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Advanced drug delivery systems can assist in targeting coronavirus disease (COVID-19): A hypothesis

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ABSTRACT

The highly contagious coronavirus, which had already affected more than 2 million people in 210 countries, triggered a colossal economic crisis consequently resulting from measures adopted by various goverments to limit transmission. This has placed the lives of many people infected worldwide at great risk. Currently there are no established or validated treatments for COVID-19, that is approved worldwide. Nanocarriers may offer a wide range of applications that could be developed into risk-free approaches for successful therapeutic strategies that may lead to immunisation against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which is the primary causative organism that had led to the current COVID-19 pandemic. We address existing as well as emerging therapeutic and prophylactic approaches that may enable us to effectively combat this pandemic, and also may help to identify the key areas where nano-scientists can step in.

Introduction

The worldwide infections caused by the novel SARS-CoV-2 pathogen has made an immense impact on global and everyday lives of millions of people around the world [1]. SARS-CoV-2 is a positive sense single stranded RNA virus. This virus has 4 different types of proteins which constitute the structure of virus, the virus capsid and its exterior is made up of envelope protein (E) and membrane protein (M) whereas the association of virus to host membrane is facilitated through spike protein (S) and nucleocapsid protein (N) holds viral RNA [2,3]. The term corona means crown and the coronavirus got its name from crown-like or clove-trimeric projection of 2 subunits (S1: receptor-binding and S2: membrane fusion) of section ectodomain of S protein. Along with ectodomain S protein also have 2 more sections which are intracellular tail and single-pass transmembrane anchor and all sections are involved in guiding host cell [4]. Receptor binding component or receptor binding motif (RBM) of S protein helps the virus to enter human/host cell via attachment to angiotensin-converting enzyme 2 (ACE2) receptors [1,5,6] which are concentrated at the regions of lung, intestine and kidney of human body suggesting that corona virus can potentially target these organs [7]. This suggests that the direct strategy to neutralize SARS-CoV-2 is to block the recptors, as adopted in other viral therapies of its type [8].

