Review Article

Nanotechnology and COVID-19: Potential Application for Treatment

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Abstract

The novel coronavirus (2019-nCoV) emerged in China at the end of 2019 and then spread worldwide, particularly to Italy, Spain, the USA, and Iran. Currently, Coronavirus Disease 2019 (COVID-19) is a main public health issue. As of April 21, 2020, more than two million confirmed cases of COVID-19 with more than 170,000 deaths have been reported in 210 countries by WHO. The 2019-nCoV can be spread by direct contact or droplets between humans and shows great potential for a pandemic. At present, there is no particular antiviral therapy for 2019-nCoV-infected persons. However, a wide range of therapeutic agents are being examined. The capabilities inherent to nanotechnology hold a large guarantee in presenting innovative approaches in the field of COVID-19 prevention, diagnosis, and cure. We in this article discuss how nanotechnology can improve the treatment of persons infected with the COVID-19 virus.

Keywords: *2019-nCoV, COVID-19, Coronavirus, Nanotechnology.*

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Introduction

The novel coronavirus disease (2019-nCoV), called by the World Health Organization (WHO) as Coronavirus Disease 2019 (COVID-19), was first reported on December 31, 2019 (Wuhan, China) (1). Compared to the other known coronaviruses like as the Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV), the mortality rate of COVID-19 is considerably lower; however, it is more transmissible (2), so far, it has spread to many countries around the world, infected more than two million people, and it has led to the death of tens of thousands of people. Coronaviruses are a big family of viruses that attack the upper and lower respiratory tracts in humans, leading to a range of disease from the common cold to very severe, even fatal forms. But, it is the third time in the 21st century that a coronavirus explosion turns into a global health emergency. More than hundreds of coronaviruses have until been known, most of that is transferable between animals like pigs, camels, and bats, however, in several cases, a genetic mutation is all these viruses require to spread to humans (3). So far, seven coronaviruses have been diagnosed with human diseases, four of which are NL63, OC43, 229E, and HKU1, which cause moderate to severe disease, and the other three are even fatal (4). The first was SARS-CoV, which appeared in late 2002 and disappeared in 2004; the second is MERS-CoV, which appeared in 2012 and yet spread between camels (2, 5); and the third is SARS-CoV-2 that causes COVID-19 – first reported in China and according to numerous researchers, is leading the world toward the grips of a pandemic (6). The SARS-CoV-2 virus is in the form of spheres with a diameter of 125 nm, with lipid-based viral envelopes and positive-sense single-stranded RNA genomes. The SARS-CoV-2 virus has four kinds of structural proteins: envelope (E), spike (S), nucleocapsid (N), and membrane (M) proteins (6, 7), which the S protein has a vital role in connecting the virus to its host's cells and facilitating it to penetrate the cells (5). The most frequent symptoms and signs of COVID-19 are fever, cough, and dyspnoea. After a week or more, it could cause shortness of breath, about 20% of the patients requiring hospital cure. In many patients, particularly the elderly and those with chronic health conditions, the early signs could develop to pneumonia, with chest tightness, and shortness of breath (4). On the other hand, the quickly increasing fatality tolls of COVID-19 have been an alarm for global health. Many researchers have lately turned their focus to this growing threat and a global attempt is underway to stop its spread. At present, there is no particular antiviral treatment accessible for COVID-19, however, a broad range of pharmaceutical agents are being examined. Nanotechnology holds a large guarantee in presenting innovative approaches to a broad range of problems regarding the prevention, diagnosis, and cure of COVID-19, in which nanotechnologists certainly play a vital role and bear their social responsibility. In the meantime, among a variety

of fields of technology and science, nanotechnology has huge probability to be of massive help in prevention, diagnosis, and cure of COVID-19. At prevention step, nano-fiber based facial respirators, with the help of nanotechnology-enabled extremely effectual antimicrobial and antiviral disinfectants have been the first personal protective ways that could prevent the extension of the virus; also, widespread research is underway to expand a vaccine for COVID-19 based on different nano-materials. In diagnostics, nanotechnology has shown significant promise in designing sensors for developing rapid-response COVID-19 tests. Last but not least, at the curing phase, nano-medicines have been at the core of many researchers' attention, several of that are at present being studied in clinical trials. Given the wide abilities of nanotechnology, it is probable that innovations in this field might have an important effect on problems associated with COVID-19. This review briefly addresses the potential application of nanotechnology for the treatment of COVID-19 disease.

