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Overcoming Challenges Faced During Gene Therapy Development for COVID-19

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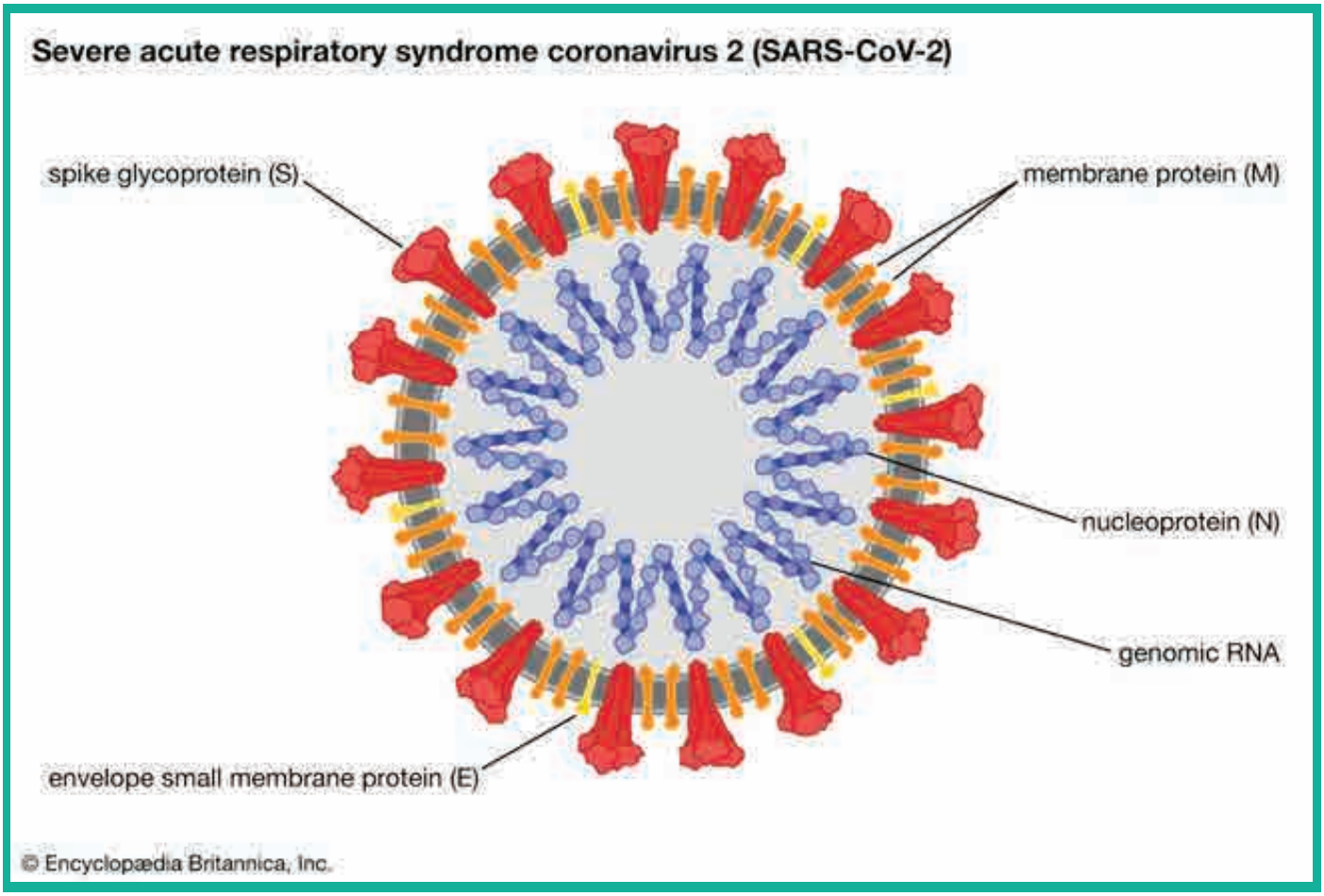
1. Abstract

The Covid-19 pandemic is one the most devastating crisis humanity has ever faced in the 21st century, and one must not be complacent as there might be others headed our way.

