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Can CRISPR Technology Help Prevent Future Pandemics Through Genome Editing?

Ana Tauqir

Student at Gems New Millennium School, Al Khail

Abstract:
The first genome editing technologies were developed in the late 1900s. More recently, a new genome editing tool called CRISPR, invented in 2009, has made it easier than ever to edit DNA. CRISPR is simpler, faster, cheaper, and more accurate than older genome editing methods. Many scientists who perform genome editing now use CRISPR.
Scientists are developing **gene therapies** - treatments involving genome editing - to prevent and treat diseases in humans. Genome editing tools have the potential to help treat diseases with a genomic basis, like cystic fibrosis and diabetes. There are two different categories of gene therapies: germline therapy and somatic therapy. Germline therapies change DNA in reproductive cells (like sperm and eggs). Changes to the DNA of reproductive cells are passed down from generation to generation. Somatic therapies, on the other hand, target non-reproductive cells, and changes made in these cells affect only the person who receives the gene therapy.

Introduction:
Genome editing is a method that lets scientists change the DNA of many organisms, including plants, bacteria, and animals. Editing DNA can lead to changes in physical traits, like eye colour, and disease risk. Scientists use different technologies to do this.
Genome editing technologies enable scientists to make changes to DNA, leading to changes in physical traits, like eye colour, and disease risk. Scientists use different technologies to do this. These technologies act like scissors, cutting the DNA at a specific spot. Then scientists can remove, add, or replace the DNA where it was cut.
In 2015, scientists **successfully used** somatic gene therapy when a one-year old in the United Kingdom named Layla received a gene editing treatment to help her fight leukaemia, a type of cancer. These scientists did not use CRISPR to treat Layla, and instead used another genome editing technology called TALENs. Doctors tried many treatments before this, but none of them seemed to work, so scientists received special permission to treat Layla using gene therapy. This therapy saved Layla's life. However, treatments like the one that Layla received are still experimental because the scientific community and policymakers still have to address technical barriers and ethical concerns surrounding genome editing.

1. Technical barriers

Even though CRISPR improved upon older genome editing technologies, it is not perfect. For example, sometimes genome editing tools cut in the wrong spot. Scientists are not yet sure how these errors might affect patients. Assessing the safety of gene therapies and improving upon genome editing technologies are critical steps to ensure that this technology is ready for use in patients.

Ethical concerns

Scientists and all of us should carefully consider the many ethical concerns that can emerge with genome editing, including safety. First and foremost, genome editing must be safe before it is used to treat patients. Some other ethical questions that scientists and society must consider are:

1. Is it okay to use gene therapy on an embryo when it is impossible to get permission from the embryo for treatment? Is getting permission from the parents enough?
2. What if gene therapies are too expensive and only wealthy people can access and afford them? That could worsen existing health inequalities between the rich and poor.
3. Will some people use genome editing for traits not important for health, such as athletic ability or height? Is that okay?
4. Should scientists ever be able to edit germline cells? Edits in the germline would be passed down through generations.

2. How does CRISPR-Cas9 work?

- The CRISPR-Cas9 system consists of two key molecules that introduce a change (mutation) into the DNA. These are:
  - an enzyme called Cas9. This acts as a pair of 'molecular scissors' that can cut the two strands of DNA at a specific location in the genome so that bits of DNA can then be added or removed.
  - a piece of RNA called guide RNA (gRNA). This consists of a small piece of pre-designed RNA sequence (about 20 bases long) located within a longer RNA scaffold. The scaffold part binds to DNA and the pre-designed sequence 'guides' Cas9 to the right part of the genome. This makes sure that the Cas9 enzyme cuts at the right point in the genome.
- The guide RNA is designed to find and bind to a specific sequence in the DNA. The guide RNA has RNA bases that are complementary to those of the target DNA sequence in the genome. This means that, at least in theory, the guide RNA will only bind to the target sequence and no other regions of the genome.
- The Cas9 follows the guide RNA to the same location in the DNA sequence and makes a cut across both strands of the DNA.
- At this stage the cell recognises that the DNA is damaged and tries to repair it.
- Scientists can use the DNA repair machinery to introduce changes to one or more genes in the genome of a cell of interest.

