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.

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"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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Revised and updated edition

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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.

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Preface

This is a book about Crispr. It is animated by many forces. I grew up reading science books that could be described as instructive or didactic, but I saw the trade begin to gradually drift into a pop science which worsened an already existing problem that much of scientific explanation is based on partial truths or weak causal links. 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 puts an emphasis on scientists as fallible agents, and 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.

Technology is accelerating. We have begun inserting ourselves into evolution, using the Crispr system to modify the genetic code of plants, sea creatures and livestock to reduce infection and promote the yields of crops. Crispr has been used to fix recessive conditions such as kidney disease in inbred Dalmatians, create super-strong beagles, cows without horns, miniature pet pigs, and it has been used to disable immune-alerting genes in pigs so that their organs can be used for human transplant. It is being used to alter the genes of mice to stop Lyme disease in the transmission cycle and to modify mosquitoes to stop the spread of Zika virus. Crispr is also being used in ways that are dubious. It has been used to disrupt genes in butterflies to affect color patterns in their wings, and as scientists suggest, it will soon be used to create customized butterflies with pretty new wing colors. Crispr is sold on the internet in kits, and is actively being used to do fiddling things, such as to create fluorescent beer. Its ubiquity and ease of use has also raised concerns about "biohackers," who view gene modification as a right and alter microbes and organisms. But bio-terrorists might use it to turn common microbes into a pathogenic weapon. The US military started a program called Safe Genes to gene modify organisms to be used in battle and anti-Crispr tools to disable bio-weapons. "Mail-Order Crispr Kits Allow Absolutely Anyone to Hack DNA," declared the headline of a November 2017 article in *Scientific American*. The iconoclast scientist Josiah Zayner has used Crispr to hack into his own genes.

Most controversially, Crispr is being used to modify human genes as a logical extension of what is called gene therapy, a decades-old strategy to slip a supplementary copy of a gene into a human cell by packaging it into a virus. Viruses can be engineered to work as tiny crafts to pilot bits of restorative gene code into our cells. Some of these viruses, such as adeno-associated virus, slip into our cells but don't integrate into a chromosome as a permanent fixture, while other viruses, such as gammaretrovirus and lentivirus, do install in a chromosome. In many ways, modern gene therapy is coming of age, effectively being used to modify the genes in the cells of living humans to treat eye diseases, which can cause blindness, such as Leber congenital amaurosis; promote the growth of healthy skin to treat the rare skin-blistering disease epidermolysis bullosa; or add supplementary copies of working genes that fix rare blood or immune system disorders, such as Severe Combined Immunodeficiency Disorder.

In the process of using viruses to randomly insert new genes into our cells or chromosomes, those same viruses can randomly disrupt the function of existing genes in the process. Gene modification tools such as Crispr enable researchers to package a pair of GPS-guided molecular scissors into a virus so that the craft travels to, and makes a break at, a specific genetic address in a sea of six billion nucleotide bases that assemble into our 23 pairs of chromosomes. In theory, this makes gene therapy far safer and also allows us to alter our existing genes. The first applications of Crispr in humans will be used to alter *somatic* cells, adult cells in our bodies with genetic code that is not passed to our children, cells in our existing organs, or blood, or immune cells. By contrast, if we use the technology to alter sperm, eggs, or embryos, it will change the heritable, or *germline,* code that gets passed forth in future generations, ushering us into a futuristic age of "transhumanism."

In humans, Crispr will be most applicable for so-called Mendelian disorders, meaning those that are caused by variations in a single gene; or by altering our immune system cells to improve their ability to seek and destroy cancer. In truth, it's unlikely we will be using genetics to predict intelligence, eliminate mental illness, or engineer "superhumans," which are far better than us. In fact, thousands of genetic variations can influence complex traits, psychiatric risk, personality traits, and capacities such as human intelligence. Genes interact in complex relationships which we call epistatic. In fact, each

of the variants in our genes can have enhancing or diminishing effects on other genes depending on the context in which they are inherited. These relationships are often indecipherable: the combinatorial interactions of a three billion nucleotide human genome are staggering. The relationships are also kaleidoscopic, meaning the context of genes and environment are ever-shifting. As the plant ecologist Frank Egler once quipped, "ecosystems are not just more complex than we think, they're more complex than we can think."