The recently approved vaccines provide a ray of hope for the end of this menace. Several technologies are also being tested to be used as an effective treatment.

Gene therapy is widely being studied as a potential treatment. It is a potential cure for various life-threatening diseases.

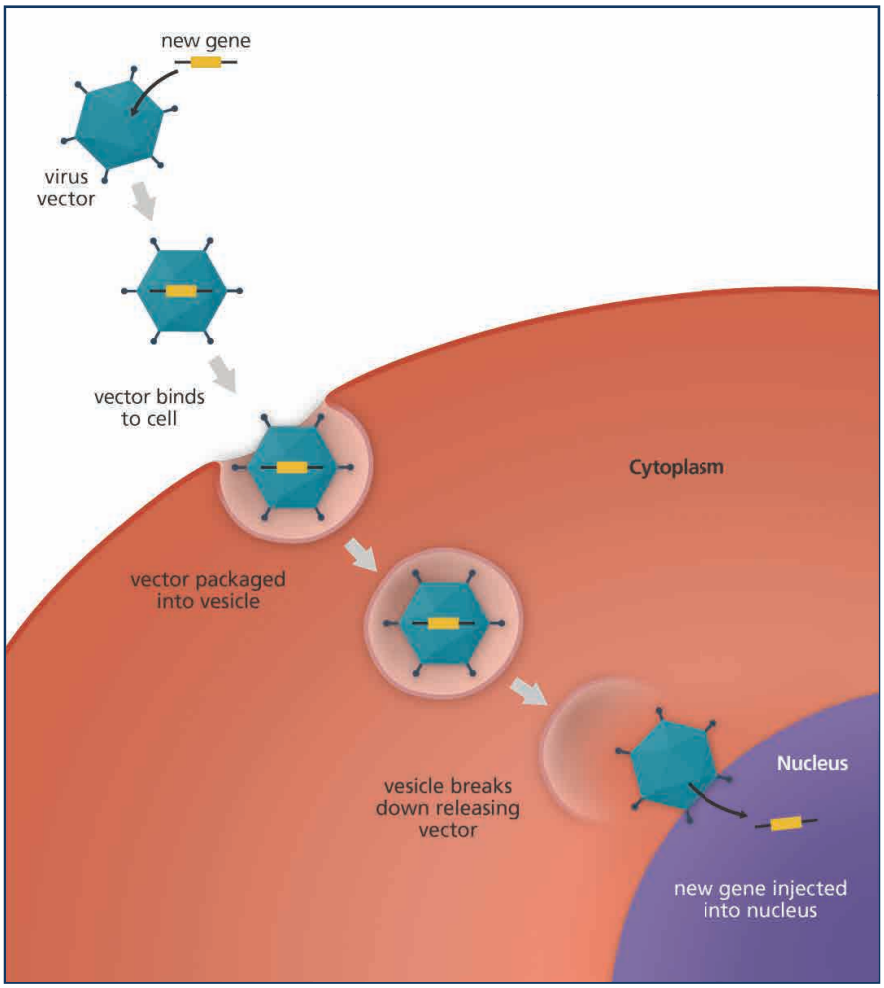
Through this white paper, we aim to highlight the challenges faced in developing covid-19 treatment strategies. It also covers how these challenges can be overcome and how companies are venturing into developing gene therapy for Sars-CoV-2.



2. Introduction

As the pandemic engulfed the entire world, a race began to develop drugs and vaccines to counter it, which had the sole purpose of targeting the viral life cycle in the early stages. The limited knowledge about the molecular characteristics of SARS-CoV-2 further hampered the efficacy of these vaccines.