Entry mechanism and replication of Coronavirus

Coronavirus spike glycoprotein has been shown as an important determinative of virus entry into host cells (2). The SARS-CoV and SARS-CoV-2 spike glycoproteins bind to the angiotensin-converting enzyme II (ACE2) cellular receptor (8, 9), also, SARS-CoV and MERS-CoV binds CD209L and dipeptidyl peptidase 4 (DPP4) cellular receptors respectively (10, 11). It is recognized that SARS-CoV entry into cells is mainly achieved by direct membrane fusion between the virus and the membrane (12). An important proteolytic cleavage event at the SARS-CoV S protein at position (S20) has been reported to mediate membrane fusion and viral infection (13). The MERS-CoV as well as the development of abnormal two-phase furin activation for membrane fusion (14). In addition to membrane fusion, clathrin-dependent and -independent endocytosis also mediates SARS-CoV entry (15). Once the virus enters the cells, the genome is released into the cytoplasm space host and translates into two structural proteins and polyproteins, which then begin to replicate the viral RNA genome (16). Delayed envelope glycoproteins are inserted into the membrane of the endoplasmic reticulum or Golgi and are nucleocapsidis created by a mixture of genetic and nucleocapsid protein. After that, the viral cells germinate into the endoplasmic reticulum-Golgi intermediate compartment. Eventually, vesicles, including virus cells, coalesce with the membrane to release the coronavirus (2). The 2019-nCoV employed the same cell entry receptor ACE2 as the SARS-CoV. Peng Zhou et al. showed that 2019-nCoV is capable to employ all ACE2 proteins, but no ACE2 mouse, as an entry receptor to enter into cells with ACE2 expression, but not cells which did not express ACE2, demonstrating that ACE2 is almost the cell receptor through which 2019-nCoV enters the cell. The COVID-19 binds to ACE2 via S-protein on its surface. During infection, the S-protein is divided into S1 and S2. S1 subunit includes the receptor-binding domain that lets coronaviruses to

straightly bind to the peptidase domain of ACE2. S2 then probably has a function in membrane fusion. Peng Zhou et al. also showed that 2019-nCoV does not employ other coronavirus receptors, like DPP4 and aminopeptidase N (7).

COVID-19 Challenge

Several issues make 2019-nCoV mainly worrying. Being a novel virus, there is no acquired immunity; 40 candidate vaccines are at present in the study phase, but specialists agree that no extensively utilizable vaccine will be accessible for at least 12 to 18 months. The case-fatality rate, that by meaning is computed only based on identified patients and is so presently hard to estimate correctly, appears to be about 4%. Here are some reasons why the 2019-nCoV appears to be a threat. First, it can kill older people with existing health problems as well as healthy ones. The information up to now shows that the virus has a fatality risk of about 4%; this rate is many times more severe than usual seasonal influenza. Second, COVID-19 is relatively efficiently transmitted (17). The average infected person spreads the disease to three or four others. That's an exponential growth rate. There is as well strong proof that it could be spread by persons who are just mildly disease or not even showing signs. This represents a challenge because it would be hard to identify patients that need to be tested for the disease because they have no symptoms or signs, but their capacity to transmit the disease would permit for amplification in an uninfected population [18]. This means 2019-nCoV will be more difficult to contain than SARS, which was only transmitted by those showing signs and were much fewer proficiently transmitted (17). So, rapid treatments are vital interventions for COVID-19.

Current treatments of COVID-19 and their limitations

As mentioned above, there is no special antiviral treatment for COVID-19. Scholars are attempting to find therapeutics to treat patients with this infection. Researchers so far have examined several drug candidates, from different classes, including protease inhibitors, nucleoside analogs, neuraminidase inhibitors, polymerase inhibitors, and DNA synthesis inhibitors, that may have potential efficacy for treatment of COVID-19 (19, 20). Currently, several drugs including ritonavir/lopinavir, darunavir, emtricitabine/tenofovir, ruxolitinib, remdesivir, favipiravir, and chloroquine are undergoing clinical trials to evaluate their efficacy to treat COVID-19 and have been achieved several promising results so far (Table1). Lim et al. showed that using lopinavir/ritonavir in patients with COVID-19 causes a reduction in viral loads, therefore improving clinical symptoms during the treatment (21). Recently, Wang et al. showed in vitro which chloroquine and remdesivir were highly efficient in control of COVID-19 (22). The Clinical Medical Research Center of the National Infectious Diseases and the Third People's Hospital of Shenzhen initiated a clinical trial on favipiravir to treat COVID-19 on February 14, 2020. Their results showed favipiravir had

more strong antiviral activity than that of ritonavir/lopinavir on patient with COVID-19.

