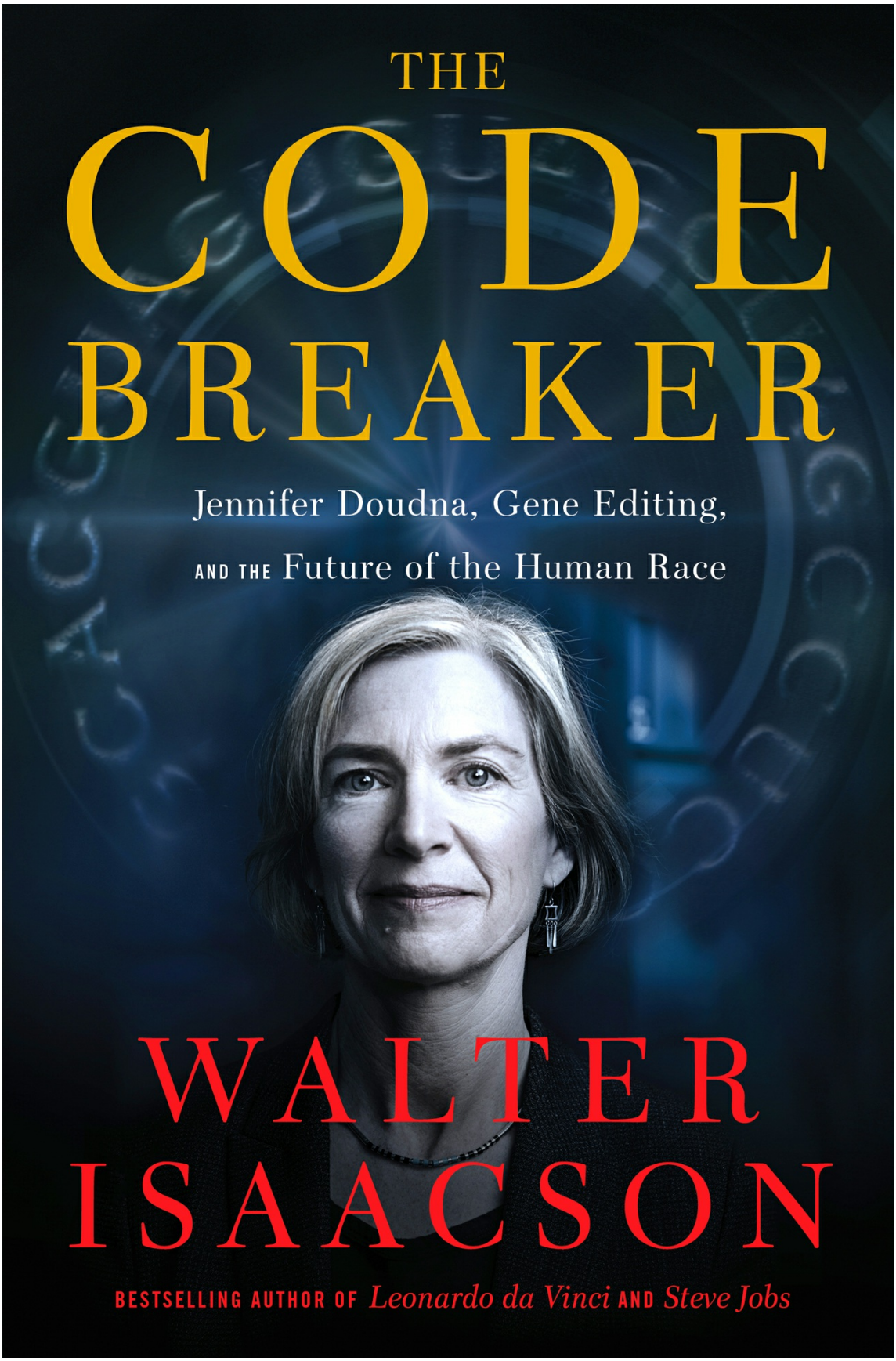
THE
CODE
BREAKER
Jennifer Doudna, Gene Editing,
AND THE Future of the Human Race
WALTER
ISAACSON
BESTSELLING AUTHOR OF Leonardo da Vinci AND Steve Jobs

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WALTER ISAACSON

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To the memory of Alice Mayhew and Carolyn Reidy.

What a joy it was to see them smile.

Into the Breach

Jennifer Doudna couldn't sleep. Berkeley, the university where she was a superstar for her role in inventing the gene-editing technology known as CRISPR, had just shut down its campus because of the fast-spreading coronavirus pandemic. Against her better judgment, she had driven her son, Andy, a high school senior, to the train station so he could go to Fresno for a robot-building competition. Now, at 2 a.m., she roused her husband and insisted that they retrieve him before the start of the match, when more than twelve hundred kids would be gathering in an indoor convention center. They pulled on their clothes, got in the car, found an open gas station, and made the three-hour drive. Andy, an only child, was not happy to see them, but they convinced him to pack up and come home. As they pulled out of the parking lot, Andy got a text from the team: "Robotics match cancelled! All kids to leave immediately!"[1]

This was the moment, Doudna recalls, that she realized her world, and the world of science, had changed. The government was fumbling its response to COVID, so it was time for professors and graduate students, clutching their test tubes and raising their pipettes high, to rush into the breach. The next day—Friday, March 13, 2020—she led a meeting of her Berkeley colleagues and other scientists in the Bay Area to discuss what roles they might play.

