CRISPR cows could boost sustainable meat production, but regulations and wary consumers stand in the way

When Ralph Fisher, a Texas cattle rancher, set eyes on one of the world's first cloned calves in August 1999, he didn't care what the scientists said: He knew it was his old Brahman bull, Chance, born again. About a year earlier, veterinarians at Texas A&M extracted DNA from one of Chance's moles and used the sample to create a genetic double. Chance didn't live to meet his second self, but when the calf was born, Fisher christened him Second Chance, convinced he was the same animal.

Scientists cautioned Fisher that clones are more like twins than carbon copies: The two may act or even look different from one another. But as far as Fisher was concerned, Second Chance was Chance. Not only did they look identical from a certain distance, they behaved the same way as well. They ate with the same odd mannerisms; laid in the same spot in the yard. But in 2003, Second Chance attacked Fisher and tried to gore him with his horns. About 18 months later, the bull tossed Fisher into the air like an inconvenience and rammed him into the fence. Despite 80 stitches and a torn scrotum, Fisher resisted the idea that Second Chance was unlike his tame namesake, telling the radio program "This American Life" that "I forgive him, you know?"

In the two decades since Second Chance marked a genetic engineering milestone, cattle have secured a place on the front lines of biotechnology research. Today, scientists around the world are using cutting-edge technologies, from subcutaneous biosensors to specialized food supplements, in an effort to improve safety and efficiency within the $385 billion global cattle meat industry. Beyond boosting profits, their efforts are driven by an imminent climate crisis, in which cattle play a significant role, and growing concern for livestock welfare among consumers.

Gene editing stands out as the most revolutionary of these technologies. Although gene-edited cattle have yet to be granted approval for human consumption, researchers say tools like Crispr-Cas9 could let them improve on conventional breeding practices and create cows that are healthier, meatier, and less detrimental to the environment. Cows are also being given genes from the human immune system to create antibodies in the fight against Covid-19. (The genes of non-bovine livestock such as pigs and goats, meanwhile, have been hacked to grow transplantable human organs and produce cancer drugs in their milk.)

thehornlesso Image not found or type unknown

The hornless offspring of a gene- modified bull (L), alongside a horned control cow, are seen at the Univ of California-Davis

But some experts worry biotech cattle may never make it out of the barn. For one thing, there's the optics issue: Gene editing tends to grab headlines for its role in controversial research and biotech blunders. Crispr-Cas9 is often celebrated for its potential to alter the blueprint of life, but that enormous promise can become a liability in the hands of rogue and unscrupulous researchers, tempting regulatory agencies to toughen restrictions on the technology's use. And it's unclear how eager the public will be to buy beef from gene-edited animals. So the question isn't just if the technology will work in developing supercharged cattle, but whether consumers and regulators will support it.

Cattle are catalysts for climate change. Livestock account for an estimated 14.5 percent of greenhouse gas emissions from human activities, of which cattle are responsible for about two thirds, according to the United Nations' Food and Agriculture Organization (FAO). One simple way to address the issue is to eat less meat. But meat consumption is expected to increase along with global population and average income. A 2012 report by the FAO projected that meat production will increase by 76 percent by 2050, as beef consumption increases by 1.2 percent annually. And the United States is projected to set a record for beef production in 2021, according to the Department of Agriculture.

Alison Van Eenennaam

For Alison Van Eenennaam, an animal geneticist at the University of California, Davis, part of the answer is creating more efficient cattle that rely on fewer resources. According to Van Eenennaam, the number of dairy cows in the United States decreased from around 25 million in the 1940s to around 9 million in 2007, while milk production has increased by nearly 60 percent. Van Eenennaam credits this boost in productivity to conventional selective breeding.

"You don't need to be a rocket scientist or even a mathematician to figure out that the environmental footprint or the greenhouse gases associated with a glass of milk today is about one-third of that associated with a glass of milk in the 1940s," she says. "Anything you can do to accelerate the rate of conventional breeding is going to reduce the environmental footprint of a glass of milk or a pound of meat."