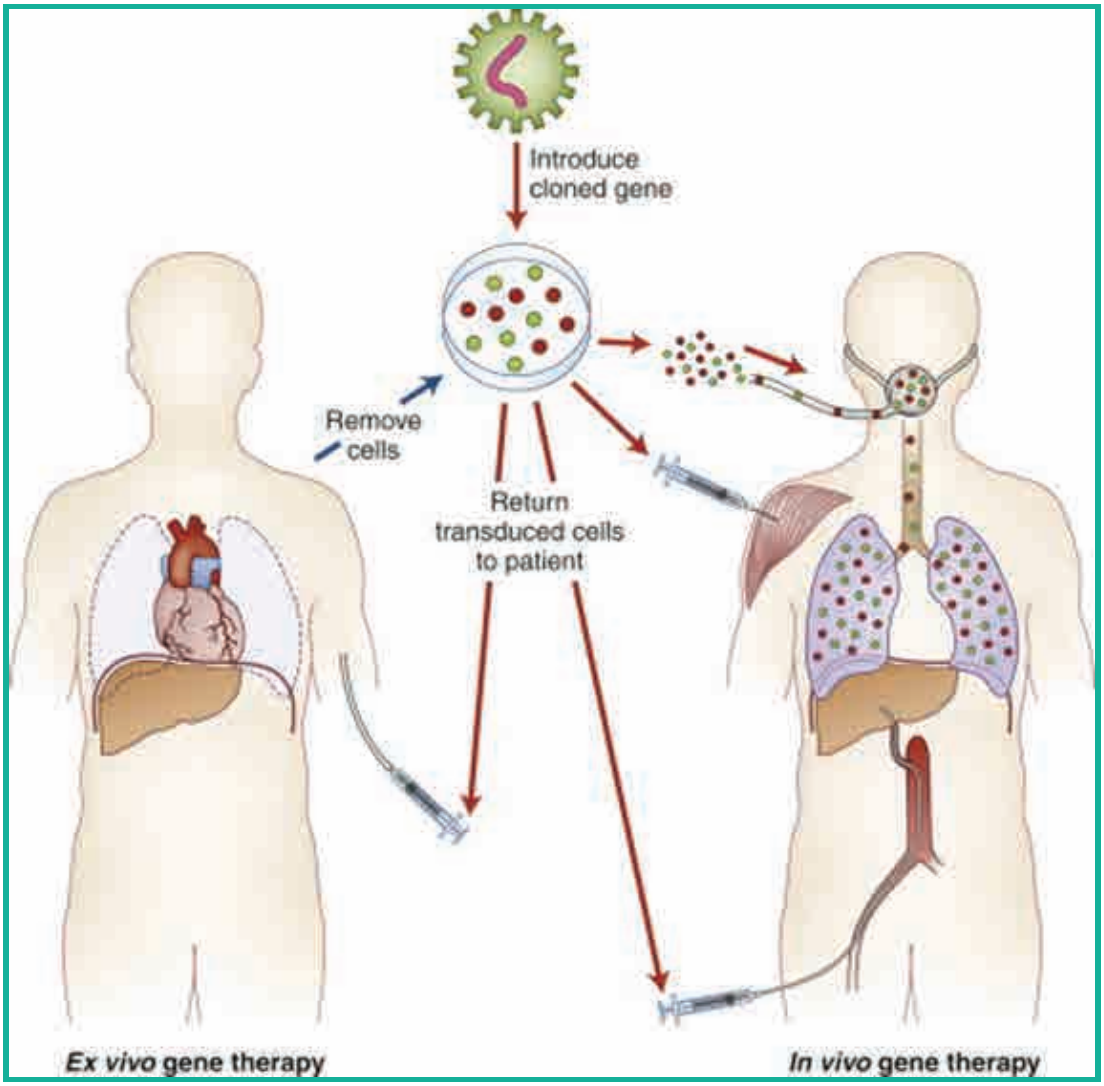
Gene therapy has emerged out to be a potential substitute. It is a process that involves the transfer of DNA with a gene to replace the mutated gene in the affected individual. It targets the different genes of coronaviruses and then stops their replication using vector-based siRNAs and dsRNAs.