It is obvious that the virus has to undergo replication in order to

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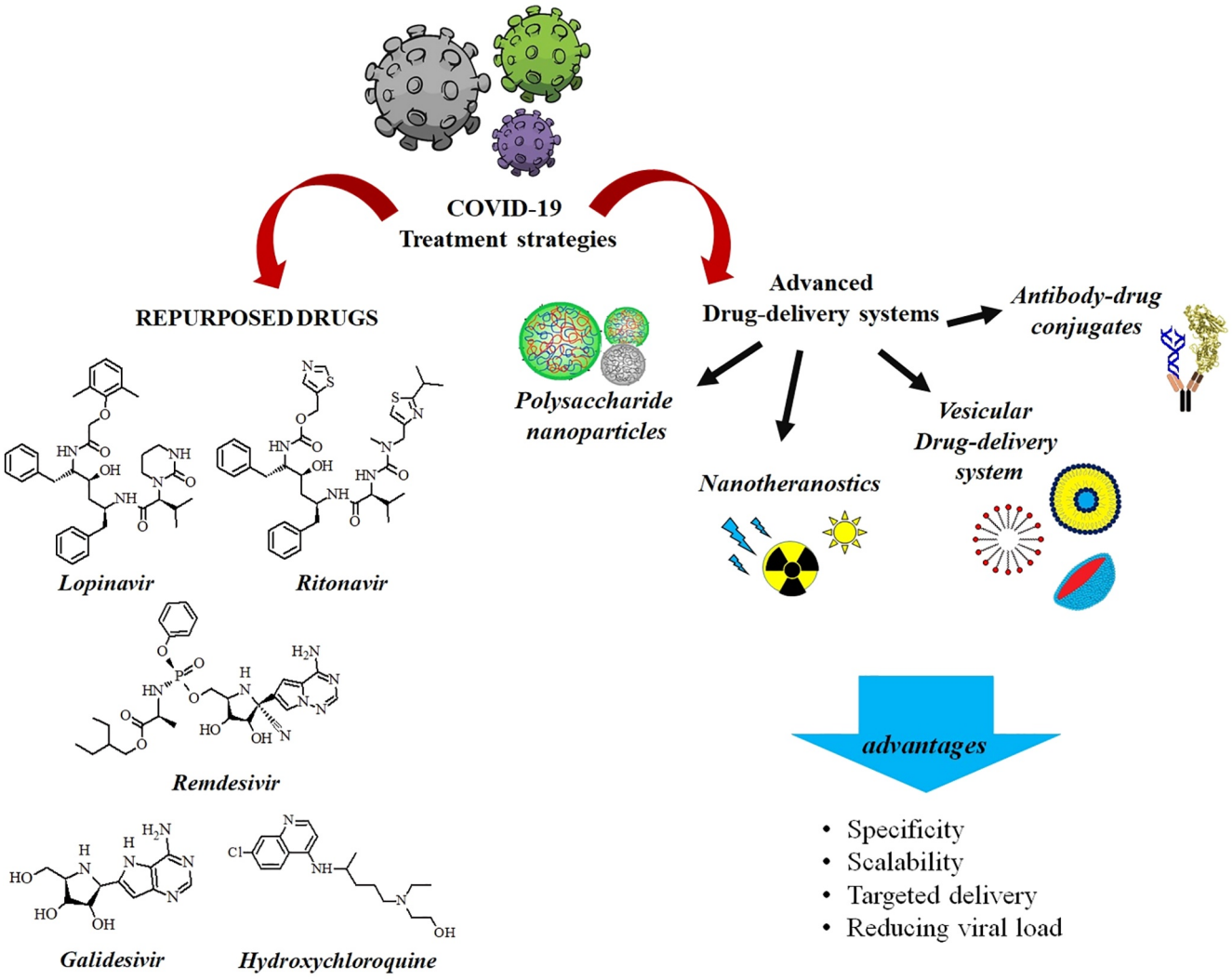

Fig. 1. Advanced therapeutics delivery strategies in targeting COVID-19.

survive by creating multiple copies of itself inside the host body. For the viral replication, as evident from previous SARS-CoV virus certain elements are required like open reading frames (OREs), slippery sequence: 5′-UUUAAAC-3′, 2 replicase genes: rep1a and rep1ab and 2 polyproteins: pp1a and pp1ab. These polyproteins have one thing in common that is protein Nsp: Nsp1-11 and Nsp1-16 which play pivotal role in replication of virus and attacking of host immune system [9]. Negative RNA genome template upon action of replicase gene encoded enzyme produces overlapping messenger RNA (mRNA) which help in producing protein that are building blocks of virus (E, M, N and S). The RNA of virus is gathered at its place with help of Nsp protein suggesting that Nsp protein can be another possible target of SARS-CoV-2 viruses [10].

Another possible reason for its increased virulence is presence of furin-like cleavage region at the S protein (absent in SARS-CoV) [11]. When SARS-CoV-2 binds with ACE2 receptors present on alveoli and epithelial of lungs, protease enzyme come into play, in order to split S protein into its 2 subunit S1 and S2 introducing structural changes and activation of S2 followed by introduction of fusion peptide in the membrane that facilitates fusion of membrane of virus with host and entry of virus inside the host cell. After the entry, the ADAM17 splits and scatters the ACE2 into extra space of membrane which will increase the permeability of pulmonary vascular system and further contributes alveolar injury (Guangdi Li & De Clercq, 2020). This is possibly the cause of negative regulation mechanism of rennin-angiotensin system where angiotensin angiotensin I is converted into angiotensin II upon action of ACE2. Further, angiotensin II induces lung pathology with respiratory torture [12]. The cytokines are produced as a result of protective mechanism after entry of antigen however, increased production of cytokines through activation of various pathways lead to “cytokine storm” which causes respiratory distress. Also, cytokine synthesis is escalated through conversion of pro-interleukin (IL)-1B into mature IL-1B via signals from caspase induction, reactive oxygen species production and Ca^{2+} influx. This suggests that another stategy to combat SARS-CoV-2 virus is depression of cytokines through IL1 blockers (anakinra, tocilizumab), steroids, immunoglobulins [13].

