CRISPR technologies hold enormous promise for farming and medicine

The Economist, February 26, 2025

OF THE MANY patients who need an organ from a donor, 90% go without. About 240m people live with rare genetic diseases, most of which cannot be treated. Each year poor diets cause more than 10m early deaths. Suffering on such an immense scale can appear hopeless. However, a technique called CRISPR gene editing promises to help deal with these issues and many more—and wise regulation can spur it on.

CRISPR is like an editor that can rewrite DNA letter by letter or gene by gene, to remove harmful mutations or add protective ones. Clinical trials will begin this summer on pig organs edited for transplanting into humans. Last year the first new therapy went on the market. It seemingly cures sickle-cell disease and beta-thalassemia, two blood disorders that afflict millions. If ongoing clinical trials succeed, a one-off therapy could provide lifelong protection against heart attacks. Farming will benefit, too: CRISPR could raise yields or protect crops from climate change. Consumers could soon get white bread with fibre-like starch or tastier varieties of healthy but unpopular foods, such as mustard greens.

But as we report in our Technology Quarterly, now is a critical moment. Since CRISPR's discovery in 2012, it has begun supplanting old ideas that never reached their potential. Gene therapy, a different technique that uses viruses to insert genes into patients, can treat many rare genetic diseases but is and will remain costly to prepare. Genetically modified (GM) crops, which borrow genes from other species, have faced misguided opposition in Europe and elsewhere. CRISPR offers an alternative to both. But if, unlike them, it is to live up to its promise, it will need to attract a continuing flow of investment—which, in turn, means chalking up some real-life successes.

For that to happen, scientists must show that they can get CRISPR into more types of cells in the body cheaply and easily. The technology would also be boosted if it could serve as a platform to create personalised therapies for people's individual mutations. That will require new science, but it would also be catalysed by a better system of regulation.

Regulations that govern drugs for rare diseases were not designed for an era of specialist medicines and will hinder patients from receiving new treatments. Developing drugs for a small group of people has always been difficult and many CRISPR companies are struggling, despite government help. But CRISPR is programmable, meaning that the same drug can be tweaked to target many different mutations. On-demand, small-batch drugs for rare diseases could be made more cheaply today if requirements on safety testing and manufacturing standards were loosened. For many desperately ill people who may die before a drug is approved, if it is developed at all, that is a worthwhile trade-off. In America the Food and Drug Administration has already taken some steps towards liberalisation.

Agriculture also badly needs reform. Gene-edited foods fall under GM regulation in many regions, including the European Union, despite being quite different: gene-edited plants have had their own genes tweaked rather than incorporating genes from other species. Mindful of the threat of climate change to food security, Britain is poised to implement new liberal laws governing gene-edited foods; the EU should follow. However, public trust in regulators and scientists could become a problem with the confirmation as health secretary of Robert F. Kennedy junior. He has invested in CRISPR therapies, but is also anti-GM. If America slows down or even goes into reverse, it will be a blow to progress—and humanity.

Can gene editing deliver on its promise?

The Economist, February 21, 2025

In early 2005 Rodolphe Barrangou and Philippe Horvath were staring at some very odd bits of repeating genetic code on a computer screen in France. The sequences came from *Streptococcus thermophilus*, a bacterium that, like other bacteria, often skirmishes with viruses. Rumour had it that these sequences of DNA might help bacteria gain the upper hand in the fight. If they did, the researchers wanted to know all about it. *S. thermophilus* is one of the microbes used to make yogurt. Stopping it

from falling prey to viruses would save Danisco, the foodmaker they both worked for at the time, millions of euros.

They compared the strange sequences from varying strains of *S. thermophilus* which were resistant to different viruses. In every case, the bits of DNA between the repeated sequences were identical to DNA from the virus to which that strain of bacterium was resistant. The researchers then took bits of DNA from a specific virus and stuck them in between the repeats in a non-resistant strain of *S. thermophilus*. Remarkably, the strain became resistant. It seemed as if bacteria which survived a viral attack kept chunks of the attacking virus's DNA in their own genomes. These functioned as a rogues' gallery in preparation for future fisticuffs: if the same piece of DNA were seen again, the cell would know it was under attack.

The discovery of this bacterial immune system was big news for the dairy industry, which suddenly had a new way to select bacteria based on desired immunity. Such strains are now the norm in most yogurt and cheese production, a nice commercial pay-off for microbiology. But in 2012 Emmanuelle Charpentier at the Max Planck Institute in Germany and Jennifer Doudna at the University of California in Berkeley took the practical implications of the work much further. The strangely Clustered, Regularly Interspaced, Short Palindromic Repeats, or CRISPR, could be hacked to make cuts at precise sequences in the genome of any organism: yeast, fish, pigs. Or humans.

Their technique worked by introducing into cells the means of making a protein called Cas9—responsible for making cuts in DNA—and a piece of CRISPR-like RNA that tells it which bit to cut. RNA, like DNA, carries a sequence of "bases", and if you know a particular sequence of DNA you can easily design a "complementary" sequence of RNA to put at the end of a piece of CRISPR RNA to which Cas9 will attach itself. When the RNA-plus-protein mechanism finds the matching piece of DNA in the cell's genome, Cas9 makes its cut.

The beauty of imperfection

From there CRISPR takes advantage of the cell's DNA-repair mechanisms. Because cells usually fix damaged sequences imperfectly, the repair process often "knocks out" the targeted gene. This ability to knock out genes sits behind the first wave of CRISPR medicines advancing towards clinics. More sophisticated techniques which make precise edits, or insert new sequences, are now commonplace in labs, and will migrate into clinics as well as seed companies and farms.

Manipulating genes to correct diseases or improve crops are not new ideas. But (especially in medicine) earlier technologies struggled due to being unsafe or prohibitively cumbersome. Building a gene editor took months. With CRISPR even high-schoolers can get hold of editing systems in the time it takes to order RNA sequences online and have them shipped by FedEx. In a short while this technology has been adopted by pharmaceutical giants and become ubiquitous in laboratories, spawning biotechs and inspiring innovations that may prove still more powerful. Governments are tweaking regulations to exploit its potential.

Everything about the technology screams "world-changing". CRISPR offers ways to achieve biological goals—not just medical goals like curbing heart disease, but also agricultural and environmental goals—in ways never before dreamed possible. As yet, though, the world seems largely unchanged. Might CRISPR fall prey to the same pitfalls and disappointments as its predecessor technologies? Or is the transformation it promised within scientists' grasp? This Technology Quarterly will offer answers to these questions.