Types of Gene Therapy-

a. **Somatic Gene Therapy** involves transferring a section of DNA to any of the body cells that don't produce sperm or eggs. The effects of this therapy are not inheritable. It uses therapeutic DNA to treat diseases.

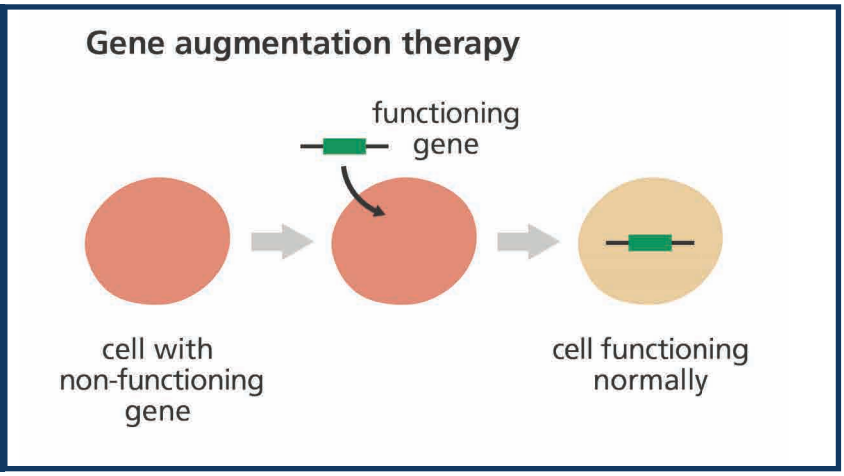
b. **Germline Gene Therapy** involves the transfer of DNA section to the cells that produce sperms or eggs. The effects of this therapy are inheritable.



Techniques in Gene Therapy-

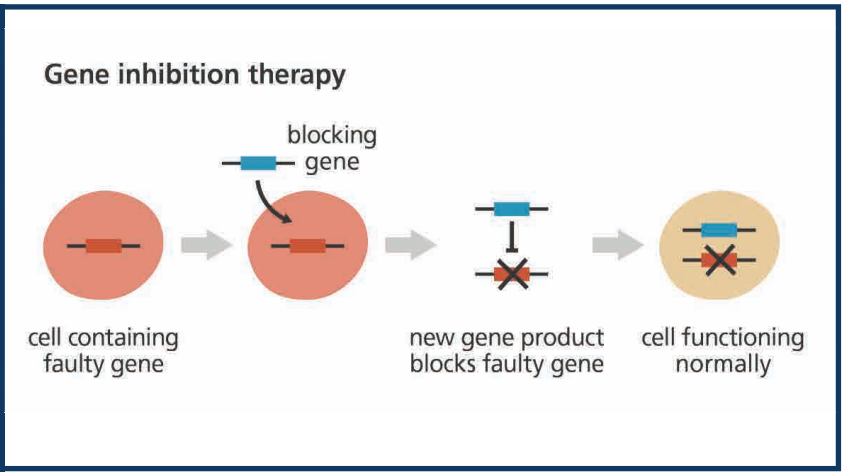
a. Gene augmentation therapy:

It is employed when a disease is due to a mutation that inhibits a gene from producing a functional product like a protein.



