TIMES evoke

A SUSTAINABLE SCIENCE

Genomics is among the most incredible scientific innovations of our times. It involves decoding DNA, often described as the 'instruction manual for life' since DNA encodes how an organism develops, functions and transmits inherited traits, including disease. Genome editing can change DNA itself. This impacts us powerfully — it unlocks possible cures for multiple ailments caused by DNA mutations, from heart disorders and diabetes to cancers and sickle cell disease, providing many with hope and relief. It enables scientists to bolster medicine more effectively — the swift response of the scientific world in developing Covid-19 vaccines through the current pandemic links back to years of genetic research. It could even help non-human species by reviving endangered birds and animals, mitigating some effects of the Anthropocene.

However, this science bears warnings. As it develops rapidly, scientists themselves are concerned about it generating health inequalities, unless such treatments are made equally accessible to all. Genomics also presents a dilemma of boundaries — how far should human genetic engineering go? Should it proceed beyond medicine, into a zone where people can choose 'desirable' qualities in babies? In 2018, a Chinese scientist created 'HIV-resistant genetically edited' twins, his 'experiment' rejected by a scientific world deeply concerned about such children's well-being. The need for an ethical framework is clearly pressing. This would also apply to non-human species — as scientists debate modifying disease-carrying vectors like mosquitoes, others worry if this could alter nature's balances within ecosystems. Should human beings assume such powers?

These questions highlight one fundamental fact — a sustainable science must be based on humility. As Times Evoke's global experts emphasise, the scientific world, and the industries that branch from it, must develop firm ethical boundaries. The 20th century, an era of untrammelled growth, saw scientific discoveries, from fossil fuel combustion to proliferating weaponry, damage nature and human society. In the 21st century, science must heal humanity, by benefitting the body, but also by inspiring the soul of the human community to approach nature — and all its life forms — with respect and empathy. Join Times Evoke on an exploration of how such science can help build a new sustainability.

'Genome editing can address multiple genetic conditions — but this must be accessible to all'

*Biochemist **Jennifer Doudna** won the 2020 Nobel Prize in chemistry for her research in gene editing. Doudna, who teaches at the University of California, Berkeley, with her co-winner Emmanuelle Charpentier, discovered 'clustered regularly interspaced short palindromic repeats' or 'CRISPR' DNA sequences that overthrow DNA from infectious bacteria. Speaking to **Srijana Mitra Das** at **Times Evoke**, Doudna discussed this discovery — and what lies ahead:*

What drew you to researching genome editing?

■ When I started investigating CRISPR, I wasn't studying genome editing at all. A colleague, Dr Jillian Banfield, came to me in 2006 to see if I would be interested in looking into something called 'CRISPR' — this was an unusual series of repeats that she had been finding in the genomes of bacteria. It appeared to be a form of immune system, but it wasn't well understood at the time.

It was basic scientific research into how CRISPR functioned in microbes that eventually led to the realisation that it could be harnessed as a tool to precisely cut DNA.

What are some breakthrough inventions in this field which you are looking forward to?

■ I spend a lot of time now thinking about delivery — how do we get genome editing therapies to the specific cells and tissues that we need to target for different diseases? If you can't get the genome editing molecules to where they need to go, it's not going to be an effective therapy, or it could have unwanted effects in other parts of the body. This is a critical area of research, and one with a lot of attention right now, so we'll be seeing some big advances there in the next few years.

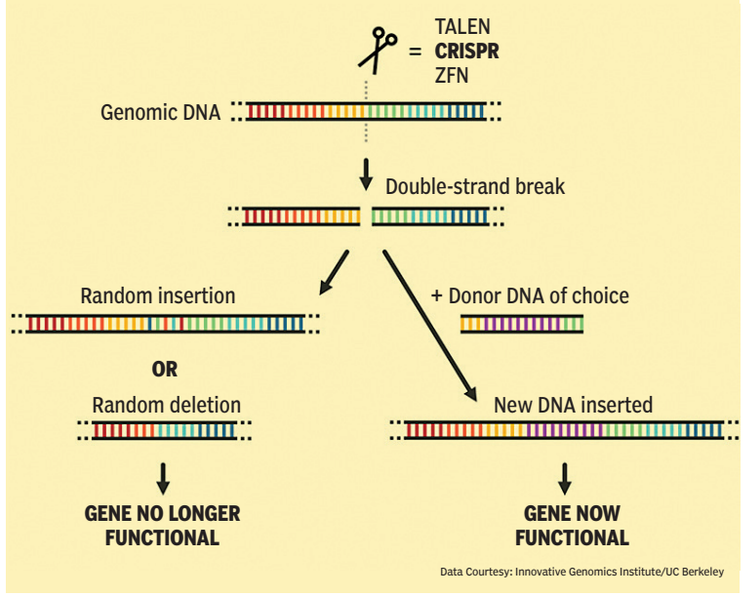
It may not sound very exciting at first glance, but when we unlock delivery, it will open the door to new therapies for a long list of unaddressed genetic diseases.