Consider that computational scientists who want to understand how genes interact in systems to create the most optimal networks come up against some hard limitations as suggested by the "traveling salesperson problem." The problem is to find the most optimal way to wire a network given some input. In the words of theoretical biologist Stuart Kauffman: "The task is to begin at one of *N* cities, travel in turn to each city, and return to the initial city by the shortest route available. This problem, so remarkably simple to state, is extremely difficult." Evolution figures it out, locking in some models of what works early on, and hammering out incrementally optimal solutions over millennia. But the best that computer junkies can do to draw up an optimal biological network is to create heuristics, which are shorthand solutions. Even if technologists had the computer power to design biology from the ground up, it's unlikely they could re-engineer man into far superior forms.

In "The Origins of Order," Kauffman introduced the concept of "complexity catastrophe," a situation in complex organisms where genetic mutations are optimized to interact so tightly together that the role of natural selection becomes diminished in selecting molecular traits which produce organisms which can claim a step-up in fitness. In short, it has tinkered and fashioned its way into a shape that it cannot easily hammer on even further to improve. If so, most of what we think is our superiority may just be another subtle variation on complex systems such as intelligence and language which may be close to optimal.[1] The greatest obstacle to evolutionary progress may be our complexity.

And, by deduction, statistics often fail because they can't capture the nuance of a situation. In the biological sciences, the contribution of any single genetic variant to its associated effect is context-dependent, while each of us has a unique genome and lives in a variable environment. In social terms, data-science may function as a salve for social problems and the struggles of existence as decisions are increasingly thought to be

"in the data" and evaluated by metrics and their consequences. Many scientists aspire to the biotech startup culture as a means to strike it rich, although biotech objectives are not the same as public health objectives. Mounting scientific evidence shows that chronic stress and poverty contribute to alterations in brain circuitry and blood pressure, dramatically influencing health and mortality.[2] Nevertheless, gene modification is having immediate value to treating genetic disorders that are traced to single genes, and it is being used to alter our own immune cells to seek and destroy cancers. But technologies, which alter or enhance our genomes, have the potential to engender qualities of "otherness," initiate new forms of techno-scientific racism, and could introduce new inequalities if not everyone can afford the same access to expensive gene-modification tricks that provide health advantages or the next generation of cancer drugs.

Biology does not work as simple computer circuits, but the Frankensteinian idea that we can control fate through reductionist mechanics is an idea that is very much alive. In 1747, French enlightenment thinker Julien Offray de La Mettrie published "*L'homme Machine*," or "*Man, a Machine*." The philosopher Karl Popper noted later that the "theory of evolution gave the problem an even sharper edge." Meanwhile, adherents to the view of biology as mere clockwork grew. The "doctrine that man is a machine has perhaps more defenders than before among physicists, biologists and philosophers," Popper observed, "especially in the form of the thesis that man is a computer." Today, the analogies of man and machine are constant, thanks in part to computational biology and Silicon Valley which seek to solve or cure human problems by fixing the "bugs" at the genetic level. A panel at the *Vanity Fair* New Establishment Summit was titled "Hacking Cancer," and after philanthropist Ted Stanley gave $650 million to the Broad Institute to investigate the underpinnings of neuropsychiatric disorders, Broad director Eric Lander's team created "Opening Schizophrenia's Black Box," a video that suggests we are on our way to "hacking" into the genetics of mental diseases. Lander has referred to "a revolution in psychiatric disease," and NIH chief Francis Collins said psychiatric genomics stands "poised for rapid advances." Whether I agree with them (I don't) should be separated from the ambition to "industrialize the human genome" – and start a conversion on how the alteration of our biology can exemplify hubris.

Take any given genetic variant. None has more than a fraction of a single percentage point of an effect on the risk for a psychiatric disorder or condition. None may be purely deleterious or advantageous, but may have pleiotropic effects, meaning enhancing or attenuating effects on other genetic variants which it is inherited along with. Genetic variants may be deleterious in some cell types, such as neurons, but advantageous in other cell types, such as immune cells. Biological features can discover new meanings and uses in different contexts. In more general terms, not every social problem in life is a science problem or is solvable with an engineering solution, but a situation of local adaptation. Certainly, gene modification will not solve our psychiatric problems; focusing our financial resources on identifying a "neuro-signature" depletes resources for social services, social and economic mobility and psychotherapy.[3] Wealth inequality contributes to the chronic stress that we all live with, and that stress imprints itself in the epigenetic code of our genes (dampening the expression of genes key to learning and development such as *GRIN1, NR3C1, BDNF*).