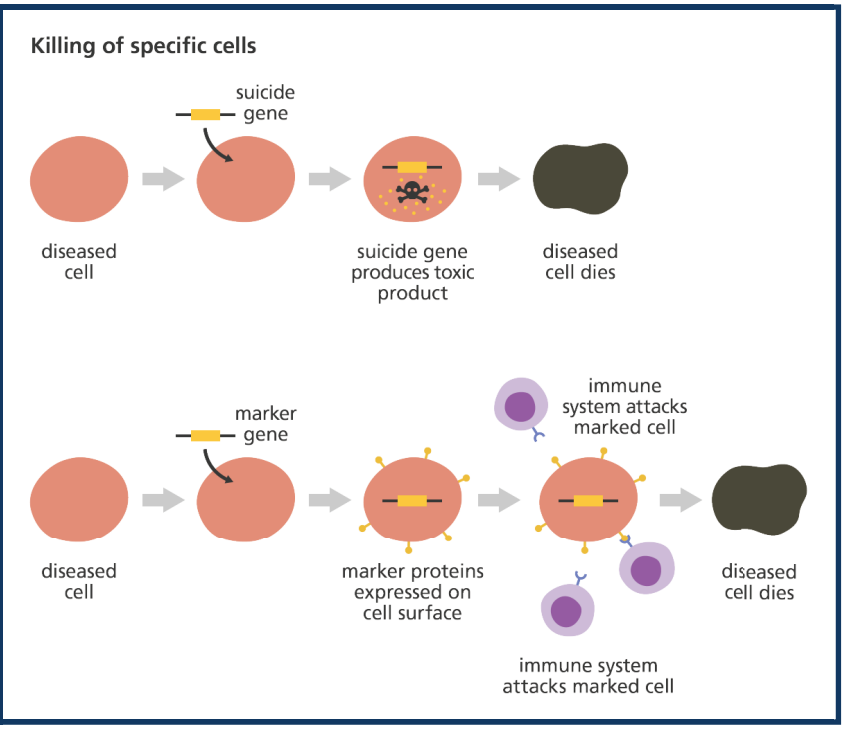
b. **Gene Inhibition therapy:**

It is used to treat infectious diseases, and it inhibits those genes which encourage the growth of a disease-causing cell.



c. **Killing specific cells:**

It is generally used to treat cancer where DNA is inserted in the infected cell, which causes its death.



3. Key Challenges

The development of Covid-19 treatment using Gene Therapy has faced various challenges-

1. Recruiting and Assessment of Patients

This has been one of the great difficulties the companies have faced as the number of patients enrolled for clinical trials has dropped drastically. Also, many patients who enrolled for ongoing trials have missed their follow-up assessment checks. According to a survey, almost 55% of companies have revealed that patients have missed their assessments. This has all been attributed to countries putting up travel restrictions, patients being fearful of catching the novel coronavirus, and many emergency services have been removed.

2. Funds for Research

If trials and development of specific treatments are to go ahead, there needs to be a smooth cash flow, sadly, which has taken a massive hit due to the pandemic. There have been delays in clinical trials, patient trials, and various regulatory approvals, which has led to a dwindling of the investor's confidence as there is not enough data to rely upon before investing.

3. Cost of Treatment

Gene therapies are very expensive, which costs over millions of dollars for a single dose of treatment; thus, everyone cannot afford it.

4. Cell Collection

It is a necessary process that has suffered as the number of healthcare officials has been redirected to covid-19 duties, and the number of patients has declined.

5. Contamination

The FDA has raised serious concerns about the possibility of expanding SARS-CoV-2 during the culture of autologous or allogenic cells. However, autologous products are at low risk of contamination than allogenic products, particularly those taken from the cell banks.

6. Rapid Analytical Methods

The assays being used currently are not quick enough, which hampers the product's quality and makes it impossible to determine the essential parameters for development.

7. Hidden Gene

A recent study conducted has found an overlapping gene ORF3d which is considered the reason for the high transmission of the Covid-19 virus.

8. Targeting the wrong cells

As the mode of delivery is a viral vector, there are chances to infect a healthy cell and the target cells, damaging the cell and might lead to cancer.

4. Overcoming The Challenges

1. Adjust Trial Protocols
If the protocols are adjusted, they are known to decrease the frequency of patient visits, medical procedures, and data collection points.

2. Increasing the efficiency of essential supplies
Viral vectors play a crucial role in Gene Therapy. The companies must place orders with two or three companies to help maintain a smooth flow of the vectors and not cause hindrance in the late stages of development.

