Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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COVID-19 infection and nanomedicine applications for development of vaccines and therapeutics: An overview and future perspectives based on polymersomes

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ABSTRACT

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which emerged in December 2019 and caused the coronavirus disease 2019 (COVID-19) pandemic, took the world by surprise with an unprecedented public health emergency. Since this pandemic began, extraordinary efforts have been made by scientists to understand the pathogenesis of COVID-19, and to fight the infection by providing various preventive, diagnostic and treatment opportunities based on either novel hypotheses or past experiences. Despite all the achievements, COVID-19 continues to be an accelerating health threat with no specifically approved vaccine or therapy. This review highlights the recent advances in COVID-19 infection, with a particular emphasis on nanomedicine applications that can help in the development of effective vaccines or therapeutics against COVID-19. A novel future perspective has been proposed in this review based on utilizing polymersome nano-objects for effectively suppressing the cytokine storm, which may reduce the severity of COVID-19 infection.

1. Introduction

In December 2019, an outbreak of severe pneumonia resulting from an unknown cause occurred in Wuhan, Hubei province, China (He et al., 2020). A few days later, the causative agent of this mysterious pneumonia was identified as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The corresponding infectious disease was named coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO) (He et al., 2020). SARS-CoV-2 rapidly spread worldwide to become a serious health threat, and on March 11, 2020, WHO declared a global SARS-CoV-2 pandemic (WHO, 2020b). Since January 21, 2020, when the virus began to spread outside China, including countries such as South Korea, Japan, and Thailand, the WHO started releasing daily situation reports. So far, there are more than 62 million confirmed COVID-19 cases worldwide, with more than 1.45 million deaths (WHO, 2020b).

A wide range of clinical manifestations is seen in patients with SARS-CoV-2, ranging from mild to moderate to severe and rapidly progressive

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and fulminant disease (Wu et al., 2020b). As most of the patients infected with SARS-CoV-2 display mild or moderate symptoms, this makes it difficult to detect them, as they may present either no symptoms at all or symptoms highly similar to conventional flu (Wu et al., 2020b). The common clinical features of COVID-19 include fever, cough, sore throat, headache, fatigue, myalgia and breathlessness, as well as conjunctivitis (Singhal, 2020) (Fig. 1).

The current healthcare strategies for COVID-19 patients are limited to bed rest and supportive treatments including immunomodulating therapy, organ function support, respiratory support, bronchoalveolar lavage (BAL), blood purification, and extracorporeal membrane oxygenation (ECMO) (Wu et al., 2020b). In addition, some protocols use antiviral therapeutics and antibiotics as auxiliary approaches, but without clear mechanisms of action against SARS-CoV-2 (Wu et al., 2020b). According to the 'COVID-19 treatment and vaccine tracker' report provided by the Milken Institute, as of September 3, 2020, there were 237 vaccine candidates and 319 therapeutic substances being studied against COVID-19 over the world (COVID-19 treatment and vaccine tracker, 2020). So far, however, there have been no approved vaccines or antiviral drugs against SARS-CoV-2. This implies that identifying the drug treatment options as soon as possible is critical for an appropriate response to the COVID-19 outbreak (Lu, 2020). Therefore, there is a serious need for a vaccine or an effective antiviral drug to cope with this pandemic outbreak.

Although many reports have discussed a variety of nanomedicine applications that may help in the fight against COVID-19, the majority of them have emphasized the diagnostic rather than the therapeutic or vaccination approaches. This review represents the recent advances in the use of nanomaterials in development of vaccines and therapeutics against COVID-19. A novel approach for using polymersomes to suppress the cytokine storm, which may reduce the severity of COVID-19 infection, has been proposed as a future perspective.