3. What other techniques are there for altering genes?

- Over the years scientists have learned about genetics and gene function by studying the effects of changes in DNA.
- If you can create a change in a gene, either in a cell line or a whole organism, it is possible to then study the effect of that change to understand what the function of that gene is.
- For a long time, geneticists used chemicals or radiation to cause mutations. However, they had no way of controlling where in the genome the mutation would occur.
- For several years scientists have been using 'gene targeting' to introduce changes in specific places in the genome, by removing or adding either whole genes or single bases.
- Traditional gene targeting has been very valuable for studying genes and genetics; however, it takes a long time to create a mutation and is fairly expensive.

- Several 'gene editing' technologies have recently been developed to improve gene targeting methods, including CRISPR-Cas systems, transcription activator-like effector nucleases (TALENs) and zinc-finger nucleases (ZFNs).
- The CRISPR-Cas9 system currently stands out as the fastest, cheapest and most reliable system for 'editing' genes.

4. What are the applications and implications?

- CRISPR-Cas9 has a lot of potential as a tool for treating a range of medical conditions that have a genetic component, including cancer, hepatitis B or even high cholesterol.
- Many of the proposed applications involve editing the genomes of somatic (non-reproductive) cells but there has been a lot of interest in and debate about the potential to edit germline (reproductive) cells.
- Because any changes made in germline cells will be passed on from generation to generation it has important ethical implications.
- Carrying out gene editing in germline cells is currently illegal in the UK and most other countries.
- By contrast, the use of CRISPR-Cas9 and other gene editing technologies in somatic cells is uncontroversial.

5. What's the future of CRISPR-Cas9?

- It is likely to be many years before CRISPR-Cas9 is used routinely in humans.
- Much research is still focusing on its use in animal models or isolated human cells, with the aim to eventually use the technology to routinely treat diseases in humans.
- There is a lot of work focusing on eliminating 'off-target' effects, where the CRISPR-Cas9 system cuts at a different gene to the one that was intended to be edited.

6. Virus transmission can occur through multiple pathways.

- Some viruses can travel within the droplets of mucus and spit that are ejected when an infected person breathes, talks, coughs, or sneezes. The virus can be passed on when those **respiratory droplets** land in the mouth or nose of someone else. Larger respiratory droplets are heavier than air, so gravity pulls them to the ground almost immediately after leaving a person's body. Social distancing recommendations are meant to prevent the spread of a virus through these larger respiratory droplets.
- Smaller droplets (those below 5 microns, or 5 millionths of a meter; about the size of a red blood cell) are sometimes called **aerosols**. These smaller, lighter droplets can be suspended in air for longer periods of time, and they can travel longer distances. This can lead to **airborne transmission** of a virus.
- With **fomite transmission**, virus particles from an infected individual can end up on surfaces, where they can linger. The virus can spread if someone touches that surface, then touches their own mouth, nose, or eyes.
- **Transfusion-transmitted infections** occur as a result of viruses that are transmitted through the blood, often through blood transfusions.
- Viruses that cause malaria, West Nile, and rabies rely on **vector-borne transmission**. In this case, a virus is present in a vector such as a mosquito, flea, or tick but doesn't cause any harm. When the

vector comes into contact with the bloodstream of a suitable host, such as when a mosquito bites a human, the virus is passed on, leading to infection in the host.

- Viruses also can be passed from mother to child in a process called **vertical transmission** or **maternal-fetal transmission**. This can occur in utero or during childbirth.

7. Virus mutation and evolution

Viral infection is a highly dynamic process, which lead to constant evolutionary changes on both sides of the viral–host interface. The high mutation rates of viruses, coupled with short generation times and large population sizes, allow viruses to rapidly adapt to the host environment. However, this high mutation rate also comes at a cost to the viral population, as deleterious mutations are constantly created, leading to a plethora of defective genomes. Here, we will discuss the basic tenets that govern the evolution of viruses: mutation rates, population size, selection, the multiplicity of infection, and how these factors modulate infection as viruses evolve within a host, during transmission to novel susceptible hosts, and as viruses establish infections in new host species.

Virus mutations create genetic diversity, which is subject to the opposing actions of selection and random genetic drift, both of which are directly affected by the size of the virus population. When the population size is large, selection will be predominant and random drift less common. This means that deleterious alleles will be efficiently removed from the population, while adaptive alleles will have an opportunity to take over the population. However, when the population size is small, random effects may obscure the effects of selection. Under these conditions, slightly deleterious alleles may rise to an unexpectedly high frequency in the population, and adaptive alleles may be lost by chance.

