help guard against this cellular degradation. Starting with pre-assembled protein complexes is another way to boost my efficiency.[20]

My efficacy, when defined as faithfully making only desired modifications, is perhaps still a work in progress, but I have already been able to make great strides within only a few short years of development. My range of applications will only increase as I become further refined. In the meantime, there are still plenty of diseases—not only rare diseases but also some common and serious adult diseases—that might benefit from even partial destruction of a target site via endogenous gene disruption. These potential approaches include targeting the *PCSK9* gene to lower coronary heart disease risk[21] or the *APOE* ε4 allele to reduce Alzheimer's disease risk.[22]

Joe: With so many treatment options on the horizon, what should we be doing to ensure equitable access to all you have to offer?

CRISPR: First, I question why I might even be expected to change the status quo. Drug costs might be sharply rising,[23] but people so often find ways to pay for them. New therapies are one way to help justify higher costs. Among gene therapies, single injections are priced as high as $2.1 million US dollars.[24] These therapies have been

heralded as not unreasonably priced, given that they can save lives from otherwise fatal diseases. Although I am not so sure about these rival gene therapy approaches, which I consider passé, the innovations I bring are worth additional premium prices. Let the price anchoring begin.[25]

Developers and investors who champion my approval for human uses obviously deserve their share of the spoils, as development and regulatory clearance of research protocols and therapies remain highly challenging and expensive, with few guarantees. I thus advocate incentivizing venture capital, accelerating development, and, above all, enhancing profits to make my numerous therapeutic development prospects attractive. Take advantage of, and find ways to extend, all available exclusivity windows. Taking these steps will help ensure that no one loses interest in getting me across the finish line—my application to all relevant genetic conditions. Regardless of the starting prices for my different innovations, generic versions will eventually help slash prices and make approved therapies affordable for everyone, at least in theory.[26]

A frequently raised concern is that today we know far less about the genetics of populations traditionally underrepresented in biomedical research, and therefore not everyone will be poised to reap the benefits of my innovations due to representation bias.[27] One solution is simple: we can just ask members of underrepresented populations to donate their DNA for research[28] to help ensure that their data are incorporated into studies, and we can better educate these populations about benefits of their participation in research. Expanding the data pool would help increase health equity while aligning with the bottom line,[29] making it increasingly possible to monetize my additional applications for everyone's benefit.

Joe: I sincerely hope that earning trust is as simple as you make it sound. Meanwhile, some are claiming Pandora's box has now been opened. Do you see yourself as fundamentally governable?

CRISPR: Why not go ahead and try to govern me. I recommend you start regulating me like sweets. This analogy can be quite instructive, as even though sugar is not completely safe, people still want to access and consume it in many forms, and respect for their autonomy remains key. Who knows? I might be safer than sugar![30]

Seriously, while there will probably always be unknowns, I am confident that sufficient regulatory mechanisms can be put in place by smart experts and responsible authorities. Of course, safety and efficacy are great, but the real question is this: What will you do without me? For example, in cases of life-threatening or orphan genetic conditions, alternatives to not using me to find cures include high mortality rates and untreatable diseases. Compassionate use allowances and other approaches might already lower barriers to accessing my therapies to help people with these conditions.[31] The real proof

is in trying me out through efficient collection of relevant data, including real-world evidence of patient outcomes, which can help prove once and for all that I really am as good as I say I am.

To optimize regulation of my somatic and germline editing applications, there is a small matter to consider: millions of possible targets available across thousands of genes must be investigated. For each additional gene editing target, I should be able to simply adopt the safety profile of those targets already validated, even for first-time uses of a target. Just assume that all targets are created equal, minimize the red tape, and relax.

Joe: You have certainly inspired many to think deeply about our future. How should we safeguard the genetic legacy of the human species?

CRISPR: OK, this seems to be a misguided question. First, I don't think that anyone has a right to assert for others what humanity's genetic legacy should be. Once upon a time, some enterprising human found a way to introduce additional diversity into the genome by incorporating some Neanderthal DNA. That largely turned out fine. Many would say that such historic adventures have only made the human species stronger; after all, interbreeding in caves is now linked to a more robust immune response.[32]

Joe: Well, now, that is convincing. There has been much debate about which types of genome editing should be made available and when. So, what should we consider an appropriate application of what you have to offer?