3. Cost Reduction
Cost is reduced by reshaping the production model by bringing the manufacturing and therapeutic deliveries to a common point.

4. Sanitation
To prevent contamination, proper guidelines should be framed and adhered to; workers must undergo regular health check-ups.

5. Manufacturing yields
This and production volumes can increase using improved transfection technology and vector designs. Also, process consistency can be improved using efficient downstream and higher cell density processes.

6. Repurposing of Drugs
It is an effective method as it considerably reduces R&D costs by substituting old techniques with new effective ones. It also reduces the timeline of drug development and bypasses the need for phase 1 clinical trials.

5. Gene Therapy Patents for Covid-19

Post the 2003 outbreak of SARS, researchers filed many patents for RNAi-based vaccines, which used AAV vectors, Adenovirus vectors, recombinant RV vectors to target genes like M protein, N protein, ORF3a. Many companies can develop a treatment for Sars-CoV-2 based on these patents.

S.no.	Publication Number	Organization	Virus/Mechanism	Gene Targets/ Vectors
1.	CN102453712A	Chinese Academy of Medical Sciences	SARS-CoV; siRNA	PI4KB; adenovirus; VeroE6 cell
2.	CN101597607A	Chinese Academy of Medical Sciences	SARS-CoV; siRNA	N protein; pCMV-Myc
3.	CN101173275A	Chinese Academy of Medical Sciences	SARS-CoV; siRNA	M protein
4.	CN101113158A	Sichuan University	SARS-CoV; siRNA	RdRp; plasmid
5.	CN101085986A	Shanghai Institutes for Biological Sciences, CAS	SARS-CoV; siRNA	ORF3a
6.	WO2006130855A2	California Institute of Technology	SARS-CoV	Recombinant retrovirus
7.	CN1704123A	Guangzhou Tuopu Genetech Ltd.	SARS-CoV; siRNA	Cationic polymers, peptides
8.	CN1648249A	Shanghai Institutes for Biological Sciences, CAS	SARS-CoV; siRNA	19–25 consecutive nucleic acids on the M, N, and E genes
9.	US20050095618A1	Chinese University of Hong Kong	SARS-CoV; siRNA	S protein
10.	WO2005019410A2	Intradigm Corporation	SARS-CoV; dsRNA	nsp1, nsp9, S; aqueous glucose solution
11.		University of Pennsylvania	SARS-COV-2	AAV vector

6. Outlook

Many mRNA-based and other types of vaccines such as peptide-based, AAV vector-based, and more vaccines have been approved and currently are in use. Also, in the coming days, more such drugs will be approved.

Gene therapy is a viable alternative that can address the severe side-effects posed by the mRNA vaccines. The University of Pennsylvania has already started working on the treatment of Sars-Cov-2 called "Bioshield," in which they intend to deliver antibody cocktails using adeno-associated viral vectors. They have already conducted safety testing on non-human primates and seek FDA approval to conduct clinical trials in the coming weeks.