Modern gene-editing tools may fuel that acceleration. By making precise cuts to DNA, geneticists insert or remove naturally occurring genes associated with specific traits. Some experts insist that gene editing has the potential to spark a new food revolution.

Jon Oatley, a reproductive biologist at Washington State University, wants to use Crispr-Cas9 to fine tune the genetic code of rugged, disease-resistant, and heat-tolerant bulls that have been bred to thrive on the open range. By disabling a gene called NANOS2, he says he aims to "eliminate the capacity for a bull to make his own sperm," turning the recipient into a surrogate for sperm-producing stem cells from more productive prized stock. These surrogate sires, equipped with sperm from prize bulls, would then be released into range herds that are often genetically isolated and difficult to access, and the premium genes would then be transmitted to their offspring.

Furthermore, surrogate sires would enable ranchers to introduce desired traits without having to wrangle their herd into one place for artificial insemination, says Oatley. He envisions the gene-edited bulls serving herds in tropical regions like Brazil, the world's largest beef exporter and home to around 200 million of the approximately 1.5 billion head of cattle on Earth.

Brazil's herds are dominated by Nelore, a hardy breed that lacks the carcass and meat quality of breeds like Angus but can withstand high heat and humidity. Put an Angus bull on a tropical pasture and "he's probably going to last maybe a month before he succumbs to the environment," says Oatley, while a Nelore bull carrying Angus sperm would have no problem with the climate.

The goal, according to Oatley, is to introduce genes from beefier bulls into these less efficient herds, increasing their productivity and decreasing their overall impact on the environment. "We have shrinking resources," he says, and need new, innovative strategies for making those limited resources last.

nelore cows flickr christopher borges e

Image not found or type unknown

Nelore cows, the most common breed in Brazil. Credit: Christopher Borges/Flickr

Oatley has demonstrated his technique in mice but faces challenges with livestock. For starters, disabling NANOS2 does not definitively prevent the surrogate bull from producing some of its own sperm. And while Oatley has shown he can transplant sperm-producing cells into surrogate livestock, researchers have not yet published evidence showing that the surrogates produce enough quality sperm to support natural fertilization. "How many cells will you need to make this bull actually fertile?" asks Ina Dobrinski, a reproductive biologist at the University of Calgary who helped pioneer germ cell transplantation in large animals.

But Oatley's greatest challenge may be one shared with others in the bioengineered cattle industry:

overcoming regulatory restrictions and societal suspicion. Surrogate sires would be classified as gene-edited animals by the Food and Drug Administration, meaning they'd face a rigorous approval process before their offspring could be sold for human consumption. But Oatley maintains that if his method is successful, the sperm itself would not be gene-edited, nor would the resulting offspring. The only gene-edited specimens would be the surrogate sires, which act like vessels in which the elite sperm travel.

Even so, says Dobrinski, "That's a very detailed difference and I'm not sure how that will work with regulatory and consumer acceptance."

In fact, American attitudes towards gene editing have been generally positive when the modification is in the interest of animal welfare. Many dairy farmers prefer hornless cows — horns can inflict damage when wielded by 1,500-pound animals — so they often burn them off in a painful process using corrosive chemicals and scalding irons. In a study published last year in the journal PLOS One, researchers found that "most Americans are willing to consume food products from cows genetically modified to be hornless."

Still, experts say several high-profile gene-editing failures in livestock and humans in recent years may lead consumers to consider new biotechnologies to be dangerous and unwieldy.

In 2014, a Minnesota startup called Recombinetics, a company with which Van Eenennaam's lab has collaborated, created a pair of cross-bred Holstein bulls using the gene-editing tool TALENs, a precursor to Crispr-Cas9, making cuts to the bovine DNA and altering the genes to prevent the bulls from growing horns. Holstein cattle, which almost always carry horned genes, are highly productive dairy cows, so using conventional breeding to introduce hornless genes from less productive breeds can compromise the Holstein's productivity. Gene editing offered a chance to introduce only the genes Recombinetics wanted. Their hope was to use this experiment to prove that milk from the bulls' female progeny was nutritionally equivalent to milk from non-edited stock. Such results could inform future efforts to make Holsteins hornless but no less productive.