Also, Chen et al. reported that favipiravir, compared to arbidol, does not significantly improve rate of clinical recovery at day 7. In this clinical trial, favipiravir showed remarkably improvement in time-to-relief for cough and fever (23).

In recent days, an international team reported that human recombinant soluble ACE2 (hrsACE2) can remarkably inhibit primary stages of SARS-CoV-2 infection. Angiotensin-converting enzyme 2 (ACE2) has been reported as an entry receptor for SARS-CoV-2 infection and it has been proposed which blocking this interaction might be used in treatment of persons with COVID-19 infection (24).

Table 1. Current therapeutics used in treatment of COVID-19.

Candidate Therapeutics	Class	Mechanism of Action	Currently being trialled COVID-19?
Corticosteroids	Steroid hormones	Inhibition of the effector function of Th2 cells, eosinophils, and epithelial cells (25)	Yes NCT04244591
Chloroquine	Heme polymerase inhibitor, Antimalarial agent	Inhibition of glycosylation of newly synthesized proteins in many viruses (26), Increase endosomal pH needed for virus/cell fusion (27)	Yes (27) NCT04261517 ChiCTR2000029542, ChiCTR2000029559, ChiCTR2000029609, ChiCTR2000029740, ChiCTR2000029760, ChiCTR2000029761, ChiCTR2000029762, ChiCTR2000029803, ChiCTR2000029826, ChiCTR2000029837, ChiCTR2000029868, ChiCTR2000029898, ChiCTR2000029899, ChiCTR2000029935, ChiCTR2000029939

Ritonavir+ Lopinavir (Kaletra)	Protease inhibitors, Antiretroviral	Inhibits virus-specific processing of viral Gag-Pol and Gag polyproteins in cells infected with virus through inhibition of viral proteases (28)	Yes NCT04255017 ChiCTR2000048824, ChiCTR2000048919, ChiCTR2000048809, ChiCTR2000048991, ChiCTR2000048992, ChiCTR2000049015, ChiCTR2000049065
IFNα2b (PegIntron®, Sylatron®, IntronA®)	Type I interferon made by leukocytes during viral infection	Inhibition of viral replication, Stimulation of innate antiviral responses in patients infected with virus (29)	Yes ChiCTR2000048684
Emtricitabine+ tenofovir (Truvada)	Non-nucleoside reverse transcriptase inhibitor + DNA synthesis inhibitor	Incorporated into the viral DNA strand by virus reverse transcriptase and terminates DNA chain elongation (28)	Yes ChiCTR2000048919
Ruxolitinib (Jakafi or Jakavi)	Janus kinase (JAK) 1 and 2 inhibitor	Inhibition of virus replication in lymphocytes and macrophages (30)	Yes ChiCTR2000049088

Darunavir (with cobicistat) (Prezista®/ Prezcobix® and Generic)	Protease inhibitors, Antiretroviral	Inhibits virus-specific processing of viral Gag-Pol and Gag polyproteins in cells infected with virus through inhibition of viral proteases (28)	Yes ChiCTR2000048992, NCT04252274
Baloxavir marboxil (Xofluza)	Endonuclease inhibitor, Antiviral	Inhibition of cap-dependent endonuclease of influenza virus (31)	Yes ChiCTR2000049013
Favipiravir (or T-705 or Avigan)	Experimental antiviral drug. Pyrazinecarboxamide derivative viral RNA polymerase inhibitor.	Inhibition of the RNA dependent RNA polymerase of RNA viruses (32)	Yes ChiCTR2000049015, ChiCTR2000049013, ChiCTR2000049042
Arbidol (Umifenovir)	Russian-made small indole-derivative molecule. Antiviral	Inhibition of the different steps of the viral life cycle (33)	Yes ChiCTR2000049069, ChiCTR2000049065, NCT04252885
Novaferon, Nova	Recombinant protein produced by DNA-shuffling of IFN-α	Inhibition of viral replication (34)	Yes ChiCTR2000049065, ChiCTR2000048809