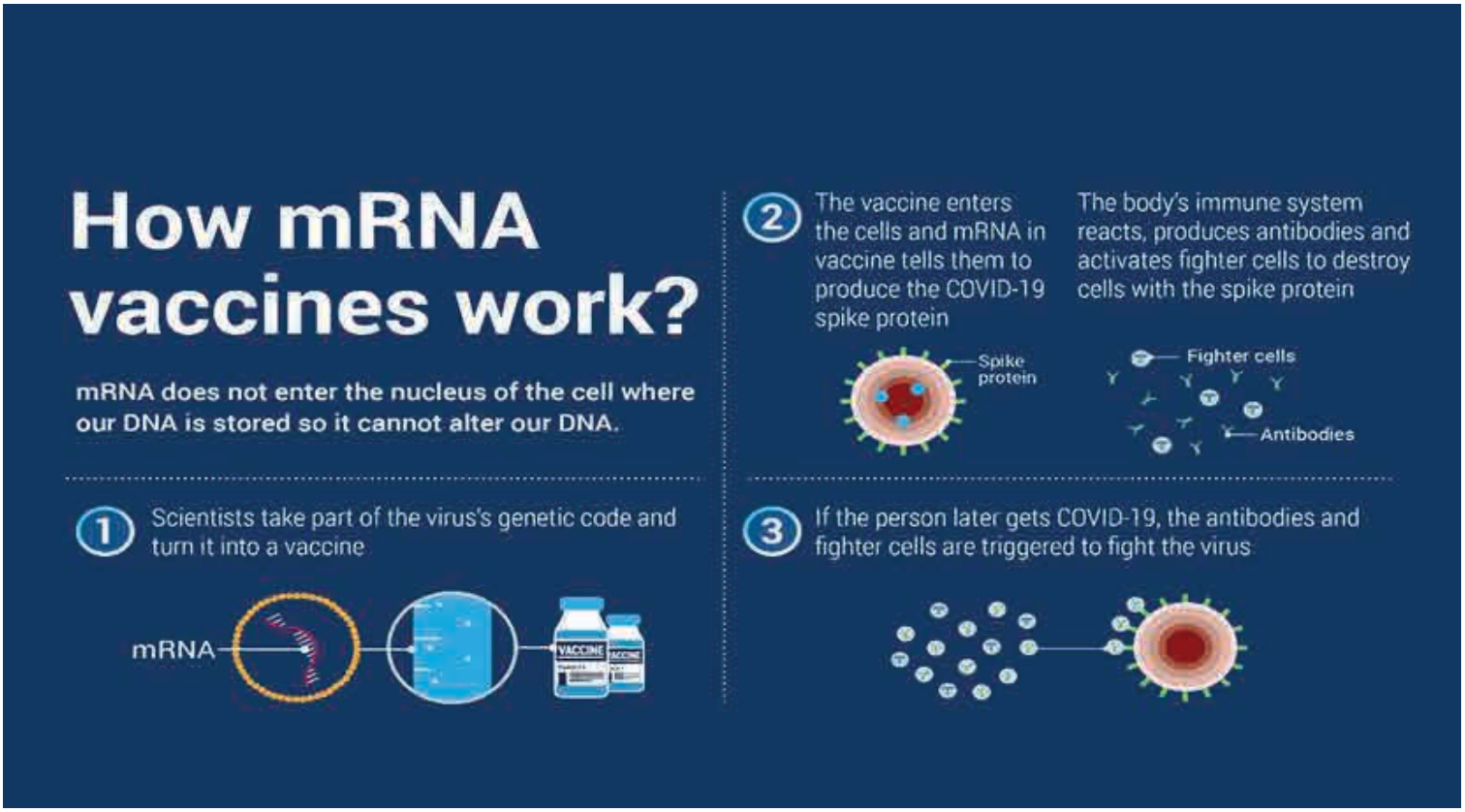
Biopharmaceutical companies having gene therapy for SARS viruses can study more for CoV-2 viruses to treat COVID-19. They can tie-up with academic and other companies to accelerate developing Gene Therapy treatment for Covid-19.

