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Opinion Article

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# Inhibition of Reverse Transcriptase as A Clue for Curing RNA Viral Infections

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Scientists provide evidence showing that delayed chain discontinuation is a plausible mechanism of action of Remdesivir. This mechanism was described previously in the context of reverse transcriptase (RT) inhibition of human immunodeficiency virus type 1 (HIV-1) and hepatitis B virus

How does the body fight Covid-19 infection?
When the virus enters the body, it mainly passes into the airways and digestive tract. The virus then binds to specific receptors found on the surface of epithelial cells to enter these cells. Viral replication within the cells results in cell damage and cell death. The result is the release of specific signaling molecules that alert the local immune system.

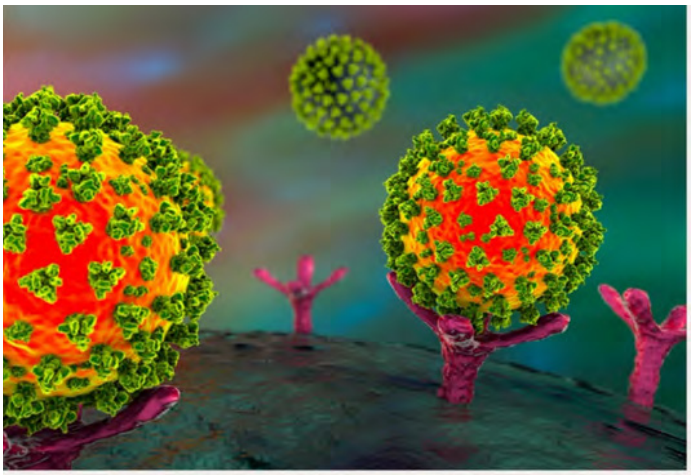


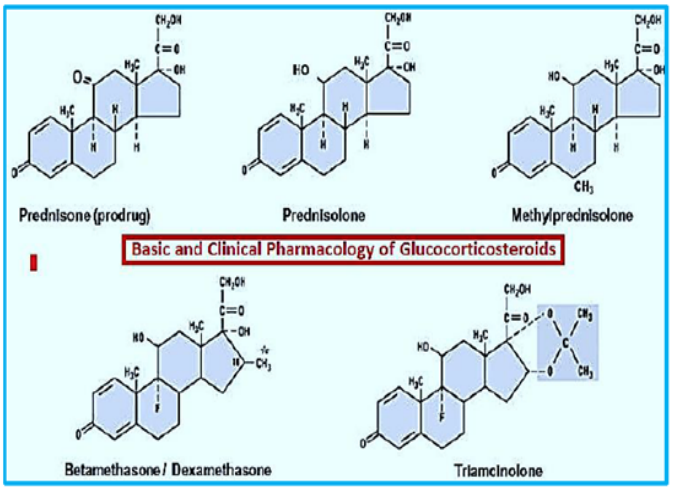
Illustration of the initial stage of Covid-19 infection: SARS-CoV-2 virus particles binding to specific receptors on the surface of cells.

Illustration of the initial stage of Covid-19 infection: SARS-CoV-2 virus particles binding to specific receptors on the surface of cells.

Immune cell armies are then sent to initiate antiviral response. Some of these cells specialize in detecting and identifying the virus, while others cause a specific immune attack. The immune response causes the release of cytokines, chemokines and antibodies, which in many cases can defeat the virus, and the patient recovers.

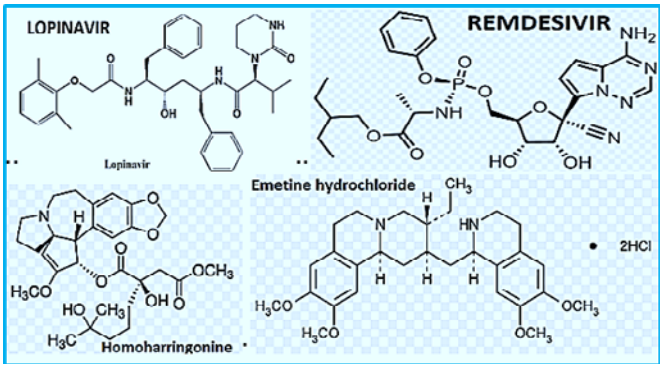
Sometimes the immune system is dangerous on high alert and over-responsive. In this case, the immune cells have a particularly strong inflammatory response - one that goes beyond what is necessary to kill the virus. This particularly strong attack releases massive amount of cytokines and chemokines throughout the body, resulting in a cytokine storm that causes widespread inflammation and tissue damage in patients with severe Covid-19.

One of the causes of an abnormal immune response and causing an immune response lies in the digestive tract. Millions of interactions occur constantly between the immune system and trillions of non-dangerous microbes living in the body. These interactions educate the immune system how to function, and more importantly, how not to react to infectious microbes. Could this help explain why some people are more likely to develop uncontrolled inflammation after Covid-19 infection.