The experiment seemed to work. In 2015, Buri and Spotigy were born. Over the next few years, the breakthrough received widespread media coverage, and when Buri's hornless descendant graced the cover of Wired magazine in April 2019, it did so as the ostensible face of the livestock industry's future.

But early last year, a bioinformatician at the FDA ran a test on Buri's genome and discovered an unexpected sliver of genetic code that didn't belong. Traces of bacterial DNA called a plasmid, which Recombinetics used to edit the bull's genome, had stayed behind in the editing process, carrying genes linked to antibiotic resistance in bacteria. After the agency published its findings, the media reaction was swift and fierce: "FDA finds a surprise in gene-edited cattle: antibiotic-resistant, non-bovine DNA," read one headline. "Part cow, part… bacterium?" read another.

Recombinetics has since insisted that the leftover plasmid DNA was likely harmless and stressed that this sort of genetic slipup is not uncommon.

“Is there any risk with the plasmid? I would say there’s none,’’ says Tad Sonstegard, president and CEO of Acceligen, a Recombinetics subsidiary. “We eat plasmids all the time, and we’re filled with microorganisms in our body that have plasmids.” In hindsight, Sonstegard says his team’s only mistake was not properly screening for the plasmid to begin with.

While the presence of antibiotic-resistant plasmid genes in beef probably does not pose a direct threat to consumers, according to Jennifer Kuzma, a professor of science and technology policy and co-director of the Genetic Engineering and Society Center at North Carolina State University, it does raise the possible risk of introducing antibiotic-resistant genes into the microflora of people’s digestive systems. Although unlikely, organisms in the gut could integrate those genes into their own DNA and, as a result, proliferate antibiotic resistance, making it more difficult to fight off bacterial diseases.

“The lesson that I think is learned there is that science is never 100 percent certain, and that when you’re doing a risk assessment, having some humility in your technology product is important, because you never know what you’re going to discover further down the road,” she says. In the case of Recombinetics. “I don’t think there was any ill intent on the part of the researchers, but sometimes being very optimistic about your technology and enthusiastic about it causes you to have blinders on when it comes to risk assessment.”

The FDA eventually clarified its results, insisting that the study was meant only to publicize the presence of the plasmid, not to suggest the bacterial DNA was necessarily dangerous. Nonetheless, the damage was done. As a result of the blunder, a plan was quashed for Recombinetics to raise an experimental herd in Brazil.

Backlash to the FDA study exposed a fundamental disagreement between the agency and livestock biotechnologists. Scientists like Van Eenennaam, who in 2017 received a $500,000 grant from the Department of Agriculture to study Buri’s progeny, disagree with the FDA’s strict regulatory approach to gene-edited animals. Typical GMOs are transgenic, meaning they have genes from multiple different species, but modern gene-editing techniques allow scientists to stay roughly within the confines of conventional breeding, adding and removing traits that naturally occur within the species.

That said, gene editing is not yet free from errors and sometimes intended changes result in unintended alterations, notes Heather Lombardi, division director of animal bioengineering and cellular therapies at the FDA’s Center for Veterinary Medicine. For that reason, the FDA remains cautious.

“There’s a lot out there that I think is still unknown in terms of unintended consequences associated with using genome-editing technology,” says Lombardi. “We’re just trying to get an understanding of what the potential impact is, if any, on safety.”

Bhanu Telugu, an animal scientist at the University of Maryland and president and chief science officer at the agriculture technology startup RenOVAte Biosciences, worries that biotech companies will migrate their experiments to countries with looser regulatory environments. Perhaps more pressingly, he says strict regulation requiring long and expensive approval processes may incentivize these companies to work only on traits that are most profitable, rather than those that may have the greatest benefit for livestock and society, such as animal well-being and the environment.