2. SARS-CoV-2 structure and mode of infection

SARS-CoV-2 is a single-strand positive-sense RNA virus that originated in bats, albeit with the intermediate host remaining unknown. During coughing or sneezing, SARS-CoV-2 is transmitted by the aerosol droplets produced and disseminated in the air by infected patients (Rothe et al., 2020). These aerosol droplets can spread up to 2 m in distance, and the virus can retain infectivity on surfaces for a few days in the absence of mechanical attrition or chemical attack. Via direct inhalation or by touching the nose, mouth or eyes after touching the surfaces contaminated with the infected droplets, the virus enters the host body and targets the type I and II alveolar epithelial cells expressing the angiotensin-converting enzyme 2 (ACE2) (Singhal, 2020), which has been reported as the receptor for SARS-CoV-2 (Sun et al., 2020). During COVID-19 infection, the trimeric spike (S) glycoprotein on the virion surface mediates receptor recognition and membrane fusion (Yan et al., 2020).

2.1. Virus structure and cell fusion

Both SARS-CoV-2 and SARS-CoV are human *Betacoronavirus* strains that use transmembrane serine protease 2 (TMPRSS2) to prime the S protein prior to ACE2 cellular ligand (Hoffmann et al., 2020a; Mousavizadeh and Ghasemi, 2020). Among RNA viruses, coronaviruses have the largest genome ranging from 26 to 32 kilobases (kb) (Perrotta et al.,

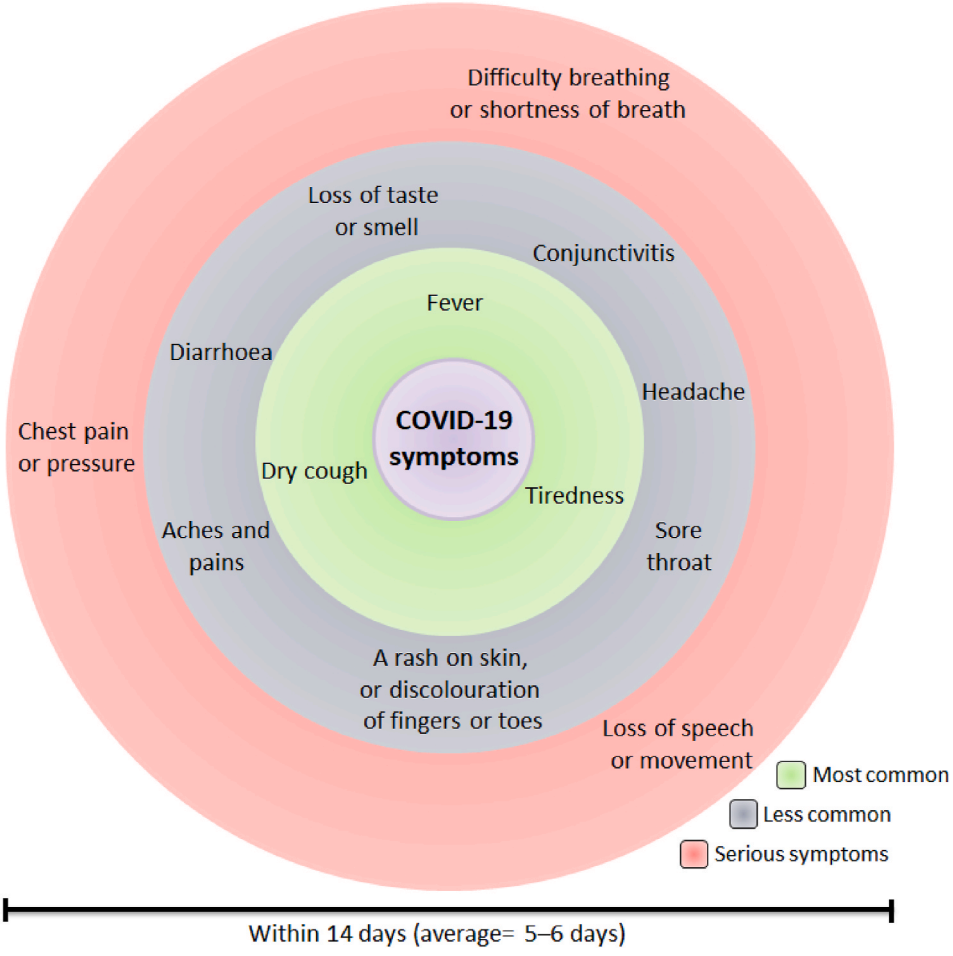

Fig. 1. COVID-19 symptoms according to WHO classification (WHO, 2020a).