In fact, genetic variants that contribute to psychiatric risk with small effect sizes may even provide evolutionary advantages when inherited in the right genetic background, or at certain developmental stages, or in specific environmental niches. In the 19th century, French physiologist Claude Bernard and Belgian scientist Adolphe Quetelet applied statistics to establish "norms" in the population that could be used in theory to present any metric, height, body mass index, weight, blood pressure, into bellcurves. In 1943, French philosopher Georges Canguilhem challenged the status quo of normalcy, noting it failed to capture what evolutionary biology says about human nature. For Canguilhem, no matter how deviant or rare a genetic variant or trait is, it could still be considered "normal" if it contributes to survival in a given niche. A reason that scientists will not eliminate conditions such as psychiatric disorders or conditions such as autism is that some of the risk for these disorders almost certainly comes in trade for small competitive advantages, such as heightened sensitivity, concentration, or openness to experience.

"In 'Enormous Success' Scientists Tie 52 Genes to Human Intelligence," screamed a headline from *The New York Times* in May 2017, which went on to say that no single genetic variant contributed more than a tiny fraction of a single percentage point to intelligence. Danielle Posthuma, a senior author of the study, noted "It means there

is a long way to go." (But to what ends? So that we can use these small effect-size variants to better subdivide our children into tracks earlier in school, or to bring us one small step closer to the thinking of Oxford ethicist Julian Savulescu, who has argued that if we have a drug to cognitively enhance ourselves, we may have a moral obligation to buy it?) I don't believe that we will use data-science or biochemical transformations to engineer our way out of the entanglement of psychological pain, or the stressful situation of being alive. But data will be used to support an illusion of superiority, or to sell one.

In fact, much of science is sales-pitched based on a utopian view of human nature. The tragic version of human nature, otherwise known as the "constrained view," is a concept that can be traced to economist Thomas Sowell and suggests that people are guided by innate self-interests, and limitations into what we can know and do, and thus society requires checks and balances. It is contrasted with an unconstrained or neolibertarian worldview which suggests that people are essentially good, even perfectible, and that "self-anointed" leaders including those in biotech should further be free of regulation and moral checks because they are leading us to a world that is more just, disease-free, equitable for everyone. Under this utopian vision, biotech leaders are moving us into a brighter future, and human life will come closer to utopia through technology. The $1.8 billion Cancer Moonshot promises to "end cancer as we know it"; the Sean Parker Cancer Institute has similar ambitions, but claims proceeds on patents that turn into blockbuster drugs; the $1.4 billion Broad Institute has been in an elbow-throwing battle for rights to Crispr, in which it granted exclusive rights for medical applications to one of its own spin-off companies, Editas Medicine; the $3 billion Zuckerberg Chan Initiative promises to "advance human potential" and "cure all diseases," while maintaining exclusive rights to commercial patents. While the utopian vision is sold, the dystopian reality is evident in the financial structure of these institutions, which create salaries for management that can reach $1 million per year and engage in fights for exclusive patents. Layers of financial deals are resulting in a new class of biologic medicines so expensive some insurance companies may not pay for it.

Importantly, gene- and cell-based therapies have emerged at a time in science when research is becoming highly contractual, highly structured around large scientific hubs. A seismic shift is occurring in science

whereby tax-exempt research institutes established under an emerging model of "free-market philanthropy" or "philanthrocapitalism" can amass money to protect and defend commercial interests. The Broad Institute, the Parker Institute for Cancer Immunotherapy and the Chan Zuckerberg Biohub are tax-free shelters which retain the exclusive right to commercialize inventions and prosecute patents. Scientific research is becoming more organizational, investment-driven, perhaps even more authoritarian, as control over basic research is exerted hierarchically from the top of the organization. Science, once considered a public trust, is increasingly defined by an ownership culture bent on monetization.

