Pondering ‘what it means to be human’ on the frontier of gene editing

By Joel Achenbach Joel Achenbach Reporter covering science and politics Email Bio

Scientist Jennifer Doudna, of the University of California at Berkeley, helped invent a revolutionary gene-editing tool that has triggered heated ethical and legal debates. (Nick Otto /For The Washington Post)

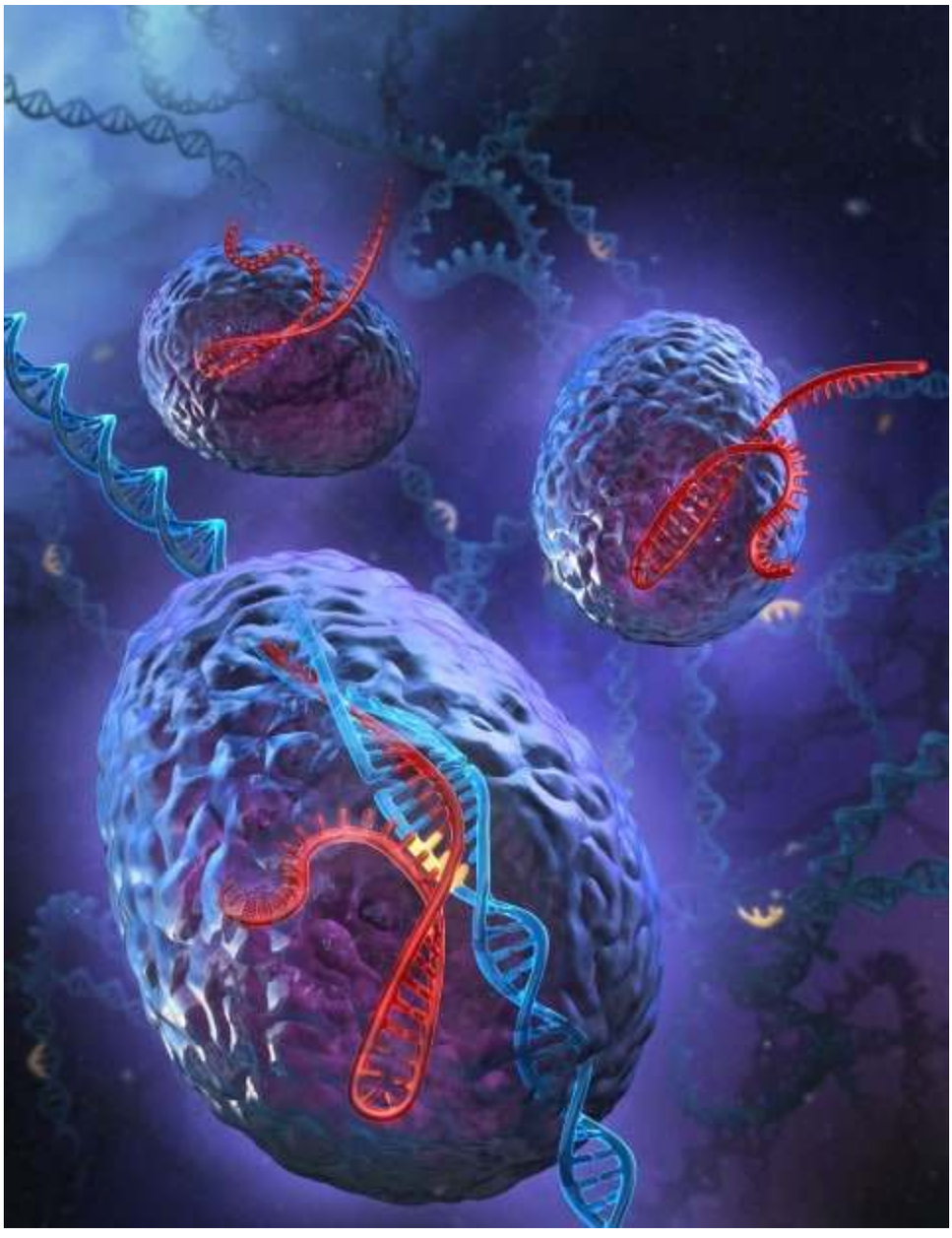
People in pain write to Jennifer Doudna. They have a congenital illness. Or they have a sick child. Or they carry the gene for Huntington’s disease or some other dreadful time bomb wired through every cell in their body. They know that Doudna helped invent an extraordinary new gene-editing technology, known as CRISPR.

But they don’t all seek her help. One woman, the mother of a child with Down syndrome, explained: “I love my child and wouldn’t change him. There’s something about him that’s so special. He’s so loving in a way that’s unique to him. I wouldn’t change it.”

The scientist tears up telling this story.

“It makes you think hard about what it means to be human, doesn’t it?” she says.