2020) and consisting of structural and non-structural proteins. Many non-structural proteins, including RdRP, are involved in RNA replication and transcription processes (Ashour et al., 2020; Narayanan et al., 2015). Meanwhile, structural proteins consist of four major proteins, including S, envelope (E), membrane (M), and nucleocapsid (N) proteins (Chen et al., 2020b; Malik, 2020). Apart from constructing a complete viral particle, these four major proteins (S, E, M and N) have their respective functions in mediating the viral pathogenesis and the replication cycle. The conserved order of their genome is replicase *S, E, M* and *N* genes (Graham and Baric, 2010) with numerous open reading frames (ORFs) in-between the 5′ cap and the 3′ poly (A) tail structure (Fehr and Perlman, 2015). While 5′ cap encodes for structural proteins, 3′ tail encodes for accessory proteins including polyproteins pp1a and pp1b that further divided for non-structural proteins (Anastasopoulou and Mouzaki). Some coronaviruses also contain the hemagglutinin esterase (HE) protein (Belouzard et al., 2012; Wang et al., 2020b).

The M protein is the most abundant structural protein and it acts as a central organizer that forms budding with other structural proteins to allow for virus assembly (Neuman et al., 2011; Schoeman and Fielding, 2019). The E protein is a small integral membrane protein involved in morphogenesis and pathogenesis. Without *E* gene, recombinant coronaviruses exhibit defective virions (Schoeman and Fielding, 2019). Meanwhile, N protein protects the viral genome by packaging it into helical ribonucleoprotein complexes. It also interacts with RNA and mediates transcription and translation (McBride et al., 2014).

In coronaviruses, S protein serves as the most prominent feature for the virion structure by giving a crown-like appearance on the surface; hence the name, coronavirus (Fehr and Perlman, 2015). The extended structure of S protein on the virus surface is leading the viral entry into host cells. Currently, S protein is targeted for COVID-19 vaccine research as well as drug treatment due to its role in virus entry, which leads to subsequent pathogenesis effects. The S protein comprises two subunits: S1 and S2 (Astuti and Ysrafil, 2020; Walls et al., 2020) with a combined length of 1273 amino acids (Wu et al., 2020a). The S1 contains the receptor-binding domain (RBD), which directly binds to the peptidase domain (PD) of ACE2, while S2 mediates membrane fusion (Li et al., 2005). When S1 binds to the host receptor ACE2, another cleavage site on S2 is exposed and is cleaved by host proteases, a process that is critical for viral infection (Belouzard et al., 2009).

It is interesting to note that the S2 subunit of SARS-CoV-2 consists of furin-like cleavage site, which is lacking in SARS-CoV (Coutard et al., 2020). Thus, the high expression of furin in the lungs is being exploited by SARS-CoV-2 to activate the S protein and hence enter the host cells via ACE2 receptor, causing respiratory failure.

2.2. Replication of SARS-CoV-2 in host cell

After successful internalization, SARS-CoV-2 begins its life cycle in the host cells (Fig. 2). Conformational changes after the binding of S protein to ACE2 receptor facilitate the virus-cell fusion. Once the viral envelope fuses with the cellular membrane, the viral RNA is released inside the host cell cytoplasm. The virion genomic RNA is then translated to generate replicase polyproteins pp1a and pp1b, which get further cleaved into smaller proteins by viral proteinases (Kumar et al., 2020; Shereen et al., 2020). Viral RNA replication produces both genomic and many smaller sub-genomic RNAs through negative-strand intermediates by discontinuous transcription for relevant viral proteins translation (Kumar et al., 2020; Malik, 2020). The latter serve as a template for structural proteins (S, E, N and M) and several accessory proteins which are known to be at least six, including 3a, 6, 7a, 7b, 8, and 10 (Kim et al., 2020). However, there is some discrepancy between recent studies regarding the accessory proteins of the SARS-CoV-2 genome. For instance, Gordon et al. have reported that only 5 canonical accessory proteins are involved (3a, 6, 7a, 7b and 8) (Gordon et al., 2020).