What are the most positive implications of genome editing for human biology?

■ The vast majority of medical research is directed at a small number of the most common diseases. This means that there are thousands of rare diseases that remain unaddressed, but the people affected by them are just as deserving of our attention. We have amassed a body of knowledge about the underlying causes of many diseases, but these simply aren't well handled by existing pharmaceutical approaches. For genetic diseases, or diseases that have some genetic component, genome editing gives us a way to think about these rare ailments more holistically — one core approach could address multiple diseases. I find this prospect extremely exciting.

CRISPR SOLUTIONS

The CRISPR-Cas9 system is used to make a precise cut in an organism's DNA — scientists can thus stop a harmful gene from working or add a helpful sequence



Data Courtesy: Innovative Genomics Institute/UC Berkeley

GENETIC ENGINEERING

What are some of the most worrying implications of genome editing for human society?

■ As with any powerful technology, the concern is always misuse of the technology and we have already seen this with the CRISPR-edited babies in 2018. What gets less attention, but concerns me greatly, is the possibility that some of the advances we make in genome editing will only benefit a small fraction of society. We have seen this inequity happen with new technologies in the past, so it's very important that we work consciously now to make advances in medicine accessible and affordable to all those who can benefit.

How can such diverse ethical challenges be resolved?

■ Ethical considerations are contextual, cultural and generational. There aren't always clear answers — in fact, it's likely to be an ongoing public debate and a balancing act. In the case of human germline editing, or any of the ethically contentious issues that arise around genome editing applications, there will undoubtedly be a rise in regulations over time around the world. However, they need to be carefully crafted, so that they protect from harm, but don't stifle innovation at the same time.

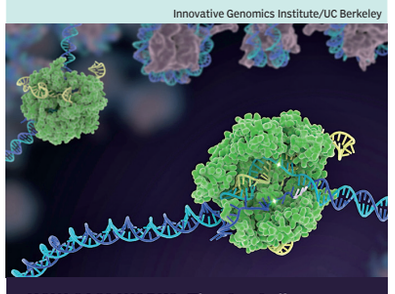
As a scientist, what has been the most important learning for you from the Covid-19 episode so far?

■ It's hard to see the positives when the pandemic has been such an overwhelming tragedy, but I have really taken to heart how much we can achieve when scientists come together behind a unified goal — there has been so much progress so quickly. At the Innovative Genomics Institute, the research institute I founded at UC Berkeley, we were able to set up a Covid-19 testing lab in a matter of weeks, and have now run over 2,00,000 tests. This would have sounded impossible just a year ago. We have to learn from this moment and carry the spirit of collaboration and shared goals forward to other big challenges facing humanity.

WHAT DIFFERENT GENES MEAN

- **Microbial Genetics:** Microorganisms have physiological characteristics that scientists study closely — **bacterial genetics is the basis of viral genetics** which fights pathogens across species
- **Molecular Genetics:** This studies the **structure of DNA, its cellular activities and how it shapes organisms.** It leads to genetic engineering — this is used in the biotech industry, which makes insect-resistant agri-products, etc.
- **Population Genetics:** This studies genes in animals, plants and microbes to understand **evolution and adapting**

Innovative Genomics Institute/UC Berkeley



HOW CAS9 WORKS: The Cas9 discovery is extraordinary as it found an RNA-guided protein which can search through a vast amount of genetic material to find a sequence of DNA which matches its programmable guide — Cas9 then uses two molecular blades to cut through the DNA helix and repair enzymes, sealing the gap in DNA, sometimes even inserting new genetic information. This can change disease-causing mutations by altering the underlying genetic code itself

- **Human Genetics:** This studies hereditary human gene traits to **treat genetically influenced health conditions.** This investigates haemophilia, cystic fibrosis, etc.
- **Genomics:** This sequences **the DNA of whole genomes, used to diagnose, edit and treat human disorders,** including cancers of various kinds