Another target of SARS-CoV-2 is c-Jun N-terminal kinase (JNK) pathway, which accelerate synthesis of pro-inflammatory factors through recruitment of proteins like ORF3b, ORF7a and ORF3a which causes lung damage. In order to enter the human cell, virus first spilts the spike (S) protein so for its cleavage virus make use of certain protease enzymes like Trypsin, TMPRSS11a, Cathepsin L, Furin and Plasmin [14]. Therefore, proteasomal inhibitors can be used in the therapy to target these proteases referring from its use in other viral treatment (like HIV).

Currently, over 40 different drugs including antivirals and immune-modulating compounds have been investigated for their efficacy against COVID-19. Such therapies are essentially focused on the delivery of agents that either block or inhibit the action of proteases (e.g. lopinavir/ritonavir antiviral drugs) in the host cells. In principle, these

agents may thereby prevent or block the entry of the virus into the host cells [15]. Other possible therapies that are currently under clinical studies involve several nucleoside analogues which target the RNA-dependent polymerase. These analogues repress viral RNA synthesis (e.g. remdesivir), or directly interfere with the viral genetic material and indirectly decrease the production of pro-inflammatory cytokines and/or activate $CD8^+$ T-cells.

Ironically, a number of these drugs are associated with adverse effects that restrict their use in severe cases, and thus prevent prophylactic use. For instance, chloroquine, a potent anti-malarial drug could induce nausea, diarrhoea, vomiting and other adverse effects even at recommended doses, and may sometimes cause fatal cardiovascular toxicity at higher doses [16]. Lopinavir and ritonavir, tested as a COVID-19 treatment options have potential adverse effects that include, vomiting, nausea and hepatic injury [17]. The availability of a controlled release formulation that could maintain a minimal effective concentration (MEC) of a specific drug substance could largely reduce adverse effects and could minimize liver burden too [18]. Several nanosystems have been researched so far to evaluate their action against SARS COV like polysaccharides nanoparticles [19], mesoporous nanoparticles [20], graphene oxide silver nanocomposites [21], magnetic hybrid colloid silver nanoparticles [22] and quantum dots [23] (Fig. 1).

This article explains drug development approaches to improve the efficacy of such drugs through either targeted delivery or through controlled release. If successful, these strategies will help to increase the usefulness of medications to reduce the number of deaths in this serious disease and furthermore, provide healthcare professionals with the means to increase recovery and to strengthen our response to future epidemics.

Hsypothesis

Clinical development of the drugs targeting the COVID-19 virus necessitates the identification of a suitable delivery system that ameliorates drug absorption and ensures a superior intracellular delivery, while maintaining an appropriate concentration gradient between the organ of interest (lungs) and systemic circulation. The targeted delivery of the payload drug by the carrier system ensures an optimal activity on-site and minimal toxicity, while controlled release systems sustain an effective drug concentration across the target site while minimizing the steady-state concentration of the cargo drug thereby, alleviating the imminent side effects. Thus we hypothesise that advanced systems for drug delivery can help to cope with coronavirus disease.

Polysaccharide nanoparticles

For long, aerosol-based drug delivery systems presented themselves as the mainstay for contemporary pulmonary disorders. However, the fugitive emission of aerosols and droplets containing respiratory pathogens, during the administration of aerosol therapy increases the likelihood of unintended transmission of viral particles. The delivery of aerosolized medication to COVID-19 patients, therefore, sporadically jeopardizes the safety of healthcare workers [24]. Novochizol, an advanced drug delivery system, comprising of a nanoparticle-based aerosol formulation offers potential advantages and holds considerable promise for the effective transport of potential COVID-19 drugs, and in addition, maintaining optimal concentrations in the infected lungs. This first-in-class polysaccharide nanosystem constitutes fully biodegradable and biocompatible chitosan nanoparticles that adhere strongly to the lung epithelia while, ensuring a sustained drug release. Moreover, the system also endures the unwanted systemic distribution of the cargo drug [25].