GS-5734/ Remdesivir	Nucleoside inhibitor	Incorporation into nascent viral RNA chain and pre-mature termination of RNA chain elongation (22)	Yes NCT04252664, NCT04257656

Despite the promising effects of the drugs used to treat COVID-19, several challenges remain with current treatments. One of the challenges is the administration of the drug by the oral route that can create both topical and systemic side effects. The drug delivery to the lung to treat pulmonary diseases by oral therapy requires high doses of drug, also rapid clearance of drugs leads to a need for daily treatment with several drug candidates for the long periods (35). The other significant challenge in viral infectious diseases is emergence of drug resistance (28), which may also occur in patients with COVID-19 disease.

Potential applications of Nanotechnology in treatment of COVID-19

Nanotechnology offers promising solutions to overcome the challenges of oral administration of drug and to treat drug resistance. Nanotechnology-based drug delivery systems (nano-DDS) have several unique physical properties, such as high water-solubility, sensitivity to temperature, simple surface modification, controlled release capability of encapsulated drugs, and high surface-area-to-volume ratios (36). The medical scientists can use these unique properties to overcome the challenges related to enhanced drug resistance of infectious agents.

Nano-DDS can be adapted (i) to increase the solubility of drugs, (ii) to protect drugs from degradation, (iii) to reduce drug-associated toxicity, (iv) to modulate drugs release, (v) to enhance cellular uptake of drugs and their blood circulation time, and (vi) to target drugs to affected cells, tissues, and organs (37-40).

Unlike oral administration, systemic delivery of therapeutics via lungs allows that therapeutic can bypass harsh conditions of digestive tract and avoid first-pass metabolism (41). Also, compared to the digestive system, the lungs show a low level of enzymatic activity (42).

Local delivery of therapeutics to lungs has many advantages as it improves the efficiency of the treatment by enhanced accumulation of therapeutics in the lungs, also, reduces systemic side-effects of drugs on other tissues and organs through reduction of required dosage of delivered drugs and prevention of their penetration into the systemic circulation (43).

The different types of nanocarriers such as polymeric and solid lipid nanoparticles, liposomes, and micelles have been used for delivering therapeutics to the lung due to their flexible and controllable biological properties. These nanocarriers can be administered through distinct routes, including oral, inhalation and intravenous (44). The administration route is as significant as drug formulation for reaching therapeutic goals. Table 2 lists several nano-DDS that are used for treatment of pulmonary infections.

In recent years, nanoparticle DDS has been designed for improvement of therapeutic stability, efficacy, safety, and patient compliance (45). The therapeutic benefits of nanoparticles (NPs) as drug carrier are well controlled release properties, high bioavailability, low toxicity, high stability, feasibility of incorporation of both hydrophobic and hydrophilic therapeutics, and high encapsulation efficacy for therapeutics (46, 47). The development of nanoparticle DDS is one of the best ways to gain higher drug levels in the lungs, drug-loaded NPs can be used for direct pulmonary delivery via the aerosol route (48).

The inhalational delivery of a drug in form of suspension aerosol or inhaled dry powder has two potential limitations including, limited bioavailability of drug because of its microparticulate nature and poor solubility that leads to restricted dissolution and diffusion of a drug at the site of action, and reduced residence time of drug due to its fast alveolar macrophage uptake and ciliary clearance that results in elimination of long-term effects of drug. In contrast, inhalational delivery of a drug in form of nanosuspensions and nanoparticles has several potential advantages including, fast start of action of the drug because of its rapid dissolution and diffusion, prolonged drug residence time at the site of action due to enhanced adherence of nanoparticulate drug to mucosal surfaces, and lower phagocytic clearance of NPs compared to microparticles (49).

The effective pulmonary delivery of an inhalable therapeutic depends on many factors, such as shape, size, and surface features (42). These factors affect all aspects of pulmonary delivery of drug, such as deposition in respiratory tract, dissolution in lung lining fluid and clearance process (50).