Scientists can appeal to a mythos of bringing us closer to reality, as if peering into neuroimagery or analyzing the genome gives us information that is more true than life as we experience it. To some extent we learn bits and pieces of what makes us who we are. But, ironically, science can weaken our sense of reality due to the obsession with statistical signals, which are often taken out of context and put our problems into simplistic reductionistic terms. As Sowell put it, "The march of science and technology does not imply growing intellectual complexity in the lives of most people. It often means the opposite." If there is a coming backlash against science, it is due to an ongoing struggle for freedom in a scientific age, due in part to the perception or subliminal wish for scientists to explain who we are and regulate our lives. To the extent that science seeks to remove "the self," this process can lend itself to repression, even devaluation.

In 2008, the President's Council on Bioethics released a 555-page report, titled *Human Dignity and Bioethics*, which fielded essays by a wide array of thinkers including Dennett and conservatives such as Leon Kass. As Dennett put the problem, "When we start treating living bodies as motherboards on which to assemble cyborgs, or as spare parts collections to be sold to the highest bidder, where will it all end?" The solution of rescuing the human spirit from the commercial forces of science, Dennett noted, cannot involve resorting to "traditional myths" because this "will backfire," but instead concepts of human dignity should be based on our sovereign right to "belief in the belief that something matters."

Dennett argues that belief is important in an everyday sense, such as most people have belief in democracy even as "we are often conflicted,

eager to point to flaws that ought to be repaired, while just as eager to reassure people that the flaws are not that bad, that democracy can police itself, so their faith in it is not misplaced." The point is also true about science, "since the belief in the integrity of scientific procedures is almost as important as the actual integrity." In fact, we engage in a sort of "belief maintenance" insofar that "this idea that there are myths we live by, myths that must not be disturbed at any cost, is always in conflict with our ideal of truth-seeking" and even as we commit to ideas in public or just in our hearts, "a strange dynamic process is brought into being, in which the original commitment gets buried" in layers of internal dialog and counterargument. "Personal rules are a *recursive* mechanism; they continually take their own pulse, and if they feel it falter, that very fact will cause further faltering," the psychiatrist George Ainslie wrote in the *Breakdown of Will*. If science can challenge beliefs, dignity is more primal – it is the right to hold beliefs, make use of science, and exercise belief maintenance.

The question of dignity is thornier than we might imagine, as science tends to challenge the belief in abstract or enduring concepts of value. How to uphold beliefs or a sense of dignity seems ever confusing and appears to throw us up against an age of radical nihilism as scientists today are using the gene-editing tool Crispr to do things such as tinker with the color of butterfly wings, and genetically alter pigs and humans. Indeed, dignity may be tricky to defend against the explication and engineering of human life by means of chemical processes, and it is complicated by the reality that many people increasingly look to science to shape their world view and moral direction, as we are living through a new age of resurgent scientism – an assumption that science encodes social values. A century ago, scientism appeared to be all but dead. The modernist break caused rupture between the moral and cultural commitments and sheer existence – hence it led to existentialism and the struggle over defining our commitments. Whatever it meant to live a good life, it couldn't be predefined by culture or science. In Anton Chekhov's 1889 short story, "A Boring Story," Nikolai Stepanovich, an internationally recognized scientist and professor of medicine, slips into melancholy near the end of his life. Despite his incredible success, his life seems ever more ambiguous, as the modernist movement comes to displace his authority. Katja, a young girl, and a representative of the new

generation, comes to him asking for advice and guidance, but Nikolai knows he has no way to tell her how to live. The irony is freedom has invoked a melancholy. Physician friend Mikhail Fyodorovich confides in Nikolai, "Science, God knows, has become obsolete. Its song has sung. Yes . . . Humanity has already begun to feel the need of replacing it with something else."

But the use of science as a means to shape values is now an the rebound. People today look to science for answers as a resurgent scientism is taking hold once again. And yet, that ardent trust in scientists puts us at risk that some of them will exploit this trust as a free pass. In August 2017, Shoukhat Mitalipov at Oregon Health and Science University published an article in *Nature* demonstrating that he could use Crispr to correct the gene *MYBPC3* in an embryo. When mutated, a single copy of that gene can increase risk for the heart condition hypertrophic cardiomyopathy, a disease affecting one in 500 people. The Mitalipov paper reported that 42 of 58 embryos, or 72 percent, had two mutation-free copies of the gene in every cell.[4] But, within a week, Maria Jasin and colleagues published a paper suggesting the experiment did not work as flawlessly as reported. Mitalipov's findings were *technically* controversial, but the experiment was widely recognized as crossing a threshold with details that scientists would muddle through until they got right. Importantly, producing an embryo without the dangerous mutation can already be accomplished by screening embryos that don't have the mutation, as a carrier of the mutated gene could typically pass on the mutation only to 50 percent of their offspring. Other genes such as a mutated *APP* gene, which can predict early-onset Alzheimer's, or mutated *BRCA* genes, which can predict breast or ovarian cancer, are also mutated genes which can be avoided by *in-vitro* screening. In theory, scientists could also use Crispr to add enhancements such as disrupting the *PCSK9* gene to lower LDL cholesterol or the *CCR5* gene to make their future children immune to HIV.