Subsequently, the translated viral RNA and proteins assemble in the endoplasmic reticulum (ER) and the ER-Golgi intermediate compartment (ERGIC) into new particles. Virions are then transported via vesicles prior to their being released out of the host cells via exocytosis by the plasma membrane fusion (Kumar et al., 2020; Shereen et al., 2020).

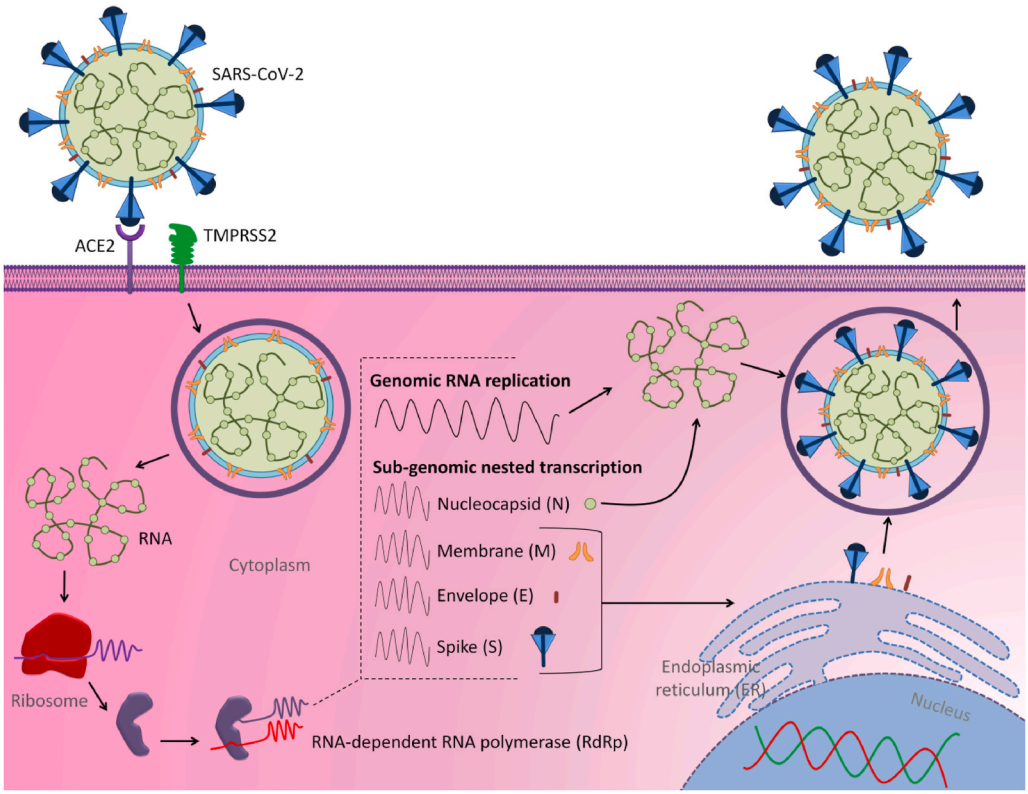

Fig. 2. Schematic mechanism of replication of SARS-CoV-2 in a host cell. S protein on the surface of SARS-CoV-2 recognizes the ACE2 receptor on the cellular membrane of the host cell. The conformational changes at the S1 and S2 subunits facilitate the virus-cell fusion via endosomal pathway. The viral genome is released into the cytoplasm and translated through ribosomal frame shifting to generate replicas of polyproteins pp1a and pp1b. Following the genomic and sub-genomic synthesis, the viral proteins and the genomic RNA are inserted into virions and assembled in the ER-Golgi intermediate compartment (ERGIC) and then transported in the vesicles to the plasma membrane before being released out via exocytosis (Al-Hatamleh et al., 2020).

Despite previous replication and transcription studies that have been done on other coronaviruses, studies have been conducted to determine the new SARS-CoV-2 transcriptome and identify possibly other unknown components in this specific organization of the genome. Identifying these elements could help in the design of therapies specific to this novel coronavirus.