Doudna (pronounced DOWD-na) has been doing a lot of hard thinking lately as she ponders the consequences of CRISPR.


An illustration of the powerful genome editing tool, CRISPR/Cas9. (Stephen Dixon)

The world of molecular biology is mad for this new form of genetic engineering. Scientists have turned a natural bacterial defense system into a laboratory tool for cutting or reordering genes in a cell — an innovation that could be used to target genetic mutations linked to numerous diseases.

CRISPR is not the first method for manipulating genes, but it’s by far the cheapest, easiest, most versatile. Its many attributes have generated incredible excitement as well as apprehension. While the approach hasn’t been applied yet in humans for therapeutic purposes, that’s on the horizon. So are worrisome scenarios involving genetic enhancements and purely cosmetic applications.

The technology is still being honed. Two Harvard biochemists reported recently in Nature that they had found a way to target a single letter in a genome in the laboratory experiment.

This is all happening with dizzying speed. CRISPR has spawned two contentious, parallel debates, with Doudna squarely in the middle of both.

The first is the ethical issue raised by the mother of the child with Down syndrome: How far should we go in editing the human genome? The new technique potentially enables changes in the human “germline” cells, which could entail changes not only to a single person’s

genome but also to that of any of the person’s descendants. Many researchers say they worry about unintended consequences with long-term effects.

The second debate covers the tricky matter of who exactly invented CRISPR and thus should be awarded the patents. Big money is in the balance. Prestigious science institutions are doing battle with one another. Invective flies on social media. Message: Science is a business.

Both issues are so prickly that it’s easy to overlook the way CRISPR has already changed how countless scientists do basic research. Thousands of them are using it to understand the genetic origins of diseases. This isn’t the future; this is now.

Soon, CRISPR could lead to genetically modified plants that wind up in your grocery store. It already has been used to develop a mushroom that won’t turn brown as quickly, which the U.S. Department of Agriculture has decided doesn’t need regulatory approval because no genes from other organisms were required for its creation.

Doudna is a party to the patent battle even as she’s among the most outspoken figures in the ethical debate.

“It’s a bit of a crazy life right now,” she says.

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The 52-year-old Doudna is highly conscious of being a woman in a male-dominated scientific profession. She never used to be, though. She kept her head down. She did her lab work. She published. She was promoted and lauded. But as she became more well known, and routinely cited as a possible winner of a Nobel Prize, she noticed all the glass ceilings above her and most women generally: “Seeing boardrooms that have no women in them. Seeing upper levels of administrations that have no or few women in them.”

Doudna was born in the nation’s capital. Her father, a speechwriter for the Air Force, got the itch to become a professor of English and, after getting a doctorate at the University of Michigan, moved the family to the one place that offered him a job: the University of Hawaii at Hilo, on the Big Island.

Young Jennifer never imagined being a scientist. In grade school she didn’t think she had any particular knack for it. But she did take interest in the natural world.

“We had special kinds of toads that were only on our island. We had all kinds of plants that had evolved in this kind of environment. There were blind spiders that lived in lava tubes,” she recounted during a visit to Washington earlier this year. She asked herself: How did that happen? How did these things evolve?

A 10th-grade chemistry teacher, Miss Wong, encouraged her. A vocational test told her she ought to go into civil engineering, whatever that meant. She still didn’t see herself as a scientist.

“I had this impression from the media that science was for old white guys, people who looked like Einstein, that it wasn’t for people like me,” she said.

At Pomona College, she studied biochemistry. Though doubtful of her prospects, she applied to Harvard Medical School. She got in and earned a doctorate in the lab of Jack Szostak, an eminent figure in origin-of-life research. Her path eventually led to her own laboratory at the University of California at Berkeley. And then CRISPR came along.

She didn’t invent CRISPR; bacteria did. It’s an amazingly nifty immune system that testifies to the innovations that emerge from Darwinian natural selection.

In the genetic code of bacteria are repeated sequences that until recently were viewed as junk DNA. Scientists who studied them began to refer to them as clustered regularly interspaced short palindromic repeats — CRISPRs.

Researchers gradually figured out that these sequences were akin to copies of DNA segments in viruses that had previously attacked the bacteria. At its core, life is built around information, and the humblest bacterium keeps a record of bad stuff that has previously come down the pike.

The CRISPR system takes fast action. When a virus shows up, the system identifies the invader as familiar and then directs molecular machinery to slice up and disable it.

How this natural system became leveraged by human beings as a laboratory tool is a controversial tale that is keeping patent lawyers busy. The narrative prominently features Doudna. She co-authored, with French scientist Emmanuelle Charpentier, a 2012 paper showing how the CRISPR system could be exploited to cut genes in a test tube and create a new method of gene editing.