CRISPR could yet save millions of lives. Here's how

The Economist, February 21, 2025

FOR 20 YEARS Tamani Harris lived a life of pain. She was born with sickle-cell disease. Her red blood cells, made flat and stiff by a mutant version of haemoglobin, struggled to move smoothly through her blood vessels. Several times a month she would have a "crisis" where her cells got stuck somewhere in her body, causing excruciating pain. She needed strong opioids and often blood transfusions to recover. She had accepted that she might die young.

Her parents encouraged her to partake in a trial for a CRISPR-based therapy for sickle-cell disease and beta-thalassemia, another debilitating genetic blood disorder. The therapy, Casgevy, was made by

Vertex Pharmaceuticals, a pharmaceutical firm in Boston, and CRISPR Therapeutics, a Swiss biotech co-founded by Emmanuelle Charpentier, one of the inventors of CRISPR. In May 2021 Ms Harris travelled to New York from college in Florida to have her DNA edited.

Out with the old, in with the new

Sickle-cell disease can be treated by a bone-marrow transplant containing stem cells which lack the faulty haemoglobin gene and thus produce healthy red blood cells. But without a well-matched donor—and even siblings might not be similar enough—the transplant will fail or attack the recipient's body. What Casgevy does is turn a patient's own cells, already a perfect match, into a transplant. Doctors harvest stem cells from the patient's bone marrow and then send them off to a lab, where CRISPR is used to turn up the production of another, functional version of haemoglobin. This version is used during fetal development but is turned down at birth. The patient—having had his or her old cells destroyed first by a brutal chemotherapy regime that often kills fertility—then receives their own edited cells as a transplant.

The treatment seems to have cured Ms Harris; she has not had a crisis in three years. It appears to have worked in 39 of 42 participants in her trial. The beta-thalassemia patients who received Casgevy have had a similar turnaround. In 2023 Casgevy became the first CRISPR treatment to win approval from regulators, first in Britain and then in America, and reach the clinic. It has a list price of $2.2m in America.

Casgevy delivers on CRISPR's original promise that diseases can be genetically cured. In the late 2010s and early 2020s that promise spawned huge excitement and investment; gene-editing biotechs shot up, pulling in hundreds of millions of dollars despite having little clinical data. When the covid pandemic broke out, the idea that biotechnology was going to save the world only fuelled more hype.

Then interest rates spiked, dampening investor interest. And when the whole industry seized up CRISPR still had a lot to prove. Could it ever be anything other than a gruelling bone-marrow transplant? Would health-care systems pay the high price for a one-and-done cure? What was more, too many companies were going after the same diseases in the same ways.

Hard years followed. Companies discarded drugs for rare genetic diseases in favour of "high-value" diseases with more patients. One biotech firm, Editas, stopped work on its therapy against inherited retinal diseases despite good results in early trials, then shut down its successful programme for a rival to Casgevy. Prime Medicine, another biotech, slashed its pipeline from eighteen therapy programmes to five. Tome Biosciences, which had entered the field with more than $200m in funding, closed shop. It was a harsh reckoning. "So much for the Nobel prize-winning promise of CRISPR as a panacea," says Fyodor Urnov, a geneticist at the University of California, Berkeley.

CRISPR has spawned new editors that can fix mutations

And yet. The fact that Casgevy works matters. So does the emergence of tools that can enable more precise edits than CRISPR. Base editing, invented in 2016 by David Liu at the Broad Institute in Massachusetts, in effect swaps out one base pair in DNA for another. Base editors first entered human trials in 2022, and preliminary data look promising. Prime editing, Dr Liu's next invention, can rewrite anything from one base to whole sections of DNA by copying from a custom template. That began human trials in 2024.

And markets are being established. More than 50 people have begun the process to get Casgevy (not counting trial participants). That is only a tiny fraction of the 8m people with sickle-cell disease, but at current prices Vertex believes Casgevy to be a multibillion-dollar prospect. Analysts agree, citing public-payer deals in America and England and a coming expansion into the Middle East, which has a high prevalance of both sickle-cell disease and beta-thalassemia.

In vivo veritas

But for CRISPR to transform medicine it will have to expand beyond ruinously expensive cures for diseases that require gruelling bone-marrow transplants. It will need to cure ailments in gentler ways at lower costs. Sending away cells for editing is pricey. A number of companies are working on *in vivo* treatments, which work by doing all the editing inside the body rather than via transplant. These medicines would be cheaper and kinder on patients, and would allow companies to treat more common diseases. But it has been a challenge to deliver them to the right places in the body.

To attack this problem the field has bet heavily on lipid nanoparticles (LNPs). These tiny bubbles of fat, which are given as an infusion, proved they could be produced at scale when they delivered mRNA

vaccines against covid. Each nanoparticle would contain both a CRISPR guidance system and an mRNA molecule that would produce the editing protein. Verve Therapeutics, a biotech firm in Cambridge, Massachusetts, has a nanoparticle-delivered base-editing system in clinical trials that would treat heart disease by silencing a cholesterol-regulating gene called PCSK9. The editor showed good early results, but the firm had to pause a trial in 2024 because one of the participants had an adverse reaction to the LNPs. Another trial with a different LNP formulation is under way.

If Verve can work out the kinks in delivery, the prize would be big. The LNP trial is aimed at treating premature coronary-artery disease and people with familial hypercholesterolemia, a genetic condition that affects millions globally, causing high cholesterol and a serious risk of atherosclerotic cardiovascular disease (ASCVD). But the company's ultimate goal is to treat anyone with ASCVD—a patient pool of more than 300m people—and, one day, those merely at risk of it.

And if LNPs can be made to deliver editors safely, the next big leap would be making versions that could be delivered to organs besides the liver, where LNPs naturally accumulate (and which works for treating heart disease). If LNPs—or an alternative vehicle—could be made that could reach, say, the brain, gene editors could work on a host of brain diseases currently beyond the reach of CRISPR. Some researchers have turned to virus-like particles, which are capsules that exploit viral proteins to get taken up by cells but without a viral genome to cause infection. Jennifer Doudna, who co-invented CRISPR, is working on a version she calls "enveloped delivery vehicles", which can be manufactured like LNPs but are decorated with molecules recognised by specific cell types.