Polymeric NPs are achieving fast importance to delivery of drug to the lungs. Various polymers have been studied for pulmonary applications. Polymers possess multiple benefits, including high capacity for encapsulation of drugs and their protection from degradation, and extended delivery of drug for a long time (51). The polymers include poly(lactic-*co*-glycolic acid) PLGA, poly(ε caprolactone) PCL, poly(lactic acid) PLA, chitosan, alginate, and gelatin are commonly used for therapeutic purposes (52, 53). By modifying chemical and surface properties of polymers, they can be biodegradable (54, 55). Several studies have been carried out using polymeric NPs to delivery of anti-infectious drugs to the lungs (Table 2).

Solid lipid nanoparticles (SLNs) are other group of NPs that have widely been investigated for potential pulmonary drug delivery. SLNs are nanocrystalline suspensions in water, prepared from phospholipids, physiological lipids, and primarily triglycerides (56). SLNs are popular for pulmonary delivery of drug since the formulations are prepared with the use of physiological components (57). The SLNs have advantages like good tolerability, scaling-up possibility, low toxicity, the ability to encapsulate hydrophilic/hydrophobic drugs, and increased stability of encapsulated drugs (58). To treatment of lung infections, different anti-infectious drugs have been incorporated in SLNs (Table 2).

Liposomes are a popular DDS for pulmonary drug delivery, as they are formed mainly from phospholipids, that are inherent in lungs (59). Liposomes possess properties like capacity to incorporate of drugs in core or within their membrane bilayer, ability to decrease toxicity of drugs and change their pharmacokinetics, and potential for sustained release of drugs to increase their effect over an extended time period, which make them attractive drug nanocarriers for the treatment of pulmonary infections (60, 61). Liposomal DDS using both lipophilic and hydrophilic drugs was used to treatment of lung infections through the inhalation route (43).

So far, liposome has been one of the most promising nanocarriers to pulmonary antibiotics delivery, with several antibiotic formulations in clinical trials (44). Conventional liposomes are easily uptake through macrophages cells of the reticuloendothelial system. Thus they form a worth delivery vehicle to target high antibiotics doses to sites where the bacteria reside (62). Also, the half-life antibiotics may extend in the body due to sustained release of these drugs from liposomes (62).

Nebulized liposomes to target drugs to the lung have been well described (63, 64). It was shown which nebulization of liposomal dispersions permitted penetration into the lung peripheral region (65). Efficient chemotherapy of pulmonary infections can be performed by drug targeting to alveolar macrophages by using aerosolized liposomes (65). However, physical and chemical long-term stability of liposome suspensions during storage, such as fusion, leakage, and aggregation, is one of key limitations in the development of these nanocarriers (66, 67).

Also, liposomes can be used as a carrier to target cell- and organ-specific using ligands. Although, therapeutic applications of ligand-anchored liposomes that are injected intravenously, can become restricted because of some factors, including leakage of contents of liposomes before they reach to the target site, and uptake of liposomes through macrophages of the spleen and liver [64]. The anti-infectious drugs which have been encapsulated as liposomal formulations are listed in Table 2.

Polymeric micelles because of their nanoscopic core-shell structure are considered as suitable carriers for delivery of poor water-soluble drugs like antibiotics and antifungal into the lung (68). The delivery of anti-infection drugs to the lung by polymeric micelles mentioned in Table 2.

Table 2: Examples of nano DDSs developed for delivery of anti-infectious drugs to the lungs.

Nano DDS	Therapeutic agent	Route of administration	Organism	Purpose/Effect of nanoformulation
PLGA nanoparticles	Isoniazid Rifampicin Pyrazinamide	Inhalation	Mycobacterium tuberculosis	To improve the bioavailability of antitubercular drugs, To prolong half-life of drugs (69)
PLGA nanoparticles	Voriconazole	Inhalation	Not tested	To improve pulmonary delivery (70)
PLGA nanoparticles	Rifampicin	Inhalation	Mycobacterium tuberculosis	To increase uptake of drug (71)
Lection –PLGA nanoparticles	Isoniazid Rifampicin Pyrazinamide	Inhalation	Mycobacterium tuberculosis	To decrease the drug dosage frequency, To improve patient compliance in chemotherapy of TB (72)
Alginate/chitosan nanoparticles	Isoniazid Rifampicin Pyrazinamide	Inhalation	Mycobacterium tuberculosis	The controlled release of antitubercular drugs (48)
Mannitol:Lectin nanoparticles	Iitraconazole	Inhalation	Aspergillus fumigatus	To improve the bioavailability of drug (50)
Polysorbate 80: poloxamer 407 nanoparticles	Iitraconazole	Inhalation	Aspergillus fumigatus	To increase water solubility of drug (73)