8. Mutation composition in a virus population.

With the advent of next-generation sequencing (NGS), it is possible to capture accurate information on rare mutations present in a population. Low MOI will tend to select for viruses that are the “fittest” under the specific growth conditions. Using a sequencing technique that reduces the high error rate of prevalent NGS techniques, Acevedo et al. (2014) could accurately record the frequency of lethal mutations, which are expected to be present in a population at a frequency equal to the basic unbiased mutation rate. Applying this method to Poliovirus 1 populations confirmed a mean mutation rate of 3.97×10^{-4}, consistent with previous measurements. However, these results yield a level of detail previously less appreciated: different pairs of bases are replaced at different rates. A further intriguing study has shown that measurements of viral mutation rates vary substantially when measured across different cell types. Thus, there are previously unappreciated layers of complexity in the ascertainment of viral mutation rates.

9. Virus detection

(COVID-19) pandemic which has created massive problems globally affecting all aspects of people's life. Due to the emergence of new strains of the SARS-CoV-2, pandemic risk still remains, despite the start of vaccination. Therefore, rapid diagnostic tests are essential to control infection, improve clinical care and stop the spread of the disease. Recently CRISPR-based diagnostic tools have facilitated rapid diagnostic. Here, we review the diagnostic applications of CRISPR-Cas system in COVID-19.

A novel coronavirus, SARS-CoV-2, emerged in 2019 and caused the global pandemic COVID-19, infecting millions and leading to significant mortality worldwide. As a highly transmissible RNA virus capable of rapid mutation, it remains a major health concern despite advances in treatments and vaccines.

Traditional diagnostic methods, such as RT-PCR, have limitations in cost, speed, and sensitivity, highlighting the need for improved detection techniques.

CRISPR-Cas technology, originally part of a bacterial immune system, has shown strong potential in diagnosing and treating infectious diseases. By enabling rapid, accurate detection of viral genetic material, CRISPR-based systems offer a promising alternative for early diagnosis and better control of disease spread.

10. CRISPR-Cas Systems in Nucleic Acid Detection

The CRISPR-Cas system has revolutionized genome editing and is now widely used for rapid and precise detection of nucleic acids. It is divided into two main classes: Class 1 systems use multi-protein complexes, while Class 2 systems (including Cas9, Cas12, and Cas13) rely on single proteins. Cas9 and Cas12 target DNA, whereas Cas13 targets RNA. Notably, Cas12 and Cas13 remain active after binding to their target, enabling them to produce detectable signals, such as fluorescence, for identifying genetic material. This property has led to the development of advanced diagnostic tools like SHERLOCK, DETECTR, FELUDA, CONAN, and VaNGuard for early disease detection, including COVID-19.

- **Editing Viral DNA/RNA Inside Infected Cells**

These treatments enter the cell to directly cut or degrade the virus's genome, preventing replication.

- HIV (DNA/Provirus Editing): CRISPR-Cas9 can remove integrated HIV-1 DNA from immune cells, potentially eliminating latent infection, as shown in lab and animal studies.
- Hepatitis B (HBV): CRISPR targets persistent cccDNA, reducing viral DNA levels by up to 98% in studies.
- RNA Viruses (PAC-MAN): CRISPR-Cas13 targets and degrades RNA of viruses like COVID-19 and influenza, stopping replication without altering host DNA.
- Herpes Simplex Virus (HSV-1): CRISPR tools can target latent viral reservoirs, significantly reducing viral load in experimental models.
- **Making Cells Resistant to Viruses**

This strategy involves editing the **host cell's genome** to remove receptors or add protective genes, rendering them immune to viral entry or replication.