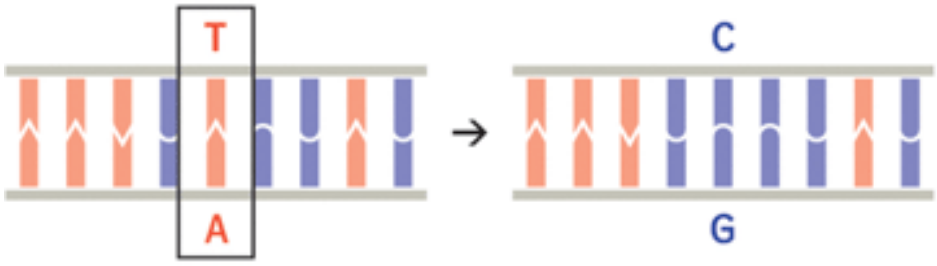
Updates are expected in the first half of 2025 for trials run by Verve and by another Cambridge firm, Intellia Therapeutics, which has an *in vivo* therapy for hereditary angioedema, a swelling disease. Conditions for investment are also looking better. Interest rates are down. And America's Food and Drug Administration (FDA) has agreed to lower its stringent regulation standards so that companies can re-use therapy components, such as editors or delivery vehicles, for different treatments without having to re-test them.

Dr Urnov welcomes the news from the FDA, but he is worried that for-profit companies have nonetheless abandoned people with rare genetic diseases. He fears that most of those potential patients will wait in vain for a biotech-developed treatment. To address this Dr Urnov, Dr Doudna and colleagues at the University of California in both San Francisco and Los Angeles have entered into a non-profit partnership with Danaher, a global conglomerate and a CRISPR manufacturer, in hopes of dosing patients with rare genetic diseases through a large, "umbrella"-style clinical trial. (It is not unlike personalised cancer-vaccine trials run by Merck, a pharmaceutical giant, where each vaccine is unique to the participant's particular mutation.)

CRISPR is still a long way from becoming the standard of care for all genetic diseases, as Dr Doudna envisions. For some there may be better alternatives that do not rely on editing DNA, such as protein-targeting drugs for cystic fibrosis (for which CRISPR cures are also in development), or "antisense" therapeutics which can block the output of genes by binding to mRNA before it is translated into proteins. However, as scientists begin to understand more about how genetics underpin or shape all kinds of diseases both rare and common, the space in which CRISPR can be useful continues to grow. To take full advantage, gene-editing's practitioners cannot afford to let up.

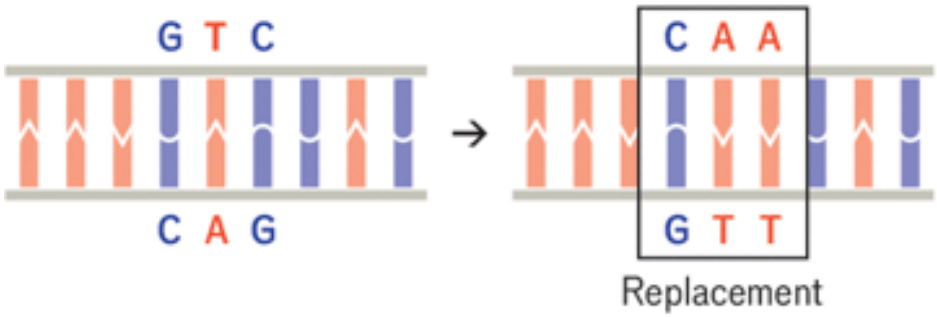
Base editing

Many genetic diseases are caused by a single error in the DNA. Base editing can precisely fix them. Adenine editors (below) in effect switch an adenine-thymine pair for guanine-cytosine.



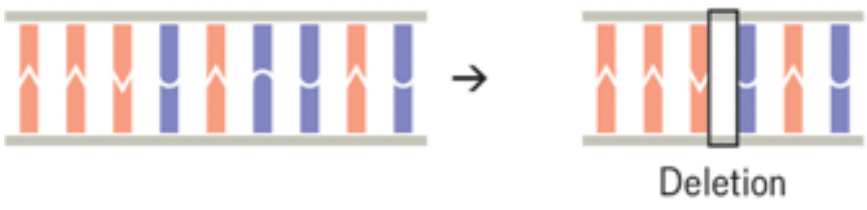
Prime editing

Prime editing is more flexible than base editing: it can swap any base for another, and add or delete short sequences. It uses a specially designed string of RNA that tells enzymes how to change the gene.



CRISPR-Cas9

Is mostly used to break genes, by deleting and inserting small chunks of DNA which disrupt the gene's function.



Sources: "CRISPR-Cas9 DNA base editing and prime editing", by A. Kantor et al., 2020; *The Economist*

Epigenetic editors are a gentler form of gene editing

The Economist, February 21, 2025

More than a decade ago Sonia Vallabh, a lawyer, and her husband, an engineer, decided to retrain as molecular biologists. They had an urgent motivation. Dr Vallabh's mother had died suddenly of a mysterious dementia. An autopsy had revealed the cause to be prion disease, in which the prion protein, the normal function of which is unclear, changes form and spontaneously clumps together and causes the brain to die. Most prion disease is infectious, set off by exposure to an already clumping protein. In this case, it was genetic. "I learned that I'd inherited her mutation," Dr Vallabh says. They needed to find a cure before the disease came for her, too.

They now run a lab at the Broad Institute in Boston. By 2024 they had created an editor that, in mice, turns off the prion gene in the brain, preventing the disease from taking hold. Next up is making it work in humans. Their editor, however, does not touch the gene at all.

No cell makes all the proteins for which it has genes. A blood cell does not need the same proteins as a neuron. One way cells turn off unneeded genes is by putting locks on them. These locks are chemical changes to the bases that make up DNA or to proteins that store DNA inside the cell. They are known as "epigenetic" marks since the changes are "on top of" the genome, not in the genome itself. What Dr Vallabh and her husband did was put a lock on the prion gene, using what they call an epigenetic editor.

Gene editing can be tough on the genome. Epigenetic editing is gentler. Rather than chopping the DNA in two, it uses an enzyme that installs or removes a chemical lock at a specific place in the genome. Chroma Medicine, an epigenetic editing company in Boston (now nChroma Bio after a merger), examined CAR-T cells, a type of manipulated immune cell showing promise in treating cancer and other diseases. Adding more edits to them could make them more effective. To achieve that several genes must be switched off, a multi-edit which kills off a lot of cells if you use CRISPR-Cas9. But doing the job by epigenetic editing, says Luke Gilbert, who co-founded Chroma Medicine, is "basically non-toxic".

Although edits are not permanent, they are long-lasting. And because the changes are more easily reversible in theory, epigenetic editing may feel less radical to the public than gene editing. Benjamin Oakes, the boss of Scribe Therapeutics, a Californian biotech firm, sees a future in which epigenetic editing becomes like getting a flu shot, but for protection against heart attacks and obesity instead of viruses. Scribe's epigenetic editor can block a gene causing unhealthy cholesterol in monkeys. "We can essentially modify your genome so you're no longer producing risk factors for cardiometabolic disease. And maybe every five years, or every ten years, you need to come back for a booster dose."