Nanotheranostics

Intranasal delivery of theranostic nanoparticles carrying the therapeutic drug molecules presents as an efficient drug delivery system for containing the transmission of COVID-19 virus. The theranostic nanoparticle-based drug delivery system provides alternative routes for the administration of therapeutics against viral pulmonary diseases, in addition to the existing representative intranasal delivery routes. They can be divided into 3 broad categories: organic, inorganic, and virus-like or self-assembling protein nanoparticles The carrier system efficiently overcomes the drug delivery challenges linked to the mucosal route and maintains a high effective concentration of the cargo drug at the site of infection, while expressing negligible adverse effects to the healthier cells and tissues [26]. As it is well-known that, the infectious viral particles including, the COVID-19 virus mainly initiate their infection at the surface of the mucous membrane, the mucosal treatment provides a viable strategy for containing the COVID-19 infection.

Vesicular drug delivery systems

Vesicular drug delivery systems present an advanced approach as theranostics in COVID-19. Importantly, the surface charge present on the vesicular system plays a critical role in deciding the pharmacokinetics of the cargo drug molecule. The presence of a surface positive charge on carrier vesicular system prompts its adherence to the negatively charged mucosal membrane via electrostatic interactions and prevents their mucociliary clearance and enzymatic degradation. Notably, the vesicular drug delivery systems improve the residence time of drugs while prolonging their release at the target site. Besides, these systems ensure the co-delivery of therapeutics with adjuvants and maintain high concentrations of the cargo molecules at the target site [27].

ModernaTX, Inc. utilizes lipid nanoparticles to encapsulate mRNA-1273, which encodes the SARS-CoV-2 full-length S-protein (NCT04283461). The T-cells that recognize the SARS-CoV-2 antigen immediately escalate an immune response in the cells expressing this viral protein. This can be a safe and successful strategy as it does not use viral particles, and thus provides mRNAs that can be expressed by immune and non-immune cells. In addition, lipid nanoparticle- encapsulation of viral mRNA prevents the mRNA from degradation and increases the effectiveness of the therapy [28].

Antibody-drug conjugates

The antibody-drug delivery system presents a robust candidate for the delivery of perspective COVID-19 therapeutics. The drug molecules are chemically conjugated to the antibodies and are released at the target site. Sorrento Therapeutics reported the preclinical findings from their studies that involved the COVID-19 therapeutic candidate antibody STI-1499, which completely blocked the viral infection [29]. The antibody reportedly inhibited the viral propagation by inhibiting the interaction of S1 protein with human angiotensin-converting enzyme 2 (ACE2), an essential event necessary for the entry of the virus into the human cells [30]. The *in vivo* investigations on STI-1499 revealed the inhibition of viral infection in healthy cells at very low concentrations. Antibody-drug conjugates (ADC) function by identifying the viral envelope proteins obligatory for the propagation of infection in healthy cells. The conjugation of the viral cell-killing 'highly powerful active pharmaceutical ingredient' (HPAPI) with monoclonal antibodies holds high potential for the development of a perspective COVID-19 drug delivery system combining the explicit synergistic effect of both the ingredients.

Several vaccine candidates in clinical trials for targeting COVID-19 base on the induction of antibody titres in test animals [31]. As such, a purified, inactivated COVID-19 virus vaccine candidate PiCoVacc reportedly induced SARS-CoV-2 specific neutralizing antibodies in animal models, which acted on several representative strains of the target virus. The immunization of animals with 3 or 6 μg per dose resulted in partial or complete inactivation of the target SARS-CoV-2 virus

infection [32]. Similarly, the animals vaccinated with CoV-RBD219N1 based on the recombinant RBD protein of SARS-CoV demonstrated virus-neutralizing antibody titres between 640 and 1280. The vaccine candidate arrests the instigation of eosinophilic lung pathology, and prevents the entry of SARS-CoV and SARS-CoV-2 pseudovirus in human ACE-2 expressing 293 T cells. The antisera specific to SARS-CoV RBD potentially neutralizes the infection by pseudovirus thereby indicating the cross-reaction of SARS-CoV RBD-specific antibodies with SARS-CoV-2 RBD thereby neutralizing the SARS-CoV-2 pseudovirus infection [33].