A dozen of them made their way across the abandoned Berkeley campus and converged on the sleek stone-and-glass building that housed her lab. The chairs in the ground-floor conference room were clustered together, so the first thing they did was move them six feet apart. Then they turned on a video system so that fifty other researchers from nearby universities could join by Zoom. As she stood in front of the room to rally them, Doudna displayed an intensity that she usually

kept masked by a calm façade. “This is not something that academics typically do,” she told them. “We need to step up.”[2]

It was fitting that a virus-fighting team would be led by a CRISPR pioneer. The gene-editing tool that Doudna and others developed in 2012 is based on a virus-fighting trick used by bacteria, which have been battling viruses for more than a billion years. In their DNA, bacteria develop clustered repeated sequences, known as CRISPRs, that can remember and then destroy viruses that attack them. In other words, it’s an immune system that can adapt itself to fight each new wave of viruses—just what we humans need in an era that has been plagued, as if we were still in the Middle Ages, by repeated viral epidemics.

Always prepared and methodical, Doudna (pronounced DOWD-nuh) presented slides that suggested ways they might take on the coronavirus. She led by listening. Although she had become a science celebrity, people felt comfortable engaging with her. She had mastered the art of being tightly scheduled while still finding the time to connect with people emotionally.

The first team that Doudna assembled was given the job of creating a coronavirus testing lab. One of the leaders she tapped was a postdoc named Jennifer Hamilton who, a few months earlier, had spent a day teaching me to use CRISPR to edit human genes. I was pleased, but also a bit unnerved, to see how easy it was. Even I could do it!

Another team was given the mission of developing new types of coronavirus tests based on CRISPR. It helped that Doudna liked commercial enterprises. Three years earlier, she and two of her graduate students had started a company to use CRISPR as a tool for detecting viral diseases.

In launching an effort to find new tests to detect the coronavirus, Doudna was opening another front in her fierce but fruitful struggle with a cross-country competitor. Feng Zhang, a charming young China-born and Iowa-raised researcher at the Broad Institute of MIT and Harvard, had been her rival in the 2012 race to turn CRISPR into a gene-editing tool, and ever since then they had been locked in an intense competition to make scientific discoveries and form CRISPR-based companies. Now, with the outbreak of the pandemic, they would

engage in another race, this one spurred not by the pursuit of patents but by a desire to do good.

Doudna settled on ten projects. She suggested leaders for each and told the others to sort themselves into the teams. They should pair up with someone who would perform the same functions, so that there could be a battlefield promotion system: if any of them were struck by the virus, there would be someone to step in and continue their work. It was the last time they would meet in person. From then on the teams would collaborate by Zoom and Slack.

"I'd like everyone to get started soon," she said. "Really soon."

"Don't worry," one of the participants assured her. "Nobody's got any travel plans."

What none of the participants discussed was a longer-range prospect: using CRISPR to engineer inheritable edits in humans that would make our children, and all of our descendants, less vulnerable to virus infections. These genetic improvements could permanently alter the human race.

"That's in the realm of science fiction," Doudna said dismissively when I raised the topic after the meeting. Yes, I agreed, it's a bit like *Brave New World* or *Gattaca*. But as with any good science fiction, elements have already come true. In November 2018, a young Chinese scientist who had been to some of Doudna's gene-editing conferences used CRISPR to edit embryos and remove a gene that produces a receptor for HIV, the virus that causes AIDS. It led to the birth of twin girls, the world's first "designer babies."

There was an immediate outburst of awe and then shock. Arms flailed, committees convened. After more than three billion years of evolution of life on this planet, one species (us) had developed the talent and temerity to grab control of its own genetic future. There was a sense that we had crossed the threshold into a whole new age, perhaps a brave new world, like when Adam and Eve bit into the apple or Prometheus snatched fire from the gods.

Our newfound ability to make edits to our genes raises some fascinating questions. Should we edit our species to make us less susceptible to deadly viruses? What a wonderful boon that would be! Right? Should we use gene editing to

eliminate dreaded disorders, such as Huntington's, sickle-cell anemia, and cystic fibrosis? That sounds good, too. And what about deafness or blindness? Or being short? Or depressed? Hmmm... How should we think about that? A few decades from now, if it becomes possible and safe, should we allow parents to enhance the IQ and muscles of their kids? Should we let them decide eye color? Skin color? Height?