DEXAMETHASOBNE AND SOME CORTICOSTEROIDS

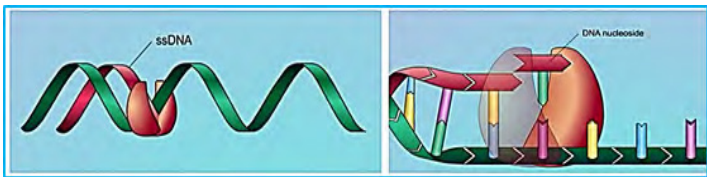
**Remdesivir, lopinavir, Homoharringtonine,and Emetine dihydrochloride were found to inhibit SARS-CoV-2**




**Some agents that affect the SARS-CoV-2 virus**

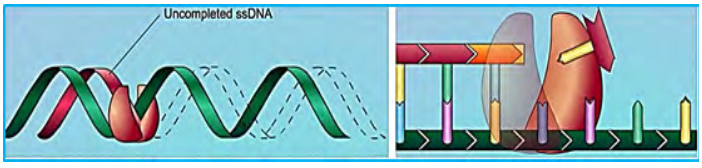
## Foreword

The biological synthesis of DNA from an RNA template, using reverse transcription, produces complementary DNA (cDNA). Reverse transcripts (RTs) use an RNA template and a short primer complementing the RNA end 3 to direct the first-strand cDNA synthesis, this can be used directly as a template for the polymerase chain reaction (PCR). The combination of reverse transcription and PCR (RT-PCR) allows detection of low abundance RNAs in the sample, and corresponding cDNA production, thereby facilitating the cloning of low-copy genes. Alternatively, the double-stranded first strand cDNA can be produced using DNA Polymerase I and DNA Ligase. These reaction products can be used for direct cloning without amplification. In this case, RNase H activity is required, either from the RT or externally provided.




**Reverse transcription**

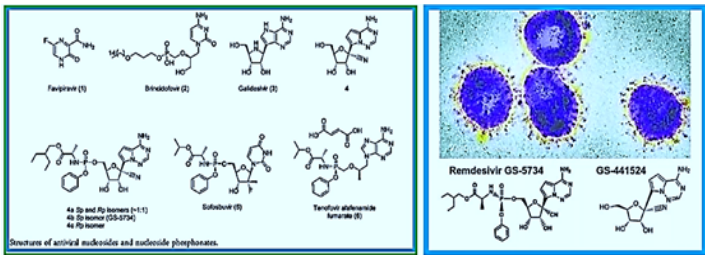
Human diseases that cause RNA viruses include Orthomyxoviruses, Hepatitis C virus (HCV), Ebola disease, SARS, influenza, polio and retrovirus include Adult Virus T Cells T Cells T-cells (HTLV-1) and Human Immunodeficiency Virus (HIV). RNA viruses have RNA as a genetic material, it may be single-stranded RNA or double-stranded RNA. Viruses use of the presence of RNA-dependent RNA polymers for intact replication Genome, or bacteroid, with two copies of single-strand Genome RNA, reverse transcriptase produces viral DNA Can be integrated into host DNA under its integration function. Studies have shown that retrovirus is endogenous They are long-term retrospective (LTR) items that account for about 10% of human or fixed genomes DNA.




**Interruptin DNA synthesis by nucleoside analog**

Gilead developed Remdesivir (GS-5734) as an adenosine-nucleotide-supplemented Angio-nucleotide protein drug 1′-Cyano that exhibits broad-spectrum antiviral activity against some RNA viruses. This compound is currently in clinical development for the treatment of Corona virus (COVID 19). Although antiviral effects have been shown in cell culture and non-human primates, the mechanism of action of the Ebola virus (EBOV) and COVID 19, SARS-CoV-2) to Remdesivir remains to be elucidated. The RNA-dependent RNA polymerase (RdRp) complex has recently been expressed and purified, allowing biochemical studies with the relevant triphosphate (TP) type of Remdesivir and its predicted target. In this study, it is confirmed that Remdesivir-TP is capable of coping with adenosine triphosphate (ATP). Enzyme kinetics revealed that EBOV RdRp and Syncytial Virus (RSV) RdRp combine ATP and Remdesivir-TP with similar efficacy.

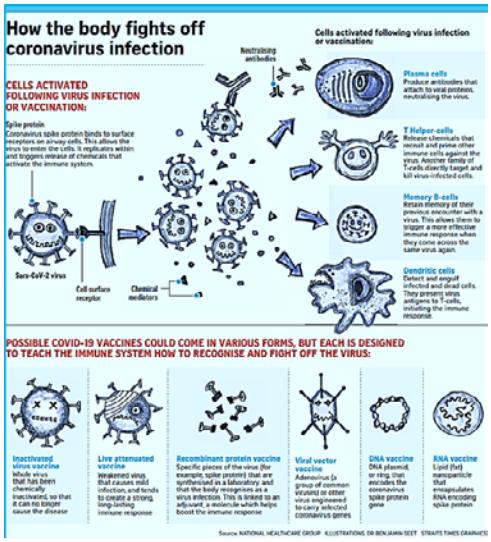
Effective treatment for the infection caused by RNA for example the AIDS virus and COVID 19, requires a combination of antiviral drugs. Currently, the standard for the treatment of antiretroviral patients is treatment with various drugs such as Ramadsvir, Chloroquine, LupineBir, Rivvirin, Pvipirir or Dexamethasone or / and by a protease inhibitor and two reverse transcriptase inhibitors [1, 2]. Remdesivir, a transcriptase inhibitor, has demonstrated clinical efficacy in both antiretroviral and experienced patients, and may also provide the possibility of a protease deprivation regimen when using two reverse transcriptase (RT) inhibitors.




