## Modern Prometheus

Editing the Human Genome with Crispr-Cas9

Would you change your genes if you could? As we confront the 'industrial revolution of the genome', the recent discoveries of Crispr-Cas9 technologies are offering, for the first time, cheap and effective methods for editing the human genome. This opens up startling new opportunities as well as significant ethical uncertainty. Tracing events across a 50-year period, from the first gene splicing techniques to the present day, this is the story of gene editing: the science, the impact, and the potential. Kozubek weaves together the fascinating stories of many of the scientists involved in the development of gene editing technology. Along the way, he demystifies how the technology really works and provides vivid and thought-provoking reflections on the continuing ethical debate. Ultimately, Kozubek places the debate in its historical and scientific context to consider both what drives scientific discovery and the implications of the "commodification" of life.

JIM KOZUBEK is a computational biologist living in Cambridge, Massachusetts. His science writing has appeared in *The New Hampshire Union Leader*, *The Providence Journal*, *The Boston Globe*, *The Atlantic*, and *Scientific American*.

"Prometheus Bound." Christian Schussele, unknown date.

Great gifts to mortal men, am prisoner made
In these fast fetters; yea, in fennel stalk
I snatched the hidden spring of stolen fire,
Which is to men a teacher of all arts,
Their chief resource. And now this penalty
Of that offence I pay, fast riveted
In chains beneath the open firmament.
Aeschylus (525–456BC), *Prometheus Bound*

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JIM KOZUBEK

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Sections of this book previously appeared in *The Atlantic*, *The Boston Globe* and *Scientific American*.

Between 14 October 2013 and 6 May 2016, Jim Kozubek worked as a staff scientist at the Brigham and Women's Hospital which is affiliated to the Broad Institute of MIT and Harvard. Although the Broad Institute is in Crispr genome editing research, development, and sharing, this book was developed independently of the author's Broad affiliation.

# Contents

# Acknowledgements

Thanks to my editor Katrina Halliday and her colleagues at Cambridge University Press, especially Jo Tyszka, Sarah Payne, and Leigh Mueller, for seeing the value in the story and bringing my manuscript into reality. The project had been in the works more than three years by the time I finally signed it over to the world's oldest publishing house. I first approached Emma Parry to advise my book project in January 2013 just as the Crispr-Cas9 genome editing system was beginning to surface in major science journals. I was aware of the Promethean myth, and it occurred to me that elements of the myth were congruent with the story as it was unfolding. DNA represents a natural power or force that could be expropriated by man, and this expropriation is neither right nor wrong, but comes with a steep learning curve. I was also aware of what Mary Shelley had been doing with her exegesis of the myth in her stunning novel Frankenstein, or The Modern Prometheus. As with most of the Romantic writers, Shelley's writing was primarily concerned with the march of industry and technology, and how the allure of its progress risked a marginalization of the tensions of inner life, existential problems, aptitude for coping with life, its slings and arrows, the kind of hard-won struggle that shapes a soul. Shelley began her novel in a form of epistolary, in other words, delivered as a series of letters. I initially started to build my book based on various scenes of the myth, where I connected scientific research tightly to stages of the myth. I even did try to begin it in a form of epistolary. It was Emma who pointed out that this setup for the book felt like a trap. I was boxing myself in. None of this worked, of course, and I think this is because so much of scientific progress is a gradual grind, based on small technical advances that accrue and build upon each other in stepwise fashion. Rarely do events occur in science that are entirely non-linear, and change the paradigm. Even the application of Crispr-Cas9 depends on a deep edifice of knowledge and applications, for instance, the ability to culture cells, to use viruses and other tools to get the system into cells, and decades of investigation on how genes work. All of these realities came crashing to the surface as I struggled to put the book together. It soon became clear

that the only responsible thing was to ditch my artistic impulse to shape the book on the stages of the myth, and to build it upon the more realistic and necessarily chronological events of science. That's when I decided to wrap up a complicated tale spanning more than 50 years into a chronology, and to introduce Crispr-Cas9 right up front in the book. I also made the decision to put myself in the book, as a thread of continuity that tied it up like a string. With these structural adjustments in place, and a deep dive into archive research at MIT, things began to come together. Tim Horvath, Ogi Ogas, Emily Loose, Jennifer Golliday, Lena Yarbrough, Chad Luibl, Erika Goldman, Michael Kozubek, Marcia Kozubek and Melanie Dickerson read excerpts along the way. Many scientists provided feedback on my manuscript, especially David Levine, Erik Sontheimer, George Church, Keith Joung, Janet Mertz, Richard Mulligan, David A. Williams and Emmanuelle Charpentier.