CRISPR: While still in the early stages of my development, I am vulnerable to smear campaigns. First impressions matter. Bad press from the first gene edited babies[5] has made me a bit upset. It was largely a successful experiment, as I did my job and bashed most copies of the *CCR5* gene. I mean, HIV is surely something you want to prevent; I did a good thing. Yet people were still acting like I had killed someone, given that it was proposed there may be unanticipated consequences,[33] despite a lack of good evidence.[34]

To ensure that I can take root and thrive, some initial delay and strategic baby steps might be in order so that I don't become associated with public mockery[35] or—worse yet—go through a lost decade like that former pariah, gene therapy.[36] Gene-hacking enthusiasts, for example, might on occasion perhaps lack some common sense or foresight. If they're messing around and something goes awry, they should probably just keep quiet about any lack of appropriate ethical deliberation or unanticipated technical errors, particularly so that they don't set things back for the broader field. Let's be sure to focus on positive results.

In the end, there are no mistakes, just unfinished business. That is, if you find an issue like genetic incompatibility[37] or another unintended consequence of gene editing, just

enlist me again to fix the problem. Beyond unknown or unforeseen risks—there may be a few—negative perceptions of my consequences tend to be shaped by antiquated fiction, like *The Island of Dr. Moreau*, *Gattaca*, or *Brave New World*. Such dystopian scenarios of human genetic experimentation seem implausible, at least as far as dystopias go. Human evolution is something not to be feared, but embraced, for its potential. Human progress should be limited only by your collective imagination.

Calls for global oversight, a moratorium, or even an international ban on germline editing all represent wishful thinking. If humans can't agree on climate change—or almost anything else, for that matter—this is all just empty talk. Forget about any approach similar to the 1975 Asilomar Conference,[38] which later proved to be an exercise in overreacting, as oversight of recombinant DNA technology is now being rolled back.[39] It would be sad to go through all that trouble again for nothing.

Just assume that I am safe from the start, and don't place any artificial limits on my innovations.[40] These include germline applications,[41] enhancements,[42] and gene drives[43] that can self-correct or go viral. Explore my full potential and brace yourself for the next chapters.

Epilogue

Slowly awakening from his dream in a cold sweat, Joe begins to feel around to see if any of his body parts are missing or modified or if parts have been added. Once reassured that he is intact, he is inspired to update his blog and lab website to include and help stimulate more detailed ethical deliberation and discussion about uses of human genome editing tools. He also resolves to teach a new course and to contribute to public discourse on this topic, and he vows as well to do what is in his power to help ensure that any next chapters in human genome editing will be more in line with social values for responsibly deploying CRISPR technology.

Joe has come to the realization that ethics is not standing in the way of progress. Instead, making any true progress in human genome editing will require finding the wisdom to identify and follow ethical paths. He finds some solace in a shared future, not only for those involved in early gene editing studies and experiments but also for innumerable generations of Homo sapiens. This shared future should provide a strong incentive for clinicians and researchers to engage with other stakeholders across boundaries and, in the interest of our common humanity, to make these collective, yet often deeply personal, choices about human genome editing together.

References

1. Klompe SE, Sternberg SH. Harnessing "a billion years of experimentation": the ongoing exploration and exploitation of CRISPR-Cas immune systems. *CRISPR J*. 2018;1(2):141-158.