Looking further into the future, epigenetic editing could undo damage accrued during life. Ageing, disease, chemical exposure and emotional trauma all influence the body's epigenetic marks. Editing might be able to erase such scars. In 2022 researchers from the University of Illinois at Chicago targeted epigenetic patterns, acquired during teenage binge drinking, which are linked to anxiety and drinking problems. They could reverse the changes in alcohol-exposed rats, with the result that they drank less and became less anxious.

Drugs that remove the scars of life, though, are a long way off.

Gene editing is already revolutionising research in the laboratory

The Economist, February 21, 2025

In the late 2010s eight macaque monkeys were born at a laboratory in Shanghai. At first they seemed much like the other infants in the colony, but differences soon became obvious. They were much more active at night than their peers. Their hormones were unusual, too. Melatonin, which typically oscillates with the day-night cycle and aids sleep, was all over the place. Cortisol, a stress hormone, was perpetually high. Then their behaviour took a turn: they sat frozen in corners for long periods of time, fled in fear from their caretakers, and began burying their little heads in their hands—all signs of mental illness.

The root of their malaise was a genetic experiment. When the monkeys were single-celled embryos, scientists had used CRISPR editing tools to silence, or "knock out", a gene that helps regulate the body's internal clock. Its disruption is linked to psychiatric conditions, such as bipolar disorder, which are notoriously difficult to study on the genetic and molecular levels. The deeply unpleasant lives of Shanghai macaques are part of a push to understand how genes shape brain disorders and to devise drugs for them.

This could have been done with old technology, but it would have been laborious. Scientists can breed knock-outs using "gene targeting", a hugely inefficient process that first inserts DNA into stem cells and then into embryos. For mice, it takes a year. CRISPR can do the job in a month. The same is true for adding, or "knocking in", genetic mutations. Manipulations in both animals and cells have become so quick and easy that scientists can model a host of diseases in the lab, tease apart intricate genetic mechanisms and create huge studies linking genes with diseases.

Hold the anchovies

CRISPR might be on the cusp of transforming medicine and agriculture, but in research things have already changed. Almost 9,000 scientific papers mentioned CRISPR tools in their abstracts in 2024, up from 300 in 2013. Since 2012 Addgene, a non-profit repository of DNA reagents, has shipped more than 300,000 CRISPR preparations to 5,000 organisations in around 100 countries. "You can just simply order everything you need," says Robin Lovell-Badge, a developmental biologist at the Francis Crick Institute in London. CRISPR RNA is about as hard to get as the pizzas researchers order when working on gene editors into the night.

That is a serious time-saver for scientists interested in fundamental biology, such as Dr Lovell-Badge, whose work concerns sexual development. In the 1990s he discovered that a gene on the Y chromosome called SRY acted as a switch that turned embryos, which by default develop as female, onto the path of male development. But it was not until the arrival of CRISPR in the 2010s that he and others figured out how it actually works. Through knock-out experiments in mice they showed that SRY, via an "enhancer" gene, activates another gene called SOX9, which ultimately drives the development of the testes.

It is often not known which variants are benign and which are not

Knock out that activation of SOX9 with CRISPR and "you now get XY females," he says. This sometimes happens naturally in humans. Other scientists recently checked the genomes of a handful of people who had developed the opposite sexual characteristics of their chromosomal sex. Their mutations were almost exactly the same as those Dr Lovell-Badge had put into his mouse embryos with CRISPR. Those people now know the genetic cause of their unusual development.

Everyone carries their own genetic variants, usually where one base has been swapped for another. Though all these variants can be easily found with genome sequencing, it is often not known which are benign and which are harmful. But in recent years CRISPR has sped up the task of telling them apart. Greg Findlay, a colleague of Dr Lovell-Badge at the Crick Institute, is using the tool to tackle a gargantuan task: he wants to understand every single variation in the human genome that is associated with disease.

Counting only mutations in genes which are implicated in disease, this would mean knocking in 30m DNA variants, Dr Findlay says. Using CRISPR and a new type of gene editing called prime editing, he now runs massive, high-throughput screening experiments, in which thousands of variants are knocked into cells and analysed. "We've gone from testing these variants in genetics one at a time to testing large pools," he says. "Now we're trying to do experiments that are close to 100,000 variants."

His results have begun to explain previously baffling symptoms. In 2024 he published a paper going through 2,268 base-swap variants of VHL, a gene involved with suppressing tumours, and showed how particular variants led to different forms and severities of kidney cancer. More such CRISPR-enabled mass screens might help doctors check for variants and tweak treatment accordingly.

But even if Dr Findlay is able to scale up his experiments, the job is probably too big. There are substantial parts of the genome that are poorly understood, and which may host large numbers of disease-causing variants. And multiple variations in the same gene—or different ones—can interact. "Even if we could test a million variants, it's still nowhere near the 10bn or whatever that are possible," he says.

To lessen the load, he plans to feed his data to an artificial intelligence (AI) model. If the model trains on all the information he has already generated, he hopes that it will make increasingly accurate predictions about mutations he has not yet tested. DeepMind, Google's AI company, put out a model in 2023 called Alpha Missense that does this kind of prediction. It was benchmarked against an experimental data set which took ten years to generate, but with the massive gene-editing screens now possible, a data set of that size could be made in a couple months, he says.

I am the one who knocks

He is not the only one energised by CRISPR's potential to create big genetic screens. Silvana Konermann, the director and co-founder of the Arc Institute, a non-profit research institute in California, has pioneered a CRISPR screen using a tool that can systematically switch genes on or increase their activity—what one might call "knocking up". Such powers mean she can flip the traditional CRISPR screen on its head. Rather than start with a genetic variant and see what its outcome is, she can take an event, like exposure to a drug or a pathogen, and see which genes do and do not influence how the body responds.

Take SARS-CoV-2. In 2022 Dr Konermann and her Arc co-founder Patrick Hsu developed a CRISPR screen in which human lung cells had genes either knocked out by classic CRISPR or knocked up using the activation tool. The cells were then infected with SARS-CoV-2, and the team were able to say which genes in the human cells helped or hindered the virus. The virus struggled to infect the cells in which the genes responsible for making mucus proteins were more activated. Such variation in gene activity could help explain why some people suffered greatly from covid while others got through the pandemic unscathed. Some probably had very active mucus genes.

The next stage in screening is to target not the genes, but their products. The cell reads genes and copies them into RNA strands. Some of those strands become mRNA that is used to make proteins, but most remain RNA molecules, acting in ways that remain poorly understood. There are CRISPR systems that target RNA instead of DNA, including some developed by Dr Konermann and Dr Hsu. Scientists are now using them to find out what these molecules do. Many of these strange RNAs have been linked to disease, including psychiatric conditions like bipolar disorder. If one turns out to be a suitable drug target, no doubt a group of CRISPRed macaques on the east coast of China will be ready to test it out.

