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EDITORIAL

# Achilles' heel of the killer virus: the highly important molecular targets for hitting SARS-CoV-2 that causes COVID-19

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## Abstract
As an immediate priority, finding a solution for the new coronavirus (SARS-CoV-2) pandemic is on the agenda of scientists of the world. Herein, we summarize all the suggested global solutions proposed by scientists and physicians so far to stop this dangerous virus. Also, the important molecular targets for hitting the killer virus are highlighted.

**Keywords** New coronavirus · Spike protein · Antiviral medicines · Angiotensin-converting enzyme 2 (ACE2) · Virus as a lesson

Currently, the ongoing pandemic of the new coronavirus (SARS-CoV-2) has become a major global problem. The spread of this virus was so rapid that it quickly infected tens of thousands of people around the world including medical staffs and killed several thousands of them, and it still continues to infect and kill humans. So, thinkers and scientists are struggling to find a solution for this rebellious virus. Looking through the lens of basic science, achieving a solution is not out of reach. The biomolecular science approach may be one of the master keys to get the facts on how to control this deadly virus. SARS-CoV-2 belongs to the coronavirus family, which has a crown-shaped (spike) protein that protrudes from its surface. Underneath its royal crown is an RNA strand acting as a genetic material for the virus. When virus infects human cells, it hijacks the existing molecular machinery to create its own proteins which are necessary to generate more viral copies. The interaction of viral spike protein with angiotensin-converting enzyme 2 (ACE2) on plasma membrane of particularly lung cells plays a central role in the infectious ability and pathogenesis of SARS-CoV-2.

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To stop this dangerous virus outbreak, all the global solutions proposed by scientists and physicians are divided into different categories including designing new vaccines with the aim to prevent this disease (1), producing antibodies with the aim of neutralizing the virus (2), reusing the therapeutic existing medicines (drug repurposing), especially the antiviral drugs (e.g., lopinavir, ritonavir, and remdesivir) (3), using the existing plant-based traditional medicines (medicinal herbs) (4), using the therapeutic capacity of stem cells (5), and designing novel synthetic and innovative therapeutic molecules (6). With these solutions, what are the key molecular goals for controlling the new coronavirus? There are few important and key molecules providing suitable targets for hitting the virus. These molecular targets can be considered as the Achilles heel of this dangerous and deadly virus. The first molecular target is the highly glycosylated spike protein.

Many vaccines that are under development and testing are designed to activate the immune system, to prevent COVID-19, and to introduce the viral spike protein into human body.

The spike protein is also the molecular target for many antibodies being tested at various stages of clinical trials. These antibodies cover the surface of the virus after binding to the viral spike protein, thus preventing it from binding to the cell membrane receptor, ACE2. The attack of spike protein with its glycan shield to the membrane receptor ACE2 can also be neutralized using lectins. Plant lectin proteins which are found in abundance, especially in legumes, can be used to achieve this goal. Also, safe herbal alkaloid compounds and antimalarial medicine chloroquine, showing anti-glycosylation activity, are likely to affect the glycosylation of the viral spike protein and its membrane receptor ACE2 and may have an important therapeutic value. Moreover, the viral spike protein is primed by a specific transmembrane serine protease TMPRSS2 after being made inside the cells converting to its mature and active form. Therefore, the designed compounds that are similar to camostat mesylate, which specifically inhibit this peptidase, are important in preventing the coronavirus from growing and multiplying in the human body. The second molecular target is the cell membrane receptor (ACE2) serving as the main entrance of the coronavirus to human cells. The designing of either antibodies or small molecules that mask the interaction interface of this membrane receptor with the viral spike protein may have therapeutic values. Also, injection of either recombinant human ACE2 protein or even catalytic domain of this protein protruding from the cell membrane into the blood stream of COVID-19 patients is another important strategy to be considered as a possible treatment plan. Similar to the specific antibodies, the soluble and free form of this protein or its catalytic domain may bind to the spike protein of coronavirus and prevent the virus from binding to the cell membrane receptor, ACE2. The third important molecular targets are the interleukin 6 receptor (IL6R) and chemokine receptor CCR5. These cytokine receptors can be targeted specifically by therapeutic antibodies such as Kevzara, Actemra, and Leronlimab or by new under-developing antibodies which subsequently reduce the presence of high levels of inflammatory cytokines, within the lungs, known as cytokine storm. In fact, the main cause of death in patients with acute respiratory symptoms is not the virus itself, but the development of an abnormal condition by coronavirus, leading to cytokine molecular storm. Also, with a similar mechanism, infusion of mesenchymal stem cells (MSCs) facilitates patients' respiratory problems, reducing high level of the inflammatory molecules in their lungs. The fourth important molecular targets are the viral RNA polymerase and viral protease, which have recently been targeted with remdesivir, favipiravir, ritonavir, and lopinavir. The use of these antiviral medicines has also had a positive effect on the treatment of the reported cases of COVID-19.

Finally, with two important approaches, one can look at the pandemic of new coronavirus. The first is the molecular and basic science perspective which provides new conditions for the exploitation of physicians and benefits of patients. Second, we can look at emergence and pandemic of this deadly virus as a lesson. Over the course of thousands of years, human history has repeatedly experienced epidemics and pandemics (global epidemics) of deadly infectious diseases, and the recent pandemic will not be the last. Therefore, joint investments of the world countries in strengthening the scientific and practical infrastructure of universities and pharmaceutical/biotechnology companies and creating highly equipped hospitals around the world will reduce the cost of overcoming similar health crises, which will inevitably occur in the future. Today, all countries need to empathize and bring science and technology together as convergent scientific data, and through the integration of science, technology, information, and experience to save people of the world from the damages of this deadly virus, wishing science and love for all nations. Finally, the reminder of Saadi Shiraz's advice is not without grace, as he says:

Human beings are members of a whole
In creation of one essence and soul
If one member is afflicted with pain
Other members uneasy will remain
If you've no sympathy for human pain
The name of human you cannot retain