Whoa! Let's pause for a moment before we slide all of the way down this slippery slope. What might that do to the diversity of our societies? If we are no longer subject to a random natural lottery when it comes to our endowments, will it weaken our feelings of empathy and acceptance? If these offerings at the genetic supermarket aren't free (and they won't be), will that greatly increase inequality—and indeed encode it permanently in the human race? Given these issues, should such decisions be left solely to individuals, or should society as a whole have some say? Perhaps we should develop some rules.

By "we" I mean *we*. All of us, including you and me. Figuring out if and when to edit our genes will be one of the most consequential questions of the twenty-first century, so I thought it would be useful to understand how it's done. Likewise, recurring waves of virus epidemics make it important to understand the life sciences. There's a joy that springs from fathoming how something works, especially when that something is ourselves. Doudna relished that joy, and so can we. That's what this book is about.

The invention of CRISPR and the plague of COVID will hasten our transition to the third great revolution of modern times. These revolutions arose from the discovery, beginning just over a century ago, of the three fundamental kernels of our existence: the atom, the bit, and the gene.

The first half of the twentieth century, beginning with Albert Einstein's 1905 papers on relativity and quantum theory, featured a revolution driven by physics. In the five decades following his miracle year, his theories led to atom bombs and nuclear power, transistors and spaceships, lasers and radar.

The second half of the twentieth century was an information-technology era, based on the idea that all information could be encoded by binary digits—known

as bits—and all logical processes could be performed by circuits with on-off switches. In the 1950s, this led to the development of the microchip, the computer, and the internet. When these three innovations were combined, the digital revolution was born.

Now we have entered a third and even more momentous era, a life-science revolution. Children who study digital coding will be joined by those who study genetic code.

When Doudna was a graduate student in the 1990s, other biologists were racing to map the genes that are coded by our DNA. But she became more interested in DNA's less-celebrated sibling, RNA. It's the molecule that actually does the work in a cell by copying some of the instructions coded by the DNA and using them to build proteins. Her quest to understand RNA led her to that most fundamental question: How did life begin? She studied RNA molecules that could replicate themselves, which raised the possibility that in the stew of chemicals on this planet four billion years ago they started to reproduce even before DNA came into being.

As a biochemist at Berkeley studying the molecules of life, she focused on figuring out their structure. If you're a detective, the most basic clues in a biological whodunit come from discovering how a molecule's twists and folds determine the way it interacts with other molecules. In Doudna's case, that meant studying the structure of RNA. It was an echo of the work Rosalind Franklin had done with DNA, which was used by James Watson and Francis Crick to discover the double-helix structure of DNA in 1953. As it happens, Watson, a complex figure, would weave in and out of Doudna's life.

Doudna's expertise in RNA led to a call from a biologist at Berkeley who was studying the CRISPR system that bacteria developed in their battle against viruses. Like a lot of basic science discoveries, it turned out to have practical applications. Some were rather ordinary, such as protecting the bacteria in yogurt cultures. But in 2012 Doudna and others figured out a more earth-shattering use: how to turn CRISPR into a tool to edit genes.

CRISPR is now being used to treat sickle-cell anemia, cancers, and blindness. And in 2020, Doudna and her teams began exploring how CRISPR could detect and destroy the coronavirus. "CRISPR evolved in bacteria because of their long-

running war against viruses," Doudna says. "We humans don't have time to wait for our own cells to evolve natural resistance to this virus, so we have to use our ingenuity to do that. Isn't it fitting that one of the tools is this ancient bacterial immune system called CRISPR? Nature is beautiful that way." Ah, yes. Remember that phrase: Nature is beautiful. That's another theme of this book.

There are other star players in the field of gene editing. Most of them deserve to be the focus of biographies or perhaps even movies. (The elevator pitch: *A Beautiful Mind* meets *Jurassic Park*.) They play important roles in this book, because I want to show that science is a team sport. But I also want to show the impact that a persistent, sharply inquisitive, stubborn, and edgily competitive player can have. With a smile that sometimes (but not always) masks the wariness in her eyes, Jennifer Doudna turned out to be a great central character. She has the instincts to be collaborative, as any scientist must, but ingrained in her character is a competitive streak, which most great innovators have. With her emotions usually carefully controlled, she wears her star status lightly.

Her life story—as a researcher, Nobel Prize winner, and public policy thinker—connects the CRISPR tale to some larger historical threads, including the role of women in science. Her work also illustrates, as Leonardo da Vinci's did, that the key to innovation is connecting a curiosity about basic science to the practical work of devising tools that can be applied to our lives—moving discoveries from lab bench to bedside.

By telling her story, I hope to give an up-close look at how science works. What actually happens in a lab? To what extent do discoveries depend on individual genius, and to what extent has teamwork become more critical? Has the competition for prizes and patents undermined collaboration?

Most of all, I want to convey the importance of *basic* science, meaning quests that are curiosity-driven rather than application-oriented. Curiosity-driven research into the wonders of nature plants the seeds, sometimes in unpredictable ways, for later innovations.[3] Research about surface-state physics eventually led to the transistor and microchip. Likewise, studies of an astonishing method that