- **CCR5 Editing for HIV:** HIV-1 typically requires the CCR5 or CXCR4 co-receptor to enter T cells. Using CRISPR or ZFN (Zinc Finger Nucleases) to disrupt (knock out) the *CCR5* gene creates cells that are resistant to HIV infection.
- **MOGS Gene Modification:** Modifying the mannosyl oligosaccharide glucosidase (MOGS) gene can prevent viruses from producing infectious offspring, meaning any virus entering these edited cells cannot spread, as seen in HIV research.
- **Receptor Deletion (HCV):** CRISPR–Cas9 can delete genes for receptors like Claudin-1, rendering liver cells resistant to Hepatitis C virus (HCV) infection.
- **Key Technologies and Advantages**
- **CRISPR-Cas9:** Uses a guide RNA (gRNA) to direct the Cas9 enzyme to a specific DNA sequence, creating a double-strand break (DSB) that disrupts the gene.
- **CRISPR-Cas13:** Targets single-stranded RNA (ssRNA) directly, making it ideal for RNA viruses.
- **Base Editing:** An improved, safer version of CRISPR that changes specific bases without inducing double-strand breaks, reducing off-target risks, particularly useful for persistent HBV.

- **Advantages over Traditional Drugs:** Conventional antivirals usually only suppress viral replication, requiring lifelong administration. Gene editing can permanently eliminate the virus or make the host permanently resistant.
- **Challenges and Future Directions**

While promising, these treatments face hurdles in transitioning from laboratory to human clinics:

- **Delivery Systems:** Efficiently delivering editing tools into all infected cells in the human body is difficult.
- **Off-Target Effects:** Risk of CRISPR accidentally editing the host's own DNA.
- **Viral Escape:** Viruses can mutate around the CRISPR-induced cleavage sites.
- **Solutions:** Using **multiplexed guide RNAs** (targeting multiple sites at once) and **advanced delivery vehicles** (like lipid nanoparticles or adeno-associated viruses) to improve precision and efficacy.

11. Challenges and Innovations in Antiviral Therapy

Viral infections cause widespread illness and death and can trigger epidemics or pandemics with serious socioeconomic impacts. Drug-resistant strains and emerging viruses demand novel antiviral strategies. Traditional drugs are limited because viruses exploit host cellular machinery, so inhibiting viral replication often disrupts normal host functions. The diversity among viruses also makes broad-spectrum antivirals difficult to develop. Consequently, newer approaches like RNA interference (RNAi) are being explored, though they have limitations

for instance, RNAi cannot eliminate HBV cccDNA, leading to potential viral reactivation if treatment stops.

12. CRISPR-Based Gene Drive: A Promising Tool for Malaria Control

However, in the era of insecticide and drug resistance, gene drive technology provides a new tool for controlling malaria spread through genetic modification of mosquitoes to reduce their vectorial capacity for Plasmodium parasites. Gene drive technology utilizes CRISPR technology to precisely edit the DNA of mosquitoes, either disrupting essential genes or inserting beneficial traits.

Methods: A literature search was done using SCOPUS and MEDLINE databases until October 2023 to identify gene drives, advantages, disadvantages, and issues.

Results: Gene drives utilize biased inheritance of target genes to spread rapidly among mosquitoes. Homing using homology-directed repair increases homozygotes among mosquitoes. Gene drives have two approaches: population modification, where gene traits are spread without reducing mosquito populations, and population suppression, where populations are reduced through sterility or sex ratio distortion. Gene drives utilizing CRISPR technology have been reported to achieve almost 100% biased inheritance in mosquitoes, rendering them infertile or unable to bite humans.

13. Long-term consequences on biodiversity and reversibility:

Through, Gene drive rapid spread can permanently introduce irreversible changes to biodiversity.

This ethical concern must be addressed through an evaluation of the long-term consequences of gene drive and the implementation of measures to reverse the negative consequences of this molecular tool. Other ethical concerns about gene drive interventions, such as the equitable distribution of benefits and access, as well as the potential for inappropriate use or misuse, can be effectively tackled through a

multidisciplinary approach, such as Planetary health. Planetary health as a multidisciplinary framework involves collaborations between researchers, policymakers, affected communities and ethicists.
This can pave the way for the development of robust guidelines and protocols to navigate these ethical concerns, ensuring the sustainable beneficial use of gene drive technology.
Safety concerns and unexpected consequences: gene drive has the potential to spread rapidly in the natural environment. The direct impact resulting from the eradication of mosquito species and the indirect effects through the cross-breeding approaches may give rise to unintended negative consequences for public health and environmental well-being, thereby raising substantial concerns regarding its use

14. Vaccine Platforms Overview

The classical vaccines, i.e., inactivated, live attenuated, and toxoid vaccines, stimulate immunity through mimicry of infection but require multiple doses.
The recombinant or subunit vaccines, like hepatitis B and HPV vaccines, use specific proteins or peptides to stimulate immunity effectively and safely.
The DNA vaccines introduce a piece of plasmid DNA directly into host cells, thus activating a strong immune response. These vaccines are thermally stable, cost-effective, and have the potential for rapid outbreak response.