3. The immune response against SARS-CoV-2

Studies have indicated a defensive function of both cell-mediated and humoral immune responses in patients diagnosed with COVID-19 (Baruah and Bose, 2020; Li et al., 2020). Accumulated evidence suggests that a subgroup of patients with severe COVID-19 could deregulate the immune response that allows the development of viral hyper-inflammation (Lagunas-Rangel, 2020). In terms of laboratory analyses, it has been noted that most of the COVID-19 patients have lymphopenia with increased levels of infection-related biomarkers (Qin et al., 2020). A report of 99 cases showed increased total neutrophils (38%) along with decreased total lymphocytes (35%) (Zhou et al., 2020). This status was also reported in another study and correlated with disease severity and death (Wu et al., 2020c). In addition, a decrease in $CD4^+$ T cells, $CD8^+$ T cells, B cells, and natural killer (NK) cells are common among patients with COVID-19 (Qin et al., 2020; Wang et al., 2020a). At the same time, the pro-inflammatory cytokines including interleukin-6 (IL-6), tumor necrosis factor (TNF) and IL-1, and chemokines (IL-8) are elevated, especially in severe cases (Qin et al., 2020). It is also reported that patients infected with SARS-CoVs have high secretion of TNF, IL-10, IL-2, IL-7, interferon gamma-induced protein-10 (IP-10), granulocyte colony-stimulating factor (G-CSF), monocyte chemoattractant protein-1 (MCP-1), and macrophage inflammatory protein-1 alpha (MIP-1α). The abruptly acute increase in the levels of pro-inflammatory cytokines causes a severe infection state known as the cytokine storm syndrome, which is suggested to be related to the severity of COVID-19 infection (Conti et al., 2020; Wong et al., 2004). However, the current data on the status of innate immunity of COVID-19 patients are still limited.

Although the ACE2 receptor is expressed in a limited amount by macrophages/monocytes in the lungs, the virus can probably enter the host cells through other, not yet discovered mechanisms (Rokni et al., 2020). Wang et al. proved that SARS-CoV-2 could infect T lymphocytes through the S protein-mediated membrane fusion (Wang et al., 2020c). As a result, the lymphocytopenia with abnormally low lymphocyte levels was reported and associated with the severity and mortality rate of COVID-19 (Zeng et al., 2020; Zheng et al., 2020). However, it is still unclear whether SARS-CoV-2 can replicate in the infected T lymphocytes. It is known, for example, that neither SARS-CoV nor MERS-CoV are able to replicate in T lymphocytes (Chu et al., 2016).

It is essential to clarify the characteristics of lymphocyte subsets in COVID-19. This could provide novel insights regarding the immune mechanisms and be an independent predictor for disease severity and treatment efficacy. Also, since the infected cells induce innate inflammation in the lungs, which is mediated mainly by pro-inflammatory secretions, good general health may not be advantageous for patients who have advanced to the severe stage. Therefore, efforts should be made to suppress inflammation and to manage the symptoms. As an essential step towards this aim, it is required to understand the innate immunity in patients infected with COVID-19 fully.

4. Why SARS-CoV-2 dangerous?

In the early 1960s, during a diagnosis of an adult with a common cold, Tyrrell and Bynoe reported the first coronavirus (B814) infected human respiratory system (Tyrrell and Bynoe, 1966). During these 60 years, several strains of coronaviruses have been discovered and subsequently recognized as causative agents of various respiratory and enteric diseases in humans and animals. Among the most important coronaviruses, SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) were discovered in 2003 and 2009, respectively (Ramadan and Shaib, 2019). The first case of infection with SARS-CoV was reported in Guangdong, China and it is believed that the virus was transmitted to the human from a bat. The number of confirmed cases of SARS-CoV infection is 8,096, with 10% mortality rate. In contrast, MERS-CoV emerged in Saudi Arabia and the spread is thought to have occurred from infected camels. With 2519 confirmed cases, the infection rate of MERS-CoV was lower than that of SARS-CoV, but, in turn, its mortality rate was higher at whole 34.4% (Rabaan et al., 2020). SARS-CoV-2 is genetically more similar to SARS-CoV (79%) than to MERS-CoV (50%), with the major structural difference being that the spike protein of SARS-CoV-2 is longer than that in SARS-CoV (Lu et al., 2020).