A non-trivial factor in the escalating discussions on gene modification is that scientists who hold the patents and technical abilities want to sell these "solutions" to consumers. Not all insurance companies and payers will pay for *in-vitro* techniques, ultimately leading to a wealthy class of people who can afford to purchase fertility technologies and "prophylactic gene modification" techniques, and

those who can't afford to pay for those updates to their children. This all plays into the notion of "legacy genetics" and unequal health advantages that are built into biotech enterprise. Indeed, none of these technologies will ultimately protect us from fate and time, stress or mental anguish.

Since this book was first published, a flurry of events have unfolded regarding Crispr patents and research applications. In February 2017, a federal patent court decided the nonprofit Broad Institute of MIT and Harvard did not interfere on the rights of UC Berkeley and the French microbiologist Emmanuelle Charpentier to patent the genome modification system Crispr-Cas9. In effect, the Broad won the right to medical applications of Crispr-Cas9. Intriguingly, as Sharon Begley wrote in *STAT*, "if there was one misstep that doomed the long and bitter fight by the University of California to wrest key Crispr patents from the Broad Institute, it was star UC Berkeley scientist Jennifer Doudna's habit of being scientifically cautious, realistic, and averse to overpromising." As Doudna admitted during the course of her research, commentary which was introduced during testimony: "We weren't sure if Crispr/Cas9 would work in . . . animal cells." Although it definitely did, a judge concluded that when scientists at the Broad used Crispr-Cas9 to edit human cells in 2013, the molecular tweaks Broad scientists made were a non-obvious advance and therefore deserving of patents.

For now, the Broad and its partners can keep its rights to a gene-editing system that's worth more than $1 billion dollars. Broad and partners swiftly sold agricultural licenses for Crispr to Monsanto Corp., and issued exclusive medical licenses for Crispr to Editas Medicine, which was founded by Broad core members, including Feng Zhang. In fact, by the end of 2016, Editas, which quickly completed a $94 million initial public offering, had paid $34.1 million to reimburse the Broad for its legal fees in the court battle for the rights to Crispr-Cas9. In return, the Broad, which also patented an application of Cpf1 (a protein similar to Cas9), granted an exclusive medical license for this protein to Editas for cash and a promissory note that can be settled in stock. The tightening relationship with a corporation clearly puts the concept of nonprofit to the test. How much stock equity should the Broad hold in Editas and how many tens of millions should they take from them? Does installation of Editas founders into the Broad's leadership bias the nonprofit to the corporation? Do kickbacks of granting exclusive licenses constitute a special favor, a quid pro quo?

In December, the Broad, possibly aware that it's nonprofit mission could be viewed as at-risk, published a guide to its intellectual property licensing philosophy noting that "non-profit institutions [like the Broad] should, in general, favor non-exclusive licenses over exclusive licenses" while immediately walking that principle back, noting investors "would need to make a large investment to turn IP into a commercial product" and "could not recoup this investment without exclusive rights." By the end of the statement the Broad made a case that special deals were good for everyone as exclusivity "may be appropriate because there is a clear case that it will better serve the public good." In fact, a nonprofit may not confer a "private benefit" to a corporation. Private benefit is defined as "non-incidental benefits conferred on disinterested persons that serve private interests." The law says any private benefit must be relatively small in size compared to the nonprofit's overall revenue and a necessary side effect of achieving the nonprofit's objectives. The Internal Revenue Service and Attorney General declined to comment on how financially entangled the Broad and Editas could become, and what, if any, breaches could trigger an investigation.