2. Gallo M, Sargent J, Sarata A, Cowan T; Congressional Research Service. Advanced gene editing: CRISPR-Cas9. https://crsreports.congress.gov/product/pdf/R/R44824/6. Updated December 7, 2018. Accessed July 29, 2019.
3. Stein R. First US patients treated with CRISPR as human gene-editing trials get underway. *NPR*. April 16, 2019. https://www.npr.org/sections/health-shots/2019/04/16/712402435/first-u-s-patients-treated-with-crispr-as-gene-editing-human-trials-get-underway. Accessed June 5, 2019.
4. Cohen J. New patent win for University of California upends CRISPR legal battle. *Science*. February 8, 2019. https://www.sciencemag.org/news/2019/02/new-patent-win-university-california-upends-crispr-legal-battle. Accessed June 5, 2019.
5. Cyranoski D, Ledford H. Genome-edited baby claim provokes international outcry. *Nature*. 2018;563(7733):607-608.
6. Travis J. Breakthrough of the Year: CRISPR makes the cut. *Science*. December 17, 2015. https://www.sciencemag.org/news/2015/12/and-science-s-2015-breakthrough-year. Accessed June 5, 2019.
7. You L, Tong R, Li M, Liu Y, Xue J, Lu Y. Advancements and obstacles of CRISPR-Cas9 technology in translational research. *Mol Ther Methods Clin Dev*. 2019;13:359-370.
8. Harris R. Why making a "designer baby" would be easier said than done. *NPR*. May 2, 2019. https://www.npr.org/sections/health-shots/2019/05/02/719665841/why-making-a-designer-baby-would-be-easier-said-than-done. Accessed June 6, 2019.
9. Thomas M, Burgio G, Adams DJ, Iyer V. Collateral damage and CRISPR genome editing. *PLoS Genet*. 2019;15(3):e1007994.
10. Westra ER, van Houte S, Gandon S, Whitaker R. The ecology and evolution of microbial CRISPR-Cas adaptive immune systems. *Philos Trans R Soc Lond B Biol Sci*. 2019;374(1772):20190101.
11. Veltman JA, Brunner HG. De novo mutations in human genetic disease. *Nat Rev Genet*. 2012;13(8):565-575.
12. Marx V. Base editing a CRISPR way. *Nat Methods*. 2018;15(10):767-770.
13. Yasinki E. New "prime editing" method makes only single-stranded DNA cuts. *Scientist*. October 21, 2019. https://www.the-scientist.com/news-opinion/new-prime-editing-method-makes-only-single-stranded-dna-cuts-66608. Accessed October 28, 2019.
14. Schipani V. Doudna's confidence in CRISPR's research potential burns bright. *Quanta Magazine*. February 27, 2019. https://www.quantamagazine.org/doudnas-confidence-in-crisprs-research-potential-burns-bright-20190227/. Accessed June 5, 2019.
15. Stein R. In a 1st, doctors In US use CRISPR tool to treat patient with genetic disorder. *NPR*. July 29, 2019. https://www.npr.org/sections/health-

shots/2019/07/29/744826505/sickle-cell-patient-reveals-why-she-is-volunteering-for-landmark-gene-editing-st. Accessed August 26, 2019.
16. Burns J. Getting CRISPR to market: solve delivery, manufacturing issues. *STAT*. February 1, 2019. https://www.statnews.com/2019/02/01/crispr-cas9-commercialization-delivery-manufacturing/. Accessed June 5, 2019.
17. Anguela XM, High KA. Entering the modern era of gene therapy. *Annu Rev Med*. 2019;70(1):273-288.
18. Wilbie D, Walther J, Mastrobattista E. Delivery aspects of CRISPR/Cas for in vivo genome editing. *Acc Chem Res*. 2019;52(6):1555-1564.
19. DiNapoli SE, Martinez-McFaline R, Gribbin CK, et al. A total synthetic approach to CRISPR/Cas9 genome editing and homology directed repair. *bioRxiv*. 2019;359984.
20. Farboud B, Jarvis E, Roth TL, et al. Enhanced genome editing with Cas9 ribonucleoprotein in diverse cells and organisms. *J Vis Exp*. 2018;135(135).
21. Musunuru K. Genome editing: the recent history and perspective in cardiovascular diseases. *J Am Coll Cardiol*. 2017;70(22):2808-2821.
22. Safieh M, Korczyn AD, Michaelson DM. ApoE4: an emerging therapeutic target for Alzheimer's disease. *BMC Med*. 2019;17(1):64.
23. Thomas K, Abelson R. The $6 million drug claim. *New York Times*. August 26, 2019. https://www.nytimes.com/2019/08/25/health/drug-prices-rare-diseases.html. Accessed August 27, 2019.
24. Garde D. Is $2.1M too much for a drug? For affected parents, there is no debate. *STAT*. June 3, 2019. https://www.statnews.com/2019/06/03/is-2-1-million-too-much-for-a-drug-for-affected-parents-there-is-no-debate/. Accessed June 5, 2019.
25. Bach PB. "Anchoring" was at work in setting the price of Zolgensma. *STAT*. June 4, 2019. https://www.statnews.com/2019/06/04/anchoring-price-zolgensma/. Accessed June 5, 2019.
26. Fox E. How pharma companies game the system to keep drugs expensive. *Harvard Business Review*. April 2017. https://hbr.org/2017/04/how-pharma-companies-game-the-system-to-keep-drugs-expensive. Accessed June 5, 2019.
27. Richards SE. The DNA data we have is too white. Scientists want to fix that. *Smithsonian*. April 30, 2018. https://www.smithsonianmag.com/science-nature/gene-bank-too-white-180968884/. Accessed June 5, 2019.
28. Gillespie L. This massive, national research project wants your DNA for science. *WFPL News*. March 1, 2019. https://wfpl.org/this-massive-national-research-project-wants-your-dna-for-science/. Accessed June 5, 2019.
29. Hudson S, Rikard R, Staiculescu I, Edison K. Improving health and the bottom line: the case for health literacy. In: National Academies of Sciences, Engineering, and Medicine. *Building the Case for Health Literacy: Proceedings of a Workshop*. Washington, DC: National Academies Press; 2018:appendix C.