Eat your GE-greens

The Economist, February 21, 2025

The slightly soggy ziplock bags are labelled "Red Giant" and "Southern Giant Curl". Bunches of green leaves, not unlike watercress, strain the plastic. They are about seven days from full maturity, the person who sent them stressed in an email, so they will not have achieved their optimal flavour profile. Somewhat gingerly your correspondent tastes one, then the other, making sure to give them a proper chew and plenty of time with the taste buds.

They are gene-edited mustard greens. Usually mustard greens produce a sharp-tasting molecule called allyl isothiocyanate, but in these leaves, the responsible gene has been switched off using a version of CRISPR. The result is a mild taste and a pleasant umami scent; both work nicely in a cheese sandwich. They were grown by Bayer, a multinational pharmaceutical and biotech firm, but were developed by Pairwise, one of a handful of biotechs bringing gene editing to agriculture. It has also developed a seedless blackberry and is working on corn, wheat, soy and rapeseed that are resistant to disease and adapted to some of the effects of global warming.

Such goals may sound familiar. Proponents of genetically modified (GM) crops made similar promises 30 years ago about seeds which had new genes added to them. And they had successes. Most American corn is genetically modified; for the most part it has a gene for herbicide resistance added which means that fields can be sprayed with weed-killer without the crops being bothered (see chart). Almost half of arable land in Latin America yields similarly modified produce.

This is good for companies which sell weedkiller and weedkiller-resistant seed, and it is good for farmers who use their wares to increase their yields. But it has also proved controversial. By 2013 there were worldwide protests against Monsanto, then a massive producer of GM seeds, and widespread public scepticism towards the GM concept itself. Europe has never warmed to the idea, and its fierce regulatory standards have dampened the technology's use in developing countries which want to sell into European markets.

This time it's...different

Keen to avoid a rerun, companies and scientists hope to persuade consumers and officials that gene-edited food is altogether different from the GM sort: gene editing is its own distinct technology and, if allowed to, it will bring benefits to consumers, society and the climate in a way that GM never managed to.

Scientifically, gene editing is indeed different. For a GM plant, a gene from another species has been inserted into its genome—such as, in some GM corn, a gene from a microbe which bestows resistance to corn-eating insects. Because the gene comes from a foreign organism, GM plants are known as "transgenic", literally genes from "the other side". With gene-edited plants, scientists can tweak the plants' own genes by editing in small mutations, in effect creating changes that could have happened naturally. That means they can improve plants without DNA from other organisms.

Gene editing can thus be thought of as equivalent to fantastically fortuitous breeding. Plants can have complicated genetics: where humans have one genome, common wheat, for example, has three. That means that a beneficial mutation often has to happen in all three genomes to have an impact. In nature that rarely happens; CRISPR can do it all at once.

Cristobal Uauy, a geneticist, grows such gene-edited wheat at the John Innes Centre, a research institute in England. He is growing several strains in buildings where he adjusts temperature and humidity to simulate different climate conditions. Some are optimised for yield, with more grains on the same plant; some are edited to have healthier, fibre-like starch; and some are tweaked to have higher amounts of accessible iron.

Gene-edited crops may help adaptation to climate change

The centre, funded primarily by the British government, operates on the thesis that editing the foods that people already eat will improve public health. People love white bread—why not make it better for them? The same goes for tomatoes. Cathie Martin, another geneticist at the centre, makes a CRISPR edit that enables a precursor to vitamin D to build up in tomatoes. Once the fruit are exposed to sunlight the precursor transforms into the real vitamin, ready to be consumed in a soup, salad or pasta sauce.

Pairwise takes a different tack, that of making healthier foods more enticing—hence the less pungent mustard greens. This approach also shows up in the handful of gene-edited products already developed by others, which include a variety of non-browning fruits and vegetables, such as a non-browning avocado, sure to delight brunch-goers everywhere.

Gene-edited crops may also help adaptation to climate change. Take rice. Scientists from the Innovative Genomics Institute at the University of California, Berkeley, used CRISPR to limit the pores through which rice loses water, making it more drought-resistant. They are also editing rice to better capture carbon from the atmosphere and store it in the ground. Others at the institute hope to edit the methane-making microbes that live in rice paddies, generating 10% of the world's methane emissions. And gene-editing biotechs are working on less resource-intensive versions of soy, potatoes, bananas and more.

What will consumers and politicians make of GE crops? A decade after the Monsanto protests, some governments appear ready to embrace the new technology. In 2023 the British Parliament passed the Precision Breeding Act which will give gene-edited crops streamlined access to the English market. EU lawmakers, previously known for their GM-scepticism, may follow. Though the EU strictly regulates plants made through gene technology, a proposal is under consideration to exclude edited plants with

only simple modifications from those rules. Similar steps are being taken in America, Brazil, Japan and India (see map).