# Author's Note

This is a book about Crispr-Cas9. It is animated by many forces. I grew up reading popular science books that could be described as instructive or didactic, but I saw the trade begin to gradually drift into simplistic story-telling which was sold as self-help. To break from this trend, I set out to write in a different style, which is the tragic vein of literature. To this end, the book is injurious throughout, while taking few moral positions. It is not designed to attack or damage anyone, per se, but to describe a more realistic, harder and more complicated situation which we endure. One motivation is my interest in the rise of business elements in science; for example, the Broad Institute draws deeply on public funding, but provides an executive pay structure. In the past few decades, there has been a rise of business elements in science. The federal funding engine is decades old, and biotech-academic partnerships have exploited that to a large degree. Given how robust the biotech industry is, and how competitive academia has become over intellectual property—with substantial partnerships between industry and academia, and elite academic salaries that can exceed $1 million, and which are designed to achieve leverage in an increasingly brutal and competitive climate, I wonder if scientific institutions are maturing to a degree that they may at some point forgo federal funding. If we continue to see scientists in battles for large windfalls and rewards, I think that more taxpayers will just say, OK, then fund and take the risks yourself. Scientists should be allowed to fail, and to be free of public support, if they use the legal system to attract, protect and defend their increasing status and wealth. If anything, science may not be capitalistic *enough*. I am also interested in how scientists develop powerful marketing arms and salesmanship, while most scientists admit that their powers are truly limited, and that the genetic drivers of cancer, autism and schizophrenia will always be with us. The world as Darwin saw it was radically decentralized, deeply unsettling, and a threat to social order. By comparison, the modern scientist has become the social order, seemingly in control of nature through clandestine knowledge and access to the gene, which only a few are said to have the ability to

properly interpret. My preferred method for reporting this book is first-person narration, and I made every effort to meet its characters in person. For more than four years, I traveled to Pennsylvania, Illinois, and Washington, buried myself in the archive collection at MIT, and ran up long email correspondence. Jennifer Doudna was also writing a book on Crispr at the time, and I took care to avoid cross-pollination of ideas with her. Thus, she has a minimal presence in the story. My writing also draws on newspaper articles, journal articles, and personal conversations, and references to novels and film. It is written very much how my life is actually like, and evidences my tendency to find truth in a novel or reflection, as much as, or more so than, in primary literature. Indeed, this book arises out of my own conflict over whether to invest more energies into science or the arts and literature, and an interest in which modalities best illuminate reality. In reporting this book, I found the only thing more competitive than Crispr science, was writing about Crispr. I had titled a chapter "Gene Hackers" and written an op-ed for *The Boston Globe* titled "Would You Change Your Genes If You Could?" in 2013, a full two years before *The New Yorker* ran its story "The Gene Hackers" and splashed "Should We Edit Our Genes?" on its cover. Eric Lander wrote a perspectives piece titled "The Heroes of Crispr" after I circulated a draft manuscript of *Modern Prometheus*. Heroism, at least as I use it in my own text, does not emphasize scientific valor as a series of achievements by right-minded people. Rather, to be a hero means to be immersed in a life-world, or lebenswelt, as the philosophers call it, to navigate complicated social, cultural and biological strata where there are no fundamentally right actions. Whereas we once had the archetype of the "Greek hero," who confronted binary decisions of whether to adhere or break with authority, the "Western hero" evolved into a pragmatic model. He knows his own moral character is not higher than his peers, but that does not stop him from enforcing justice or an ethic through a policy of pragmatism. In effect, to be a hero means to pursue one course of action, at the expense of another course. Every "scientific hero" knows he was just following one of many hypotheses and lines of thought. And, just like the valiant hero who steps into traffic to save a child, he denies it was a special act, because he is not entirely confident that he would have done it again. A genuine hero knows full well he could have easily acted otherwise.