Polymer-drug conjugates

The covalent conjugation of therapeutics and a hydrophilic polymer backbone via self-immolating linker molecule provides a convenient drug delivery strategy for delivering antiviral drugs. The hydrophilicity of the polymer backbone provides physiological compatibility, whereas, the covalent conjugation improves the circulation time of the cargo drug molecule by providing stability against enzymatic degradation [34]. Considering the peptidomimetic nature of a majority of the rationally designed COVID-19 therapeutics that primarily target the viral main protease, the polymer-drug conjugates provide highly desirable avenues as drug carriers while ensuring protection against proteases, and providing suitable hydrophilicity to the drug molecules for interacting with their cellular targets [35].

Nanosilica based materials

Mesoporous silica nanoparticles with excellent biocompatibility and chemical stability have emerged as an ideal candidate for encapsulation and shielding of nucleic acids. Nanoparticles may be modified in particular, to bind oligonucleotides of different dimensions that include DNA, RNA, and siRNA [36]. To promote the development of viral vaccines based on mRNA and pDNA, N4 Pharma, a specialist drug company well-known for pioneering nano-delivery systems, is in the process of developing a new silica-based novel technology named, Nuvec® intended for the delivery of vaccines and medicines. These novel silica-nanoparticles carrying nucleic acids have irregular surfaces functionalized with polyethyleneimine. This surface traps nuclear acids (such as mRNA/pDNA), as they pass to cells, and protects them from nuclear enzymes. The main advantage of Nuvec® is that, it does not damage the cell membrane when it reaches the cells, compared to lipid-based delivery systems; and neither does it produce any inflammatory reaction at the injection site nor excessive systemic side-effects.

Herbal-based nanodrug delivery

The plants and plant-based natural products present robust applications in the treatment of chronic respiratory diseases by targeting the composite pathways responsible for the pathophysiology of the disease [37]. However, the application of herbal strategy for attenuating the pandemic is doubtful due to a lack of accepted clinical trials suggesting their effectiveness against the causal virus [38]. The development of herbal metal nanoparticles by green methods with plant extracts and natural products presents a highly desirable approach pertaining to its physiological benevolence, minimal toxicity, cost effectiveness, and scalability [39]. The metal nanoparticle presents applications as drug delivery vector, and affords the blocking of viral entry to the host cell thereby preventing its propagation to healthy cells [40]. In addition, the unique physicochemical, magnetic and optical properties of noble metal nanoparticles, prompts the diagnosis of virus detection, and biosensing of the buildup of metabolites generated by virus infection. The green synthesized nanoparticles capped with suitable functionality, or biodegradable polymer further enhances their tolerance towards healthy cells and tissues [41].

Consequences of the hypothesis

Over the past decades, the treatment of infectious diseases which have been highly contagious and potentially fatal has influenced history, and COVID-19 is not an exception. But now, we are in an era with superior access to highly advanced technology resources, which can change the course of this pandemic. Research data on nucleic vaccines and therapeutic drugs from beyond the past 25 years have been investigated due to the global urgency of the COVID-19 pandemic. Nanotechnology based techniques may play a key role in advancing the diagnosis and production of COVID-19 vaccines. In this era of advanced nanoscience, we now have access to all the necessary tools such as theranostics, nucleic acid testing like reverse transcription polymerase chain reaction (rt-PCR), computed tomography, protein testing etc. that are essential to incorporate such techniques into feasible strategies, and play a frontline role in combating this outbreak.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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