Slow down, you move too fast

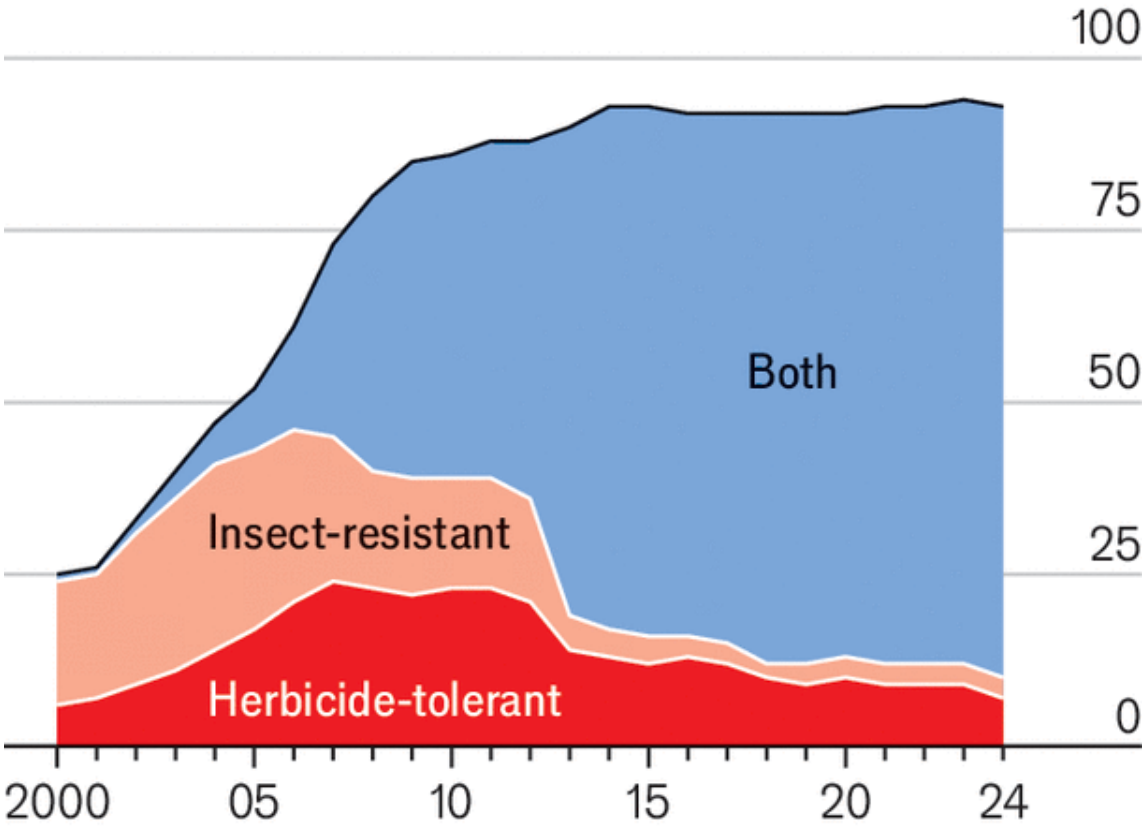
Not everyone is keen. In Europe some national authorities are alarmed at the EU proposal. “Any reference to ‘naturalness’ [of edited crops] is misleading and not a proxy for reduced risk,” Germany’s Federal Agency for Nature Conservation argued in a policy brief in 2024. The agencies want an assessment of risks from edited plants, such as for insects or other plants. A more drought-resistant plant, for example, might outcompete its native “natural” counterparts. Edited microbes will face more scrutiny, owing to their propensity to share their genes with other microbes, possibly spreading edits further than intended.

To some opponents, edited plants are just another chapter of the GM book. There is overlap in cast. The boss of Pairwise, Tom Adams, spent 20 years at Monsanto before the company was bought by Bayer. In fact Monsanto was an original investor in Pairwise. Many researchers now working on gene editing either used to or still dabble in GM plant-making themselves. Such connections, along with the novelty of the science, may fuel critiques from populist political figures.

But the key question for editing will not be whether it is a rerun of GM. It will be whether gene-edited crops can help crack challenges in public health and the climate? Judging by the recent enthusiasm, some policymakers seem to be coming round.

Fitter harvests

United States, genetically engineered corn as % of planted acres



Source: US Department of Agriculture

Editing pigs, mice and mosquitoes may save lives

The Economist, February 21, 2025

IN MARCH 15th 2024, a dark brown, gene-edited pig was driven from its home in the Midwest to a medical facility on the outskirts of Boston, Massachusetts. It had never before been outside the clean room in which it had spent its year-long life. The next day the pig had its kidneys removed. One was for research; the other was transplanted into a man called Richard Slayman. It was the first pig-to-human kidney transplant with a living patient. In the operating theatre at Mass General Hospital, after the surgical team were finished, invited attendees spontaneously clapped.

Xenotransplantation has been a dream for decades; now six people in America, so sick they were granted special permission, have received kidneys and hearts from pigs carefully crafted for their role as organ donors: a few porcine genes had been switched off, and several human genes added, to avoid the human body rejecting the organs. Only the two most recent recipients are still living; owing to their dire condition the first four, including Slayman, died within months. But clinical trials with healthier recipients are set to start this year. With more than 100,000 Americans waiting on a new organ, xenotransplantation is a leading example of how editing animals could benefit human society. But it is far from the only one.

It makes sense that the agriculture industry would toy with gene-edited animals; it is long-held practice to breed livestock that grow better and faster. CRISPR editing follows the same path. Japanese

regulators have approved several CRISPRed fish; in America the Food and Drug Administration (FDA) has given the nod to cattle that grow better in hot temperatures. But many scientists are focused more on improving health than increasing meat. Beyond giving people new organs, gene-edited animals could prevent the spread of diseases and possibly eradicate some of them.

This work is well under way for animal infections, probably because there is an obvious market for hardier livestock breeds. In 2023 Recombinetics, a gene-editing company in Minnesota, created a calf in a lab in Iowa which had been edited for protection against bovine diarrhoea virus, a pathogen dangerous to cows (and costly to farmers). Then in 2024 Genus, a genetics company outside London, established a line of gene-edited pigs immune to a virus sometimes referred to as "pig AIDS", which is responsible for as much as $1.2bn per year in production losses in America.

Animals can also be edited to protect humans. Take bird flu, a virus with obvious pandemic potential. If the spread in poultry could be stopped, it would limit human exposure and give the virus fewer opportunities to mutate. In 2023 Helen Sang, a biologist at the Roslin Institute in Scotland, used CRISPR in an attempt to edit protection against bird flu into chickens.

Fowl play

To replicate in a host cell, bird flu hijacks a protein belonging to a family of three, where the two other proteins are inactive. Switching off the gene responsible for making that protein should give the chickens immunity. That is exactly what Dr Sang's team did.

But things did not go quite to plan. Although the chickens seemed protected at first, the virus quickly mutated so that it could exploit the other proteins that had previously been useless to it. In the end, the team had to knock out all three genes to shut down infection, and it is unclear if the chickens can thrive when thus diminished. It was a lesson to scientists, says Dr Sang, to be careful about entering an arms race with a pathogen that humans might lose.

Scientists are thus trying to make sure that they win. Parts of New England are blighted by Lyme disease, a bacterial infection. People contract it from ticks that pick it up from white-footed mice. Kevin Esvelt, a bioengineer at MIT, has long wanted to release (initially on an uninhabited island) edited mice which cannot carry Lyme, and so lower the risk to humans. But it is not straightforward to prevent the Lyme bacterium from developing resistance**.**

Be careful about entering an arms race with a pathogen

Dr Esvelt begins by exposing mice to a protein from the bacterium's surface—think something like the coronavirus's spike protein. He waits for them to produce antibodies against it, then edits a new generation of mice to produce those antibodies from birth. He has previously edited one kind of antibody into normal lab mice, and says he has figured out how to edit white-footed mice, too. But he needs to edit in multiple antibodies to insure against resistance long-term. "To resist, [the Lyme disease bacterium] would need to acquire, presumably, at least four separate mutations all at once," he says. "Which, by my calculations, is pretty unlikely to occur for at least 100 years."