The UC Berkeley biologist and 2018 US Senate candidate Michael Eisen has argued that taxpayer-funded academic scientists should not patent seminal technologies such as Crispr-Cas9. In a more nuanced opinion published in *Science*, patent lawyers Jacob S. Sherkow and Jorge L. Contreras argue research institutions should limit their use of "surrogate licensors." The surrogate relationship exists to the extent Broad licenses Crispr proteins that actually make the cut in DNA, Cas9 and Cpf1, for medical applications exclusively to Editas, to an extent turning over its Crispr medical applications to a single company. The lawyers argue that, to be fair, a nonprofit such as Broad should only license Crispr exclusively for one gene at a time. "To the extent they're going to use exclusive licenses, they should do it narrowly: on a gene-by-gene basis," Sherkow told me in an email. In other words, the nonprofit should limit licensing Crispr for one specific target at a time, say, for the *CEP290* gene to develop treatments for an inherited eye disease named Leber's Congenital Amaurosis, for which Editas wants to develop a treatment. A clause in the contracts allows Editas to permit "third parties" to licence Crispr for gene targets it doesn't plan to monetize. But the clause may be moot, because Editas can sublicense Crispr. For instance, Editas has already signed a $737

million deal with Juno Therapeutics and a $90 million deal with another company named Allergan. Instead of licensing Crispr through the Broad, the requirement for other companies to access Crispr through Editas creates layers of sublicensing deals, in which investors take a cut at each step, driving up the costs of drugs. This is not trivial. The first Crispr drugs will cost more than a half million dollars per treatment.

In truth, the significance of the Cas9 protein has been lessened to a degree that a number of other proteins have been discovered including Cpf1, which makes an uneven break to a double-stranded DNA helix, leaving 4 or 5 nucleotides dangling off the end of the track. In effect, this type of break creates a template that can be used in repair, and thus enables more precise and cleaner gene editing repairs. Jennifer Doudna and Berkeley colleagues' discovery of two more Crispr proteins, CasX and CasY, also expand gene-editing toolkits.

Crispr systems are essentially free for academic purposes, and the impact on basic research has been swift. Of particular note is the invention of "Crispr screens," which enable cancer researchers to deactivate each gene, one by one, in a cancer cell line. Further work by Prashant Mali and colleagues has developed screens that can deactivate multiple genes in combination to identify vulnerabilities in cancer cell lines. "Synthetic lethals" are two or more genes, of which a cancer cell requires at least one functioning to survive, while deactivating the set of all genes leads to cell death. Researchers may use this technology to identify weaknesses of various cancer cells, or secondary genes that can be disabled to hinder a cancer cell that has become drug-resistant.

Crispr systems may also be used to weaponize our own immune cells to attach to cancer cells. Of particular interest is the emergence of the first clinical trials using Crispr to engineer T-cells to fight cancer. In 2017, the first human trials using Crispr were already underway in the United States under the watchful eye of the FDA. They made use of Crispr to disable a gene called Programmed Death, or PD-1, in a patient's own immune system T-cells. Cancer cells can spit out a small ligand called PD-L1, which binds to PD-1 protein and deactivates T-cells. This engages a natural brake on the immune system which is called a checkpoint blockade. Indeed, cancer cells do this to evade the immune system's surveillance. In fact, drug developers have already created antibodies such as Opdivo and Keytruda which target PD-1 as a kind of anti-defense system which stops cancer cells from shutting down the

T-cells. But, since up to 87 percent of patients taking any monoclonal antibody begin to produce antibodies to those antibodies (you can't beat evolution), scientists might prefer to disable the PD-1 gene using a gene modification system such as Crispr-Cas9. By using Crispr to disable PD-1, scientists hope that cancer cells will have no way to shut down an immune response. The genetically engineered T-cells would be infused back into patients and were expected to be more resistant to tactics by cancer cells to shut down the immune system.

In fact, scientists want to combine Crispr disruption of PD-1 in T-cells with other cell engineering tricks, such as "chimeric antigen receptor T-cells," or CAR T-cells, which are T-cells that are engineered with a new synthetic protein receptor on their surface which can attach to proteins which are expressed on the surface of cancer cells, or "TCR-engineered T-cells," which are T-cells genetically engineered with receptors that can attach to abnormal proteins, which are expressed on the inside of cancer cells, but displayed on the surface of those cells.