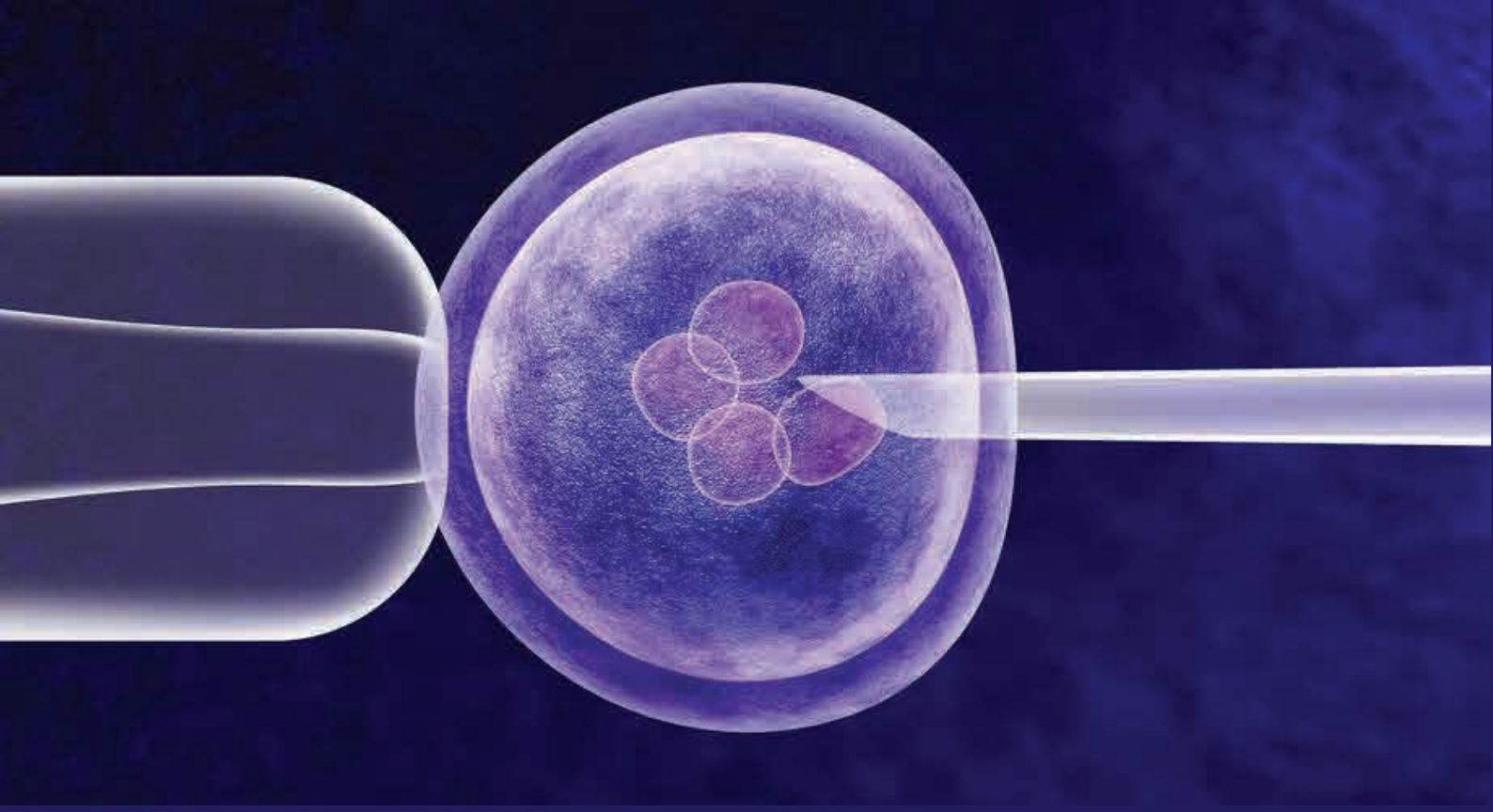
Recently, the University of Alberta and Entos pharma have announced that they will be developing a Lipid nanoparticle-based Gene Therapy for treatment and prevention of Sars-CoV-2.

Also, a patient with Wiskott-Aldrich syndrome who was being treated using gene therapy got infected with Sars-CoV-2. This patient developed early immunity and initiated antibody response against the viral antigens. There were severe anti-inflammatory complications that came up.

The above instances indicate Gene Therapy's development as a possible cure to Sars-CoV-2, and other companies should also start researching in this direction.

The pandemic has highlighted the need for intensive R&D by companies to develop new and sustainable treatments for diseases that we might encounter in the future.





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