Soon after that breakthrough, a young scientist named Feng Zhang, of the Broad Institute of Massachusetts Institute of Technology and Harvard, published a paper showing how CRISPR could be applied to mammalian cells. George M. Church, a flamboyant geneticist at Harvard Medical School, published a similar result at the same time.

Perhaps inevitably, patent applications generated a tremendous battle, pitting not only Doudna and Charpentier against Zhang but also lofty institutions, notably UC Berkeley and Broad/MIT/Harvard, against one another. The two sides have tried to settle their fight, they revealed in an April 11 filing. But it could drag on for years.

[Control of CRISPR, biotech’s most promising breakthrough, is in dispute]

The scientists also have equity stakes in start-up companies that want to commercialize the CRISPR technology. Doudna, for example, is the co-founder of three — Caribou Biosciences, Intellia Therapeutics and Editas Medicine.

There’s a lot of money flying around. Doudna and Charpentier each received a $3 million Breakthrough Prize in Life Sciences in 2015. They’ve been repeatedly mentioned as possible Nobel laureates — an honor that also comes with a seven-figure sum. But Zhang has a claim, as do Church and potentially many others. The Nobel, by rule, can go to no more than three people for any single discovery.

Eric Lander, head of the Broad Institute, published a long, almost novelistic article titled “The Heroes of CRISPR” in January in the journal Cell. He dispersed credit for CRISPR widely, starting with an obscure Spanish scientist who first started looking at these palindromic

repeats in the 1990s.

A major kerfuffle ensued. The article carried no conflict-of-interest statement, because Lander didn’t have a personal financial stake in the ongoing patent fight. Critics howled that Lander’s review didn’t give Doudna and other scientists enough credit and was subtly slanted in favor of his colleague Zhang. Lander insisted he wasn’t trying to stiff anyone.

But this is science today: People are edgy. Research is not just about the high-minded pursuit of knowledge. Breakthroughs are lucrative, and just about everyone has skin in the game.

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In laboratories around the world, CRISPR has quickly become molecular biologists’ favorite tool. They can toy with genes in a mouse, for example, and see how a mutation can lead to a tumor.

“I am absolutely confident that with CRISPR we are going to accelerate the rate at which we develop treatments that can control cancer, and cure some,” said Phillip Sharp, an MIT biologist and Nobel laureate. “It’s totally cool.”

CRISPR offers the promise of someday being a great tool for gene therapy. But the scientists admit they’re not ready to do this yet. For starters, gene therapy has a troubled history. You make a mistake and the patient could die, which happened in the tragic case of 18-year-old Jesse Gelsinger in a clinical trial in 1999.

The bigger concern comes with germline editing in human beings. If you knock out or modify a gene in a very young embryo, all the cells in that human being, including their reproductive cells (sperm and eggs), will carry the genetic modification.

That then gets passed along to all descendants. If it happened just a few times, it would be unlikely to change humanity as we know it. But if done widely, it could change the species.

Eliminating terrible diseases, such as Huntington’s, would seem a no-brainer. But most diseases and human traits have a complex genetic origin that’s hard to understand fully.

In early 2014, Doudna read a paper detailing how researchers for the first time had manipulated the genomes in monkey embryos.

She turned to her husband, a Berkeley professor of biochemistry, and asked, “How soon will it be until someone tries this in a human embryo?”

Doudna found herself increasingly troubled. She had a particularly awful dream (first recounted in the New Yorker) in which a colleague wanted her to explain CRISPR to a man with a funny little mustache — a man she suddenly realized was Adolf Hitler.

In early 2015, Doudna was among those pushing for boundaries on applications of CRISPR research. The scientific community realized it needed to come together in a manner similar to the famous 1975 conference at Asilomar State Beach in California that put restrictions on research using gene-splicing techniques.

The 2015 version of Asilomar occurred at the National Academy of Sciences in Washington in December. For three days, scientists from Europe, China and North America discussed - CRISPR. They talked about the history of eugenics. They heard from bioethicists. They considered the promises of the new technology. At the end, they hammered out guidelines, allowing research to go forward cautiously.

The scientists said, for instance, that CRISPR should not be used to edit genes in human embryos intended to establish a pregnancy. They stressed that any tinkering with human germline cells should come only after a “broad societal consensus” that such editing is a good idea.

[Scientists debate the ethics of an unnerving gene-editing technique]

Of course, a scientific agreement has no enforcing mechanism. Different countries have different laws. You can’t do CRISPR with a child’s chemistry set, but it also doesn’t require a massive laboratory.

Asked how the world could stop the misuse of CRISPR, Doudna paused. “That’s a tough question,” she finally said.

Then: “Let’s just take a step back for a second. Couldn’t we be having this discussion about any powerful technology?”

Knowledge tends to be unidirectional, whether the subject is the secrets of the atom or the marvels of DNA. Scientific discoveries can be explosive. Doudna ultimately answers her own question: “You can’t unlearn it. You can’t put it away.”