15. Limitations of Current Diagnostics

RT-qPCR has been considered the gold standard since the emergence of the COVID-19 pandemic. Nevertheless, there has been a wide range of symptoms associated with the disease, and false-negative results have been reported.

16. Advantages of CRISPR-Based Detection

CRISPR-based detection of SARS-CoV-2 has been reported to be cost-effective, time-efficient, and highly sensitive and specific. The method has been observed to be feasible for use in POC settings and does not require complicated equipment. The system has been reported to be customizable, allowing it to target various genomic regions, thus making it versatile.
Malaria remains a major public health concern, with many African nations being far from meeting their malaria elimination targets· Vector control methods including indoor residual spraying and long-lasting insecticide-treated bed nets have played a pivotal role in reducing malaria incidence, but the emergence of insecticide-resistant mosquitoes has impeded further progress. Gene drive technology, which enables the biased inheritance of selected traits and can spread through populations at rates exceeding those predicted by Mendelian genetics, has emerged as a promising new paradigm
Gene drives pose significant ecological risks, including irreversible alteration of natural populations, unintended suppression of non-target species, and unpredictable cascading effects on ecosystems. These technologies, designed to spread specific genetic traits through wild populations, could cause ecological imbalances by removing species or introducing harmful traits.

Key ecological risks associated with gene drives include:

- **Irreversible Ecological Disruption:** Gene drives can cause rapid extinction of entire species or populations in the wild, which may lead to unforeseen consequences in interconnected ecosystems, such as breaking food chain dependencies.

- **Targeting Non-Target Species:** There is a high risk that the genetic modification will spread to closely related species, causing unintentional damage to species outside the target area.
- **Irreversibility and Loss of Biodiversity:** Once released, gene drive organisms (GDOs) are difficult to recall. This persistence, combined with the intentional suppression of wild populations, can result in irreversible losses of biodiversity.
- **Uncertainty and Unpredictability:** Laboratory research is outpacing ecological field studies, leaving critical knowledge gaps about how gene-drive modified organisms behave in complex natural environments.
- **Horizontal Gene Transfer:** A potential risk of the gene drive spreading across species boundaries via unexpected mechanisms, affecting species that were not intended to be targeted

To determine how effective Cas13 was at destroying the viruses, the researchers also used it as a diagnostic tool to see how much viral RNA was being released from infected cells.

"The results are very impressive," says Chen Liang, a professor at the Lady Davis Institute at Jewish General Hospital and the department of microbiology and immunology at McGill University in Montreal, Cas13 can be used to target one virus using several guide RNAs, making it difficult for the virus to "escape." Secondly, the new study also used Cas13 to detect how much viral RNA was left over to infect cells. The amount of viral knockdown the group achieved is "very significant," Liang says. "If you can target and inactivate all three [of these] viruses, in principle, you can inactivate any virus."

Freije agrees. "We are definitely excited about future prospects of optimizing the system and trying it out in mouse models," she says. Beyond therapeutics, the team hopes to understand more about how viruses operate how they replicate and what parts of their genomes are most important. Using approaches like this, "you can really start to get a better picture of what parts of these viruses are and, most importantly, what really makes them tick."

17. Conclusion:

Research on CRISPR-Cas13 has shown efficacy against influenza, SARS-CoV-2, and other RNA viruses. Unlike conventional antiviral drugs, CRISPR-based approaches can also be rapidly reprogrammed to target new viral strains, offering a versatile and dynamic treatment strategy.[1]

Beyond viral infections, CRISPR has also demonstrated potential in addressing bacterial pandemics. Researchers are developing CRISPR-based antimicrobial strategies to combat antibiotic-resistant bacteria, which is another growing global health threat.

By selectively targeting bacterial genomes, CRISPR-based antimicrobials could provide a novel solution to multidrug-resistant infections, reducing the risk of secondary bacterial outbreaks during viral pandemics

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