Designing babies

The Economist, February 21, 2025

One of the greatest scandals in modern science began with a late-2010s advertisement for HIV-positive couples looking to have children through *in-vitro* fertilisation (IVF). The ad had been put out by a scientist named He Jiankui, a biologist then at the Southern University of Science and Technology in China. Several pairs responded. For each couple, Dr He and his team harvested their sperm and eggs and created embryos through IVF. He edited a gene in each embryo using CRISPR, then did something that had never been done before: had the edited embryos implanted into the women's wombs.

The gene, CCR5, is responsible for a cell-surface protein which plays a key role in HIV infection. A natural variant of CCR5 blocks production of the protein and confers protection against HIV. It was this protection that Dr He sought to give the embryos. In November 2018, just before the second International Summit on Human Genome Editing, *MIT Technology Review* reported both that the experiments had taken place and that two of the embryos had, when implanted in the womb, resulted in successful births. As a result there were now two little girls with edited genomes.

Science friction

At the summit, Dr He appeared unprepared for the uproar that followed. His colleagues, who considered such experimentation premature and unsafe, were outraged. Slowly it became clear that not only did Dr He's work have technical failings, but also he had broken the rules within which scientists must operate. The informed consent of the parents seemed questionable; according to Chinese news reports, he had forged approval documents from an ethics review board. On top of all that, China forbids gene editing in human reproduction, and Dr He was not licensed to practice medicine. Dr He was detained by Chinese authorities and eventually sentenced to three years in prison for the illegal practice of medicine.

The condemnation of Dr He's work reflected in part a judgment of his careless approach to the lives of the people he "treated". The world knows nothing about the twins and the state of their health, nor about a possible third CRISPR child which was reported to have been born to another couple shortly after the twins. Questions about the quality of the edits themselves and what repercussions they might have on the children thus remain unanswered.

Many will be interested in enhancements that polygenic embryo editing could offer

But underneath the outrage lay long-running concerns about the fundamental concept of editing embryos. Edits which take place that early in the developmental process are passed on to every other cell as the embryo grows, including the "germline" cells that will eventually produce sperm or eggs. If nothing is done later to reverse them, they will thus be passed on down the generations—unlike the sort of CRISPR edit that cures a disease in someone already born. By definition future generations cannot give their informed consent to a procedure that takes place long before they are conceived. For that reason embryo editing is in effect banned in many European countries under the Oviedo Convention. (Many other countries, including Britain and Canada, also legally forbid the practice.)

The main attraction of embryo editing is that it allows edits which are very difficult or impossible later on. When editing a person who has already been born, some tissues, such as the brain, are very hard to reach. Embryo editing does not have that problem, as all the cells that go on to form the organs will in theory carry the edit. There are also people who think passing on an edit is not such a bad thing. Families in which successive generations have battled the same genetic disease often wish to spare their descendants the same fate, says Dagan Wells, a reproductive biologist at the University of Oxford (he is agnostic on the procedure).

Tailored genes

In January 2025 a paper appeared in *Nature* discussing the societal benefit of polygenic embryo editing—that is, making several edits in the same embryo. Rather than just curing genetic diseases, it could tweak multiple genes that together alter the risk of conditions like Alzheimer's disease or diabetes. The authors, led by Julian Savulescu, an Australian philosopher, acknowledged that the concept is speculative but suggested that it could dramatically benefit those who are edited. But what about those who are not edited?

The question of precisely who gets edited, and for what purpose, cuts to the heart of concerns around germline editing. Families struck by a genetic disease probably would benefit but they are in relative terms a fairly small group. Many will be interested in enhancements that polygenic embryo editing could offer. At first that might mean adding protection for preventable disease. But eventually it could mean tweaking traits like appearance and intelligence—in other words, creating designer babies. Some worry the rich would edit their offspring "better" and that people with disabilities or who are simply average would be put at greater disadvantage. "Gene-editing techniques applied to non-disease traits may deepen inequalities and raise the spectre of eugenics," argued Dr Savulescu and his team in their paper.

Others think it is far from clear that edited people will indeed benefit. A genetic variant that is advantageous in one context may be bad in another. The variant of CCR5 that protects against HIV, for example, has been linked to an increased risk of complications and even death during other infections. These unknowns are worth worrying about, argues Hank Greely, a lawyer at Stanford University and the author of the book "CRISPR People: The Science and Ethics of Editing Humans". His main objection to Dr He's CCR5 project was that its risk-benefit ratio was unacceptable: the benefits, if there were any, would be limited, and the risks, both any which were known and those yet to be understood, were potentially substantial. Dr He, who is out of prison and apparently back in a laboratory—the sources of

his funding as yet unclear—is unfazed by this ignorance. His new germline project focuses on a rare variant found in Icelanders which protects against Alzheimer's, though he has promised not to create any more pregnancies.

There are also signs that editing embryos might in itself be unsafe. Like regular gene editing, germline editing depends on natural repair mechanisms stepping in after an editor has made its cut. But when Dr Wells and Nada Kubikova, another Oxford scientist, used CRISPR to make 53 double-stranded breaks in human embryos, 21 of them remained unfixed (the embryos had been donated to science and were never going to be implanted). Dr Wells reckons the problem stems from the biology of the early embryo. For the first two to three days, the embryo mostly relies on proteins and mRNA from the egg instead of its own genome. During that time it struggles to repair injuries to its DNA, and any cuts left as the embryo develops could prove deleterious. With such bad odds, couples would need many embryos to ensure success.

Fetal attraction

With so many outstanding concerns, Dr Greely does not see germline editing taking off in the next few decades. But a less ethically fraught option may be on the way. Several groups are working on *in utero* genome editing. Done late enough in development it would not alter germline cells, but would still give doctors a chance to repair a genetic mutation before the baby is born. Like embryo editing it might be able to reach otherwise hard-to-access cells.

Early results have been encouraging. At the Children's Hospital of Philadelphia, William Peranteau has averted disease in mice using fetal editing, and successfully edited fetal monkeys. A group led by Panicos Shangaris at King's College London is working specifically on fixing the sickle-cell mutation this way. In sickle-cell disease scientists must fix the stem cells that go on to make blood. During the fetal stage of development these all reside in the liver, which is easy to reach with an injection into the umbilical cord. The approach could be especially useful for when the pathology starts early. Lysosomal storage diseases, in which cells fail to break down waste properly, begin in the womb. "You miss your window treating it if you wait till after birth," says Dr Peranteau. It might even be possible for fetal edits to reach the brain.

All conditions that become more difficult to treat after birth could be candidates for such editing. Epidermolysis bullosa is a terrible blistering disease that affects all skin and the oesophagus. Researchers led by Joanna Jackow at King's College London are working on developing a "gene cream" that fixes the genetic mutation directly in the skin's stem cells, but administering it is a massive challenge because children with the condition are covered in open wounds. Fetal editing might be able to reach those cells more easily.