Polysorbate 80: poloxamer 407 nanoparticles	Itraconazole	Inhalation	Aspergillus fumigatus	Improved survival and limited invasive disease (74)
Cyclodextrin complexes	Rifampicin	Inhalation	Acinetobacter baumannii	To increase water solubility, To maximize the active drug amount, To optimize lung pharmacokinetic profile of drug (75)
Soli lipid nanoparticles	Isoniazid Rifampicin Pyrazinamide	Inhalation	Mycobacterium tuberculosis	Improved drug bioavailability and mean residence time, Reducing the dosing frequency (58)
Soli lipid nanoparticles	Amikacin	Inhalation	Not tested	To increase concentration of drug in the lungs (76)
Soli lipid nanoparticles	Budesonide	Inhalation	Not tested	To increase water solubility and adsorption of drug (77)
Soli lipid nanoparticles	Rifampicin	Inhalation	Mycobacterium tuberculosis	To reduce of toxicity of drug (56)
Liposome	Amphotericin B	Inhalation	Aspergillus fumigatus	To improve the drug chemotherapy efficacy (78)
Liposome	Amphotericin B	Intravenous	Candidosis Aspergillosis	To improve the drug chemotherapy efficacy, To reduce acute and chronic toxicities of drug (79)

Liposome	Ciprofloxacin	Inhalation	Not tested	To improve the drug chemotherapy efficacy against intracellular parasites (80)
Liposome	Ciprofloxacin	Inhalation	Francisella tularensis	Higher serum levels of drug, Prolonged drug retention in lung (81)
Liposome	Ciprofloxacin	Inhalation	Not tested	To delivery high drug concentration to target site, Reducing the local irritation (82)
Liposome	Rifampicin	Inhalation	Mycobacterium avium	To reduce of dosage of drug (65)
Liposome	Rifampicin	Inhalation	Mycobacterium tuberculosis	To improve the chemotherapy efficacy of drug (64)
Liposome	Tobramycin	Intratracheal	Pseudomonas aeruginosa	Improved efficacy after multiple treatments, Prolonged drug retention in lung (83)
Liposome	Tobramycin	Intratracheal	Burkholdera cepacia	Prolonged efficacy of drug (84)
Liposome	Polymyxin B	Intratracheal	Pseudomonas aeruginosa	To increase pulmonary level of drug, To decrease of toxic effect of drug (85)
Liposome	Cyclosporine A	Inhalation	Mycobacterium tuberculosis	To deposit of drug to the peripheral lung (86)

Liposome	Isoniazid	Inhalation	Mycobacterium tuberculosis	To increase pulmonary level of drug (87)
Chitosan-based micelles	Amphotericin B	Inhalation	Candida spp Aspergillus spp	To improve water solubility, To reduce adverse effects, To reduce the aggregation state of drug (68)

Conclusion and future perspectives

As shown in this review, remarkable works have been done in nano-formulation therapeutics for treatment of the lung infections. Nanotechnology presents an excellent opportunity for the basic improvement of current treatments and development of novel therapeutic options for lung infections formerly thought impossible or difficult to treat. Nonetheless, we are yet in the primary stages of nanomedicine in respiratory infections care, which requires physicochemical and nanotoxicological analysis for possible human applications. At present, we are entering a modern world where nanotherapeutics will change the way we practice respiratory medicine. Nanotherapeutics offer improved clinical efficacy for patients, especially to those patients who are currently treatment-resistant to conventionally administered therapeutics.

According to the above content and the potential applications of nanotechnology to delivery of anti-infection drugs to the lungs, current and potential therapeutics of COVID-19 can be encapsulated into nanocarriers and delivered to the lungs through the respiratory tract.

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Conflicts of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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