But even as scientists find ways to summon the immune system as a leviathan to fight cancer, our re-engineered immune systems can unleash dark and powerful forces which are unable to be controlled. Antibodies to PD-1 (and likely disabling the PD-1 gene in T-cells with Crispr-Cas9) can lead to unchecked T-cell activity that destroys healthy tissues in patients. And, CAR T-cells which are designed to attach to cancer cells can often throw the immune system into overdrive, causing inflammation and immune system destruction of healthy tissues in unpredictable ways.

In March 2017, Juno slammed to a halt one of its clinical trials for CAR T-cells which was designed to attach to the CD19 protein on the surface of cancerous white blood cells, after 5 of 38 patients injected with the engineered T-cells died in the trial, due to a mysterious effect of inflammatory cerebral edema, or swelling in the brain. In May 2017, Kite Pharma reported the death of a patient, also due to brain swelling, who was being treated for lymphoma with a similar CAR T-cell. However, Juno, Kite, and Novartis, who command extensive pipelines of engineered T-cells under development, show no signs of giving up cell-based therapies, quite the contrary.

Novartis showed it could use its CAR T-cell to treat a childhood leukemia, a blood cancer called B-cell acute lymphoblastic leukemia,

or ALL. A convincing selling point for Novartis' CAR T-cell drug to treat this childhood blood cancer was that 83 percent of 63 patients were cancer-free after three months. On August 30, 2017, the FDA approved it as the very first gene therapy drug for sale in the United States. Novartis' cancer drug will sell for $475,000. The sale price is nine times the median income in the United States and begs the question of just how high drug companies dare to raise the prices of biologic drugs. It is even more striking considering a general estimate of the cost to manufacture this particular drug is $25,000. The only tragedy will be if not everyone can afford these medicines, or are shamed for relying on socialized medicine, because taxpayers already socialize the costs of basic research. In effect, we already have a socialized medicine in the U.S. to the extent taxpayers subsidize the basic research of drug makers. In 2004, Noam Chomsky wrote:

"If you walk around MIT today, around Kendall Square, you see small biotech companies, spin-offs of government-sponsored research in what will be the cutting edge of the economy, namely, biology-based industries. If you looked around 40 years ago (then to the newly developing Route 128 corridor), you would have seen small electronics firms, spin-offs of what was then the cutting edge of the economy, electronics, under military cover. So Eisenhower's military-industrial complex is not quite what is generally interpreted. In part, yes, it's military. But a main function of the military, or the National Institutes of Health, or the rest of the federal system, is to provide some device to socialize costs, get the public to pay the costs, to take the risks. Ultimately, if anything comes out, you put it into private pockets."

Profoundly expensive, these "living drugs" will have transformative effect on cancer treatments but also increasingly test the limits of insurance reimbursement. The costs are not coming down as the technology will remain increasingly personalized to a patient's own cancer. Crispr systems will be used to insert receptors into our T-cells which attach to "neoantigens," small abnormal protein fragments which are unique to an individual patient's solid tumors. Neoantigens are abnormal protein products which are often unique to a patient but emerge from screwy processing in a few typical genes such as *CDK4*, catenin and caspase-8, *ERBB2IP* or *KRAS*. Doctors are already injecting patients with fragments of neoantigens specific to their own cancer, to create cancer vaccines and to initiate a stronger immune response to

the cancer, and to improve chances the cancer will not come back. And, they are selecting T-cells which have been primed and developed a memory to these specific protein fragments, a method called "adoptive T-cell therapy." Perhaps even better, by using Crispr to engineer T-cells to attach to unique neoantigen fragments in a cancer cell, researchers hope to improve the precision of cell-based therapies.

Insurance companies are bracing for how they will pay for half-million dollar gene-modification treatments as they pass through safety and efficacy trials and become marketable treatments. On June 3, 2017, at a conference for the American Society of Clinical Oncology, the author and medical doctor Siddhartha Mukherjee gave a speech warning about dividing the world "into the rich who can afford personalized cancer treatment and the poor who cannot."

The Institute for Clinical and Economic Review, or ICER, released a report in March 2017 stating there are 12 to 14 gene therapy candidates (Crispr is a future gene therapy drug) now in Phase 3 clinical trials, expected to be among the first candidates for commercial drug approval. Glybera was the first gene therapy approved in Europe for a rare enzyme disorder and priced at $1.4 million. In 2017, Novartis' $475,000 cancer-fighting T-cell became the first gene-modified cell sold in the U.S., quickly followed by approval of Philadelphia-based Spark Therapeutics' $1 million gene therapy for Leber's congenital eye disease.