Encyclopaedia Britannica, Scientific American, The Lancet

'Support 'peripheral science' — early HIV research helped quick Covid-19 vaccines'

***Ravi Gupta** is professor of clinical microbiology at Cambridge University. His research on HIV highlighted a possible cure while his Covid-19 study discovered mutant varieties. Sharing his insights with **Times Evoke**, Gupta discusses the importance of backing 'peripheral science':*

I am an infection doctor and virologist. I've been working on HIV for ten years now, including in sub-Saharan Africa where my team researched drug-resistant HIV. In 2017, we tried a possible cure in London, when a cancer patient who was HIV-positive was undergoing a stem cell transplant. We injected him with the cells of a person whose genetics didn't have a functional CCR5 fibre receptor, which made them resistant to HIV.

VIROLOGY

It worked — the 'London Patient' eventually had no HIV in his system. It's been over three years now and he hasn't needed any anti-HIV drugs.

Our work became proof of principle that if you can introduce such a gene mutation into people, it could lead to a cure on a larger scale. Such breakthroughs in gene therapy, T-cell therapy and antibody-based therapies are the next frontier in science. There will be different ways of engineering T-cells or white blood cells, programming them to recognise HIV, giving them special properties and infusing them into people — such immunotherapy is on the verge now and the discovery of new treatments for HIV is something I'm looking forward to.

The pandemic also presented our lab with new challenges. Our interest being in the biology of viruses, we studied a patient infected with Covid-19 for over a hundred days — we could document in real time how new variants of the virus would emerge. With the application of therapies, we found the virus actually started changing dramatically. We could see the virus' real-time evolution — and we noted 'selection pressure'. When plasma or medication was applied, within days, you could see huge shifts in the genetic make-up of the virus — it started looking more like HIV, in terms of how it was constantly battling against the immune system. The virus genetic had a resistant population that emerged during plasma therapy and then, disappeared when the plasma washed away, the virus shifting back to its older version. When we gave the patient more plasma, the resistant population came back. There was a one-to-one corresponding relationship between administering plasma and that specific virus population coming out. The finding was remarkable — this was clearly a selected population and the selection pressure was likely the antibodies. Engineering the mutation in the lab, we found these viruses were less sensitive and weren't destroyed to the same extent by antibodies as the normal virus.

This research was the blueprint describing how new variants will emerge — in some people, Covid-19 actually learns to defeat the immune system. That's what makes these new variants so dangerous. We'll now be testing vaccinated people to check whether the antibodies made by the vaccine can neutralise the B.1.1.7 variant we have in the UK.

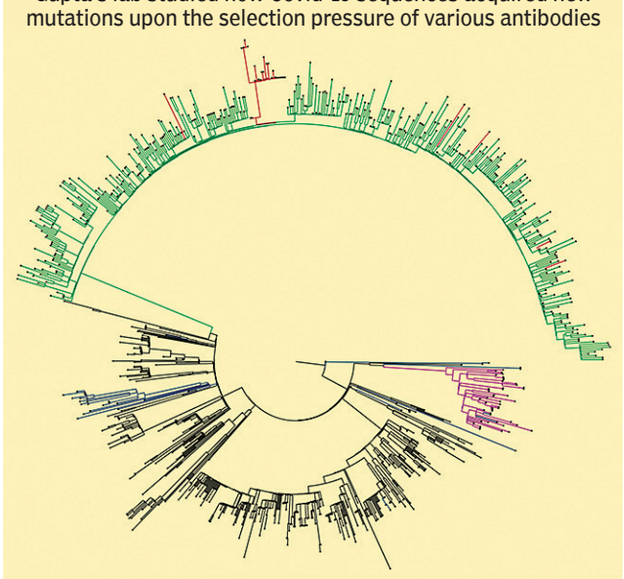
More broadly, there are important community lessons to be learnt from the pandemic. Earlier, relatively few people cared about HIV research, thinking that the ailment mainly impacted poor people in Africa. But the fact is, the science that came out of researching that virus is directly responsible for the Covid-19 vaccines we have today. The work done on the evolution of HIV enabled us to describe this evolution very quickly and precisely — supporting what people might perceive as 'peripheral science' is important because we don't know where the next threat is coming from and which bit of knowledge will help us stop that. The drugs for HIV were created by scientists studying chicken tumour viruses — that's where retrovirology came from, not from studying diseases in humans. We would have been at a huge disadvantage now if we didn't have all that other research. It's important to spread this message, especially in India, where resources are more limited and the pressure for translational science and research is high. All scientific exploration matters — and sometimes in ways we can't foresee.