The lure of germline editing, though, is unlikely to go away. Dr He's return to the lab suggests that the scientific establishment's condemnation was not as powerful as it first appeared. Rogues like him could well find patrons among the super wealthy. Billionaires with interests in reproductive technology and human enhancement—of whom there are several—might see both personal and business opportunities in embryo editing. People opposed to abortion might see germline editing as a way to avoid discarding or terminating embryos; Dr He has himself referred to editing an embryo as "saving a life". (Conversely, fundamentalist Christians may find the idea of editing embryos to be sacrilegious.) Whether CRISPR babies become a near-future reality may depend on whether such powerful interests become invested in the prospect.

Gene editing can still change the world

The Economist, February 21, 2025

At a now famous conference in 1975, a group of biologists met at Asilomar State Beach in California to discuss a new technology called recombinant DNA. For the first time, scientists could stitch together genes from different species: bacterial DNA could be put into a plant, say, or a human gene put into a fungus. The Asilomar conference agreed on a set of guidelines to ensure responsible research, and (after a few years of heated debates) a new era of biology eventually blossomed. Human insulin made by bacteria and yeast helped millions with diabetes. Doctors got tests for infectious diseases through

genetic probes that bound to the DNA of dangerous germs. And agricultural companies began producing genetically modified plants with built-in pest protection.

A similar step-change is under way now. Like recombinant DNA before it, gene editing has the potential to transform medicine, agriculture and more. CRISPR is now used by thousands of biologists in labs across the globe. A revolution in food crops could be around the corner. People with horrible diseases have been cured through alterations to their genes. With more CRISPR-based medicines in trials, some of which could benefit many millions of people, the number of edited people could soon increase.

Especially for therapies, hurdles remain. One is cost. Casgevy, the CRISPR cure for sickle-cell disease and beta-thalassemia, is expensive to make and to buy. Health-care systems in America and Britain have secured discounts and rebates to pay for it. Most people with these conditions live in African and Asian countries with much less buying and negotiating power. Another hurdle is old-fashioned regulation: many CRISPR medicines use the same components, but so far companies have been forced to test each component every time, limiting how many medicines they can invest in bringing to market. There are technical challenges, too: current methods can only send CRISPR to a subset of the body's tissues, leaving brain and muscle diseases off the table for now.

All of this has resulted in a sour business mood, and a number of gene-editing therapy companies are struggling to stay afloat. Some have dramatically narrowed their pipelines and laid off staff. Others have gone under. Five years ago, there was a frenzy of investment into CRISPR and the next-generation tools that followed. Recently those same investors have wondered just how much time and money it will take to turn these tools into actual therapies.

CRISPR just is better than what came before

But you do not become a successful artist when someone first hands you a paintbrush. Scientists first saw the potential of CRISPR just 13 years ago. They have had not just to learn how to use it, but also find the right subjects on which to lavish their skills. In medicine, that means finding the right genetic switch to flick to get a therapeutic outcome. In agriculture, it can mean editing three genomes at once while accounting for the influence of a changing climate. In disease prevention, it is about working out how to withstand resistance from pathogens. When considering this learning curve, the fact that there is a CRISPR cure on the market, pig organs going into clinical trials and non-browning avocados coming to a taqueria near you is testament to pretty fast progress.

A wealth of patients

The early hubris of the gene-editing therapy companies has hurt them, and they will have to learn from it before biotech fully re-emerges from its slump. It may yet turn out that venture-funded startups and pharmaceutical giants are poorly suited to developing and producing high-cost CRISPR therapies for the rarest of genetic diseases. Non-profits and public institutions may have to step in to fill a void should the economics of such therapies continue to be formidable.

At the same time, new doors have opened. Regulators seem willing to make it easier to bring more CRISPR medicines to market, not just because of keen advocates (one of whom describes himself as "a soldier" for Jennifer Doudna, a co-inventor of the technology) but also thanks to CRISPR's sheer potential. It just is better than what came before.

The deals between Vertex and public-payer healthcare systems in America and Britain reflect a willingness to bring cures to under-served groups, and new collaborations between the private and public sector aim to bring cures to rare diseases at a fraction of the cost of Casgevy. Outside of medicine, legislation to treat GE foods as different from GMO foods means the world might be able to turn a corner on a topic that had become needlessly contentious.

CRISPR has given scientists the means to get to know the biological world as never before. It has already carried research into a new, more productive era. That, alongside the work into delivery of ever-more-sophisticated editors, is what will fuel the next wave of CRISPR therapies, future-proof the world's food supply and lead to new scientific breakthroughs. So, while scientists and companies cannot afford to be complacent, the world should not lose hope for the age of gene editing. The best may yet be to come.

Rice variant slashes planet-warming methane emissions by 70 per cent

New Scientist, February 3, 2025

A new variety of rice created by simple crossbreeding could reduce the crop's emissions of methane, a powerful greenhouse gas, by nearly three-quarters.

Rice growing is responsible for around 12 per cent of anthropogenic release of methane, a gas that has a warming effect 25 times stronger than that of carbon dioxide.

The emissions come from soil microbes in the flooded paddy fields where rice is grown. These organisms break down chemicals known as root exudates released by the plants, producing nutrients that the plants can use, but also making methane in the process.

To learn more about factors affecting the production of methane from rice roots, Anna Schnürer at the Swedish University of Agricultural Sciences and her colleagues grew two strains of rice in a laboratory: a Japanese cultivar called Nipponbare with average methane emissions and a genetically modified strain with low methane emissions called SUSIBA2.

SUSIBA2 produced less fumarate, a root exudate known to be a key driver of methane emissions, than Nipponbare. But when both strains were treated with oxantel, a chemical that inhibits the breakdown of fumarate by bacteria, the SUSIBA2 strain still produced less methane. This meant there must be another factor causing the difference between the varieties.

It turned out that the SUSIBA2 crop was secreting high levels of ethanol, which also seemed to be suppressing methane emissions.

The team then turned to traditional breeding techniques to produce a new rice strain by crossing a high-yield elite variety with the Heijing cultivar, a strain that produces low fumarate and high ethanol.

Over two years of field trials in China, the new strain produced crop yields of more than 8 tonnes per hectare, compared with the global average of just over 4 tonnes, and it emitted 70 per cent less methane than the elite variety it was bred from.

Johannes le Coutre at the University of New South Wales in Sydney, Australia, says the study is an example of well-executed research into the culprits behind the crop's greenhouse gas emissions.

"The core point of the study is they don't use hard-core gene engineering or editing technologies or transgenic approaches," says le Coutre. "They use traditional crossbreeding in order to create new rice lines which lower the synthesis of methane."