Although the mortality rate for SARS-CoV-2 is still lower than those for SARS-CoV and MERS-CoV (Wu et al., 2020b), SARS-CoV-2 is considered more critical because of its rapid spread across the world. It was reported that the binding affinity of SARS-CoV-2 to ACE2 receptor is 10–20 times higher compared to that of SARS-CoV (Wrapp et al., 2020), with a more compact and stable conformation at the RBD-ACE2 interface (Shang et al., 2020). Furthermore, studies have shown that SARS-CoV-2 is implicated in the upregulation of autophagy, apoptosis, and p53 pathways in human peripheral blood mononuclear cells (Xiong et al., 2020).

Generally, during the reproduction of living or non-living organisms, such as viruses, slight errors, called mutations, can occur in the genetic code. Viruses comprising RNA genome instead of a DNA one are less genetically stable because they do not have a self-correcting mechanism for those errors (Bolis et al., 2016). A prior analysis of the mutation rates in 23 different viruses showed that it ranged from 10^{-6} to 10^{-4} nucleotide substitutions per site per year (ns/s/y) for RNA viruses, while for DNA viruses it was 10^{-8} to 10^{-6} ns/s/y (Sanjuan et al., 2010). Coronaviruses are a large family of positive-strand RNA viruses encoding a complex dependent RNA polymerase involving a 3′ exonuclease domain (Smith et al., 2014). Compared to their host cells, the mutation rate of RNA viruses is usually a million times higher, enhancing their evolvability and virulence (Duffy, 2018).

So far, the estimated mutation rate in the SARS-CoV-2 genome is about 1.05×10^{-3} to 1.26×10^{-3} ns/s/y (Pawelczyk and Zaprutko, 2020). This is in the similar range to the mutation rates estimated for SARS-CoV and MERS-CoV, namely 0.80×10^{-3} - 2.38×10^{-3} ns/s/y and 1.12×10^{-3} ns/s/y, respectively (Cotten et al., 2014; Zhao et al., 2004). These rates are considered similar to some extent and consistent with other RNA viruses. Towards a better understanding of the viral evolution, researchers focus on the rate of mutation and production of new strains as a critical parameter with important practical implications (Sanjuan et al., 2010). However, the mutation rate in the SARS-CoV-2 genome is changeable for as long as the virus is mutating, whereas one favorable effect is its comparatively slow mutation due to a relatively large RNA genome, given the earlier established negative correlation of the mutation rate with the genome size (Sanjuan et al., 2010). For example, although influenza viruses as the most common causes of respiratory infections are also RNA viruses, they have smaller negative-strand RNA genomes. Thus, their mutation rates are relatively higher (Bouvier and Palese, 2008).

Overall, researchers argue that the high level of similarity between SARS-CoV-2 and SARS-CoV suggests the convergent evolution of the RBD structures in both of these viruses to improve the binding affinity to the same ACE2 receptor, even though SARS-CoV-2 does not cluster within SARS-CoV in the *Betacoronavirus* genus (Lan et al., 2020; Tai et al., 2020). Data show a higher affinity of the SARS-CoV-2 RBD (four folds) for receptor binding than that demonstrated by the SARS-CoV RBD (Hatmal et al., 2020). The SARS-CoV-2 RBD binds to ACE2 with an affinity in the low nanomolar (nM) range, with the dissociation constant (K_D) for ACE2 and the SARS-CoV-2 RBD being 4.7 nM, compared to 31 nM for that between ACE2 and the SARS-CoV RBD,

indicating that the RBD is the key functional component within the S1 subunit responsible for the binding of SARS-CoV-2 to ACE2 (Hoffmann et al., 2020b; Lan et al., 2020; Rowland and Yoo, 2003; Wrapp et al., 2020). The S1/S2 processing sites (needed for priming) exhibit different motifs among coronaviruses; many of them display cleavage sites after a basic residue. It is, thus, likely that the priming process is ensured by different host-cell proteases, the choice of which depends on the sequence of the S1/S2 cleavage site. Accordingly, the MERS-CoV S protein that contains the RSVRSV motif can be cleaved by furin during viral egress (Millet and Whittaker, 2014; Zhang et al., 2020c). The SARS-CoV-2 S protein contains a putative furin recognition motif (PRRARSV) similar to that of MERS-CoV. The higher affinity of S protein for ACE2 and the presence of additional potent furine-like cleavage sites might be the key reasons why SARS-COV-2 is more contagious.