Covid-19 has also shown how scientists can come together in amazing ways. The UK had a problem in testing, with standard labs taking upto three days to deliver results. We had technology which had been used earlier to monitor HIV — this was rapidly developed to give test results within an hour. Such discoveries have been heartening, but it's also been saddening to see the private sector play a limited role. If we had received more support in the scientific fight against Covid-19, we might have been able to end this in half the time. Instead, today the WHO has half the budget a giant delivery multinational would have just in India. The agency which eradicated smallpox has shrunk just when we need to expand it to protect us. We must revisit these priorities.

What's wonderful is how the public world over has engaged with science. With pre-printed scientific papers, press coverage and social media, science has become far more accessible to more people now. Science, as it was done in the old days, was often hierarchical, exclusionist, racist and sexist — that old system needed to be updated. Interesting new ways of communicating science will now emerge. I look forward to that while we carry on with our work in the labs.

TRACKED IN REAL TIME

Gupta's lab studied how Covid-19 sequences acquired new mutations upon the selection pressure of various antibodies



Data Courtesy: R Gupta (Medrxiv, February 3, 2021)

Courtesy: Ravi Gupta

AN EPIC BATTLE: Covid-19 variants versus vaccines

'Genetics can revive endangered, even extinct species — but with safeguards'

***Henry T Greely** teaches law and biomedical ethics at Stanford University. Sharing his perspective with **Times Evoke,** Greely discusses why genome editing could be needed to mitigate human-caused climate change effects and recover dwindling species:*

The CRISPR technology democratises genome editing. It's cheap and easy and thus available to many more people. I compare it to the Model T Ford in the US — there were automobiles before the Model T, but they were expensive and difficult. Only the rich could afford them, and the mechanic and chauffeur needed to use them. But everyone could afford the Model T and, within a decade, almost everyone in the US had a car.

Genome editing should now make it easier to prevent, treat or even cure diseases that have a strong genetic basis or conditions caused by variations in just one gene. Genome editing may also change non-humans in ways that help human beings. For example, there are discussions about editing mosquitoes, so that they are immune to malaria. If mosquitoes don't get malaria, humans don't get malaria. Whether this will be possible — and under what conditions it would be wise — are vast questions, but this is plausible and very important.

BIOETHICS

My biggest concern is that we will use genome editing on non-human organisms in ways that will harm the biosphere and human society. Humans have been modifying the biosphere since we came into existence, first through what we ate, but then with uses of fire, agriculture, domesticated animals — and greenhouse gases. So far, we've done this recklessly and we've made a mess, in fact, so big a mess that I suspect just 'leaving nature alone' will not allow a stable and diverse ecology to revive. As I see it, we might be able to use gene editing to feed ourselves with less land, fertilisers and pesticides, even in the face of a changing climate. We might be able to edit insects, so that they won't spread diseases among us. We might be able to use edited life forms to cleanse pollutants or make clean energy.

On the other hand, we're likely to do more and faster with non-human organisms because we worry more about human well-being than that of others. An undergraduate with five thousand dollars of equipment today might be able to change the DNA of a mosquito species globally, for good or bad, without anyone even realising it. There is clearly great potential, and in both directions. We need to proceed carefully — but we need to proceed. Doing nothing, i.e., renouncing genetic engineering as a possible tool, might prevent mitigating the damage from climate change or preserving endangered ecosystems. But how we proceed is complicated and we should be aware of that.

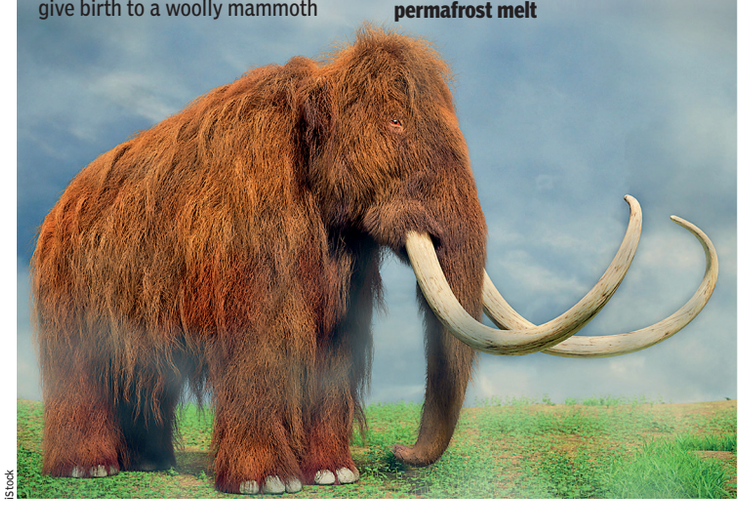
I'm sometimes asked if genetically edited non-human species can inspire the same awe as nature's creations. My response is that creatures like Bengal tigers have been around for a long time, but they still cause awe, as do great mountains and coral reefs. A 'revived' woolly mammoth would be one more cause of wonder. Personally, I would love to see a sabre-toothed cat from 20,000 years ago, or a giant ground sloth like Megatherium, about 20 feet long and four tonnes in weight.