“What company would be willing to spend $20 million on potentially alleviating heat stress at this point?” he asks.

On a windy winter afternoon, Raluca Mateescu leaned against a fence post at the University of Florida’s Beef Teaching Unit while a Brahman heifer sniffed inquisitively at the air and reached out its tongue in search of unseen food. Since 2017, Mateescu, an animal geneticist at the university, has been part of a team studying heat and humidity tolerance in breeds like Brahman and Brangus (a mix between Brahman and Angus cattle). Her aim is to identify the genetic markers that contribute to a breed’s climate resilience, markers that might lead to more precise breeding and gene-editing practices.

“In the South,’’ Mateescu says, heat and humidity are a major problem. “That poses a stress to the animals because they’re selected for intense production — to produce milk or grow fast and produce a lot of muscle and fat.”

Like Nelore cattle in South America, Brahman are well-suited for tropical and subtropical climates, but their high tolerance for heat and humidity comes at the cost of lower meat quality than other breeds. Mateescu and her team have examined skin biopsies and found that relatively large sweat glands allow Brahman to better regulate their internal body temperature. With funding from the USDA’s National Institute of Food and Agriculture, the researchers now plan to identify specific genetic markers that correlate with tolerance to tropical conditions.

“If we’re selecting for animals that produce more without having a way to cool off, we’re going to run into trouble,” she says.

A Brahman cow at the University of Florida's Beef Teaching Unit. Credit: Dyllan Furness

There are other avenues in biotechnology beyond gene editing that may help reduce the cattle industry's footprint. Although still early in their development, lab-cultured meats may someday undermine today's beef producers by offering consumers an affordable alternative to the conventionally grown product, without the animal welfare and environmental concerns that arise from eating beef harvested from a carcass.

Other biotech techniques hope to improve the beef industry without displacing it. In Switzerland, scientists at a startup called Mootral are experimenting with a garlic-based food supplement designed to alter the bovine digestive makeup to reduce the amount of methane they emit. Studies have shown the product to reduce methane emissions by about 20 percent in meat cattle, according to The New York Times.

In order to adhere to the Paris climate agreement, Mootral's owner, Thomas Hafner, believes demand will grow as governments require methane reductions from their livestock producers. “We are working from the assumption that down the line every cow will be regulated to be on a methane reducer,” he told The New York Times.

Meanwhile, a farm science research institute in New Zealand, AgResearch, hopes to target methane production at its source by eliminating methanogens, the microbes thought to be responsible for producing the greenhouse gas in ruminants. The AgResearch team is attempting to develop a vaccine to alter the cattle gut's microbial composition, according to the BBC.

Genomic testing may also allow cattle producers to see what genes calves carry before they're born, according to Mateescu, enabling producers to make smarter breeding decisions and select for the most desirable traits, whether it be heat tolerance, disease resistance, or carcass weight.

Despite all these efforts, questions remain as to whether biotech can ever dramatically reduce the industry's emissions or afford humane treatment to captive animals in resource-intensive operations. To many of the industry's critics, including environmental and animal rights activists, the very nature of the practice of rearing livestock for human consumption erodes the noble goal of sustainable food production. Rather than revamp the industry, these critics suggest alternatives such as meat-free diets to fulfill our need for protein. Indeed, data suggests many young consumers are already incorporating plant-based meats into their meals.

Ultimately, though, climate change may be the most pressing issue facing the cattle industry, according to Telugu of the University of Maryland, which received a grant from the Bill and Melinda Gates Foundation to improve productivity and adaptability in African cattle. “We cannot breed our way out of this,” he says.

Dyllan Furness is a Florida-based science and technology journalist. His work has appeared in Quartz, OneZero, and PBS, among other outlets. Follow him on Twitter @dyllonline

This article was originally published at Undark and has been republished here with permission. Follow Undark on Twitter @undarkmag