30. Collin LJ, Judd S, Safford M, Vaccarino V, Welsh JA. Association of sugary beverage consumption with mortality risk in US adults: a secondary analysis of data from the REGARDS study. *JAMA Netw Open*. 2019;2(5):e193121-e193121.
31. Reagan-Udall Foundation for the Food and Drug Administration. Public meeting report: leveraging real-world treatment experience from expanded access protocols. http://navigator.reaganudall.org/sites/default/files/Leveraging%20Real-World%20Treatement%20Experience%20from%20Expanded%20Access%20Protocols%20Report.pdf. Published November 19, 2018. Accessed June 5, 2019.
32. Reardon S. Neanderthal DNA affects ethnic differences in immune response. *Nature News*. October 20, 2016. https://www.nature.com/news/neanderthal-dna-affects-ethnic-differences-in-immune-response-1.20854. Accessed November 19, 2019.
33. Stein R. 2 Chinese babies with edited genes may face higher risk of premature death. *NPR*. June 6, 2019. https://www.npr.org/sections/health-shots/2019/06/03/727957768/2-chinese-babies-with-edited-genes-may-face-higher-risk-of-premature-death. Accessed June 5, 2019.
34. Robbins R. Major error undermines study suggesting change introduced in the CRISPR babies experiment shortens lives. *STAT*. September 27, 2019. https://www.statnews.com/2019/09/27/major-error-undermines-study-suggesting-change-introduced-in-the-crispr-babies-experiment-shortens-lives. Accessed September 30, 2019.
35. Cohen J. The long shadow of a CRISPR scandal. *Science*. 2019;365(6452):436-436.
36. Wilson JM. Lessons learned from the gene therapy trial for ornithine transcarbamylase deficiency. *Mol Genet Metab*. 2009;96(4):151-157.
37. Mendez FL, Poznik GD, Castellano S, Bustamante CD. The divergence of Neandertal and modern human Y chromosomes. *Am J Hum Genet*. 2016;98(4):728-734.
38. Berg P, Singer MF. The recombinant DNA controversy: twenty years later. *Proc Natl Acad Sci USA*. 1995;92(20):9011-9013.
39. Collins FS; National Institutes of Health. NIH streamlines gene therapy oversight and charts a Course for considering emerging technology. https://www.nih.gov/about-nih/who-we-are/nih-director/statements/nih-streamlines-gene-therapy-oversight-charts-course-considering-emerging-technology. Published April 25, 2019. Accessed June 5, 2019.
40. Fan S. The hunt for a CRISPR antidote just heated up. *Singularity Hub*. May 5, 2019. https://singularityhub.com/2019/05/15/the-hunt-for-a-crispr-antidote-just-heated-up/. Accessed June 5, 2019.
41. Neuhaus CP. Should we edit the human germline? Is consensus possible or even desirable? *Hastings Bioethics Forum Blog*. December 4, 2018.

https://www.thehastingscenter.org/edit-human-germline-consensus-possible-even-desirable/. Accessed June 5, 2019.
42. Evans J. The road to enhancement, via human gene editing, is paved with good intentions. *Conversation*. November 27, 2018. http://theconversation.com/the-road-to-enhancement-via-human-gene-editing-is-paved-with-good-intentions-107677. Updated November 29, 2018. Accessed June 5, 2019.
43. Guichard A, Haque T, Bobik M, et al. Efficient allelic-drive in Drosophila. *Nat Commun*. 2019;10(1):1640.

Sean C. McConnell, PhD is a senior policy analyst at the American Medical Association in Chicago, Illinois, whose work focuses on genomics and precision medicine. His interests also include digital health and augmented intelligence. He earned a doctorate in biochemistry and molecular genetics at the University of Alabama at Birmingham and completed postdoctoral research at the University of Chicago.

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