The endangered species are just as interesting. The northern white rhinoceros is termed a 'zombie species' — only two individuals remain, both female, old and ill. They aren't extinct yet, but they surely will be, unless modern biology intervenes, in this case, to use stored genetic matter carried to birth in southern white rhinoceros females. Gene editing could also reintroduce genetic variations lost in animals, providing a more diverse and healthier population. That idea has just been advanced by the cloning of a black-footed ferret, an endangered North American small mammalian predator, from a cell line created in 1988. The resulting ferret pup has genetic variations absent in the existing ferret population, but common 25 years ago.

Of course, some, citing the precautionary principle, will say, 'Don't do anything because you can't know what will happen'. But I'd prefer us to do a careful and intelligent weighing of the risks and benefits, with workable safeguards built in. That is the scientific way.

A MAMMOTH UNDERTAKING

- Harvard geneticists now seek to resurrect the long-gone **woolly mammoth — the shaggy Ice Age herbivore**, which lived on northern continents in climates of extreme cold, **went extinct about 4,000 years ago**, but genetics can return these
- Genetic tools enable scientists to **sequence the mammoth's genes found in fossils**, recreate and place these in the closely-related Asian elephant, for **the elephant** to then give birth to a woolly mammoth
- Reviving the woolly mammoth can help our ecological well-being — the **Siberian steppes** are composed of **permafrost** which contains vast amounts of **carbon.** With global warming, permafrost is melting, which could release more harmful carbon. But **permafrost temperature can be significantly lowered by reintroducing large animals like mammoths and bison,** which help the growth of steppe grasses that reflect sunlight back into the atmosphere, lowering heat absorption — and **reducing permafrost melt**



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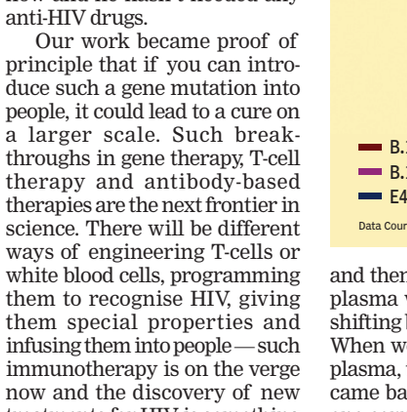
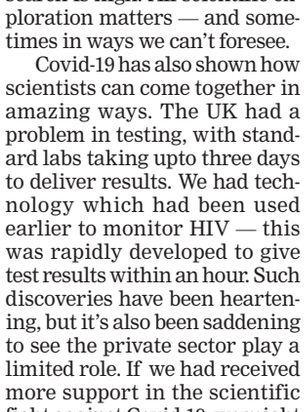


Photos: iStock

NEW PAIRS OF GENES

- Saving the **northern white rhino** is a huge scientific challenge — geneticists are creating reproductive material from frozen cells and embryos using stem cell techniques, which can be placed in related southern rhinos acting as surrogates. **Poached for their horns** used in traditional Chinese medicine, the northern white rhino, with only two members of the species left, is already considered functionally extinct — **advanced genetics could save it from vanishing altogether**



- With the destruction of forests, the **pink pigeon of Mauritius is dangerously vulnerable**, with just about 400 birds left. Its lack of genetic diversity makes it susceptible to trichomonosis disease, which attacks its chicks and curbs its population growth — scientists are **trying to pinpoint the genes that make the birds vulnerable** and find others better suited to fight the disease by adding **genetic diversity**

- The **Florida panther** was once found widely across southeast USA but by the 1970s, facing **hunting and habitat loss,** it shrank to about 20 adults only. Male panthers showed signs of inbreeding depression which could cause the group to go extinct — till **scientists combined female mountain lions with male Florida panthers to boost their gene pool.** This created a healthy and growing population

Research: National Geographic, Smithsonian Magazine, LiveScience