"With payer budgets already stretched, and reigning in costs high on the agenda, both public and private payers will likely balk at the cost of some of these gene-based treatments," ICER stated in summary. "Europe has the lead in approved gene therapies, and the first such drug to be approved had a launch price of $1.4 million. Can the US healthcare system absorb the cumulative impact of such prices, considering that 10% of the population has a rare condition linked to a genetic defect?"

The FDA has chosen to regulate Crispr as a drug, rather than a device. This means that each Crispr application to a specific gene target will have to move through a labyrinthine regulatory process. Most independent experts say that the cost of gene therapy drugs mean that Crispr will almost certainly not have a splash on pharmacological medicine as is reported in the press. However, the issue of IVF or "genetically engineered babies" continues to be a hot button issue, because insurance coverage for such fertility treatments varies widely

by state, and many ethicists argue that Crispr babies would be created by design and not per therapy and are therefore not "medically necessary," only benefiting wealthy people in the spirit of "market-based genetics." As most people do carry some form of genetic variant that predicts a disease condition, the concept of what is necessary easily becomes challenged – we can't fix everything in nature. Unlike more than 40 other countries, and an international treaty Council of Europe Convention on Human Rights and Biomedicine, the US does not have a legal ban on modification to heritable code, but it does have a strong regulatory framework on drugs, and federal agencies treat Crispr-Cas9 as a drug. But the limitations using Crispr in fertility settings to alter "germline," or on heritable code are only in effect temporarily in so far that spending is restricted on applications FDA can review.

In February 2017, the National Academies of Sciences and National Academy of Medicine published a report "Human Genome Editing: Science, Ethics, and Governance" that contends with uses of gene editing for human reproductive purposes, prospects which have been brought into vivid reality since the emergence of new biotechnology tools such as the gene modification system, Crispr-Cas9. The report suggests limitations on genetic engineering to the heritable "germline" code of embryos, or even earlier upstream in the process, sperm and ovum, which convey information passed onto subsequent generations.

In a striking reversal in the tone from scientific leadership, the report recommended, at least on theoretical grounds, that "clinical trials using heritable germline genome editing should be permitted." The statement is a reversal in outlook of leadership since just a year ago in December 2015, when the International Summit on Human Gene Editing was held at the National Academy of Sciences in Washington DC, which drew Nobel laureates, lawmakers, and bioethicists from across the globe, and declaring that a "broad societal consensus" be attained before moving ahead with altering heritable code. Marcy Darnovsky, director for the Center for Genetics and Society noted the new report appears to send from scientists to lawmakers a "green light for proceeding with efforts . . . to engineer the genes and traits that are passed onto future children and generations" while noting that it "excludes the public from participation in deciding whether human germline modification is acceptable in the first place." If that seems futuristic, recall that in August 2017 Shoukhrat Mitalipov at Oregon Health and Science

University did indeed use Crispr to genetically modify the *MYBPC3* human embryos in the United States as a teaser (he destroyed the embryos before they could be turned into babies). Any technical limitations will be overcome.

Whether Crispr will radically change modern medicine is an open question. One thing is clear: scientists have a huge financial stake in selling gene modification technologies, and therefore can't be left solely responsible for their ethical application. The allusions to scientific heroism remain, at least, insofar that heroism amounts to power, hubris, tragic flaws, and the courage to do some good, even with the inevitable side effect of harm. In *Cell*, Broad director Eric Lander wrote a now infamous essay of revisionist history named "The Heroes of Crispr" in an effort to assign more credit to some of its inventors namely George Church and Feng Zhang. In that piece, credit was the focus, not a mention of the downsides, expense or dangers of using Crispr systems to alter our genetic code. Indeed, there is a poster on the 5th floor of the Broad Institute which depicts the Acropolis in Greece with Broad Institute members' heads cropped into the bodies of Greek philosophers and heroes. 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 lifeworld, 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, or to negotiate between two or more responsibilities, 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 his own brand of justice, through an ethic of pragmatism. In effect, to be a hero means to commit to a course of action when there are no right answers in the world. 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.

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