**Remdesivir and analog compounds**

Two months after the first cases of atypical pneumonia were reported in Wuhan, China.

Four months later, there are at least 130 vaccine candidates being developed by biotech and pharmaceutical companies, as well as academic groups around the world.




**FIGHTING COVID 19 (credit ref.)**

## Foreword

This is a debate over an egg thast is not yet laied. The vaccines are in testing and the drugs are apoplied

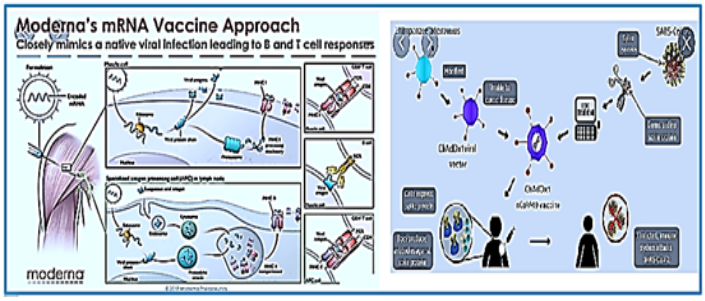
only in extreme case and exhibit only partiel success in curing COVID 19 patients [3, 4].

"Allocate $ 67 Million with Vaccine Not Yet Existing" All the eggs in one basket"

In recent days, the Israeli Department of Health has signed a corona vaccine supply agreement with the American "Moderna" company, And AstraZenica-Oxford on supply of vaccines, different in their technology. Last Thursday, July 18 2020 [5, 6].

This was published in the main edition that the Biological Institute in Ness Ziona, which itself is focusing on vaccine development. Strongly attacked the deal. It turns out that the institute did not receive a seat in the decision making and therefore decided to issue a letter to the decision-makers in the Ministry of Health and the Prime Minister's Office. "The agreement with the Modern Society was done in the dark without consulting the biological institute experts," they wrote.

"Allocated $ 67 million with a vaccine that does not yet exist and there are question marks about its true ability," the appeal to senior officials said. "Moderna is not publishing any information about the trials it has done, no preclinical research and whether there are life-threatening side effects to the vaccine." Well, let us clarify in short what it is all about [7].

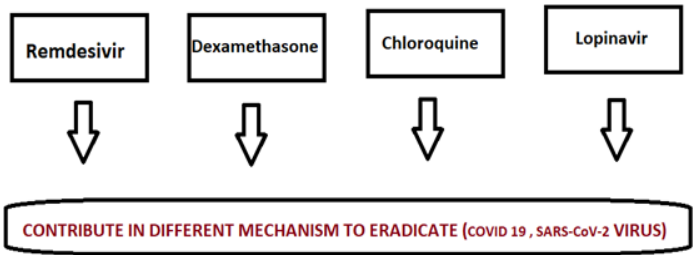



**MODERNA (credit ref) and ASTRAZENICA-OXFORD (credit ref) Vaccine approaches.**

AstraZeneca Received $ 1 billion in funding from the US Biomedical Research and Development Authority (BARDA) for the development, production and delivery of a University of Oxford vaccine candidate in 2019 (COVID-19) [8].

This press release from MODERNA Contains forward-looking statements within the meaning of the 1995 Private Litigation Reform Act, as amended, including in relation to the Company's development of a potential vaccine against the new virus, the conduct and timing of Phase I research of mRNA-1273, the design, execution and scheduling of Step 2 Potential and all subsequent mRNA-1273 experiments and potential production capabilities [9].

## In conclusion




Scientists provide evidence showing that delayed chain discontinuation is a plausible mechanism of action of remdesivir against EBOV [10, 11]. Delayed chain break has been described previously in the context of reverse transcriptase (RT) inhibition of human immunodeficiency virus type 1 (HIV-1) and hepatitis B virus (HBV). A prominent example is the mechanism of action by Antiquir, which is approved for the treatment of HBV infection. Cypher and colleagues reported that HBV polymerase inhibited at locations i + 2 and i + 3. Antacabir has also been shown to exhibit antiviral activity against HIV [12]. Our previous study with HIV-1 RT revealed that a major contributor to the delay is the chain termination delay in i + 3 condition. Footprinting experiments provided evidence showing that the enzyme was not properly positioned to support the binding of the next nucleotide [13-15]. However, the structural reasons for such an enzyme repositioning remain elusive. The inhibitory effect of remdesivir is further afield, suggesting that a delayed chain break can be caused by different mechanisms. Bad interactions between the integrated inhibitor and distinct enzyme elements, as well as structural modifications of the newly synthesized RNA, should be taken into account. This study warrants further investigation into the structures of EBOV, RSV or NiV RdRp complexes and / or double stranded RNA combined to address these questions.

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