5. Nanomedicine amid COVID-19 pandemic

In the recent two decades, nanomedicine provided a variety of applications and approaches that utilize nanomaterials in the development of vaccine candidates and antiviral drugs (Demento et al., 2012; Pati et al., 2018). In addition to this role as a vehicle for encapsulated or conjugated vaccine components (i.e., antigens, RNAi or mRNA- and DNA -coding antigens, fragments of proteins and peptides, or proteins) or antiviral drugs, nanomaterials can promote the sustained release of these components, protect them from degradation and prolong their bioavailability, while also occasionally boosting the immunity towards better immune homeostasis (Demento et al., 2012; Pati et al., 2018).

By either suppressing or stimulating the immune system response, various nanomaterials have shown immunomodulatory effects (Al-Hatamleh et al., 2019a; Mohamud et al., 2017). From this point, the concept of 'nanoimmunity-by-design' has recently been proposed by Gazzi et al., which aims to provide the next generation of nano-based immunotherapeutics via the rational design and characterization of different physicochemical properties of nanomaterials, followed by functionalization to achieve precise targeting of different components of the immune system (Gazzi et al., 2020). One of the important approaches in protection against viral infections is that of targeting the T cell-mediated immune response. Studies have shown that nanovaccines have the potential for cross-presentation of antigens to cytotoxic T cells (Kim et al., 2019). Therefore, nanomaterials such as self-assembled nanostructures, liposomes, nanocrystals, dendrimers, nanosuspensions, nanoemulsions, polymeric nanostructures, micelles and nanoparticles comprising lipids, carbohydrates or other organic molecules may emerge as promising tools in fighting COVID-19 (Lembo et al., 2018; Six and Ferji, 2019), especially in terms of enhancing vaccine development and therapeutic efficiency of the repurposed or novel antiviral drugs. A variety of nanomedicine-based strategies for development of therapeutics and vaccines are being actively tested, developed or simply being proposed as of use in the combat against the COVID-19 infection (Fig. 3).

5.1. Nanomedicine in vaccine formulations

Florindo et al. [84] have discussed the possibility of encapsulation or conjugation of potential vaccine components against SARS-CoV-2 in

Fig. 3. Potential nanomedicine-based approaches for therapeutic and vaccine formulation against COVID-19.

lipid and polymeric nanoparticles as delivery systems. Among nine promising vaccine candidates were entered Phase III of clinical trials, there are two lipid nanoparticle-formulated mRNA vaccine candidates (i.e., mRNA-1273 and BNT162). The search for a promising COVID-19 vaccine candidate reached a milestone for the first time when the mRNA-1273 vaccine candidate from Moderna Inc. started Phase III trial (ModernaTX, 2020). The move indicates that the pharmaceutical company and the National Institutes of Health, which are partners in the study, maybe a step away from getting the vaccine to the public and commercial markets. This vaccine candidate is a novel lipid nanoparticle-encapsulated mRNA-based vaccine, which encodes for a full-length, prefusion stabilized S protein of SARS-CoV-2 (National Institute of Allergy and Infectious Diseases, 2020). Since the S protein complex is crucial for membrane fusion and host cell infection, it has been the vaccine target against coronaviruses, including SARS-CoV and MERS-CoV. The mRNA-1273 drug substance is loaded into lipid nanoparticles comprising the patented ionizable lipid (SM-102) and three other commercially available lipids (cholesterol, DSPC and PEG2000DMG) (National Institute of Allergy and Infectious Diseases, 2020) (Fig. 4).

Similar to Moderna's vaccine candidate, BNT162 vaccine candidate from Pfizer Inc. and BioNTech SE also emerged as lipid nanoparticle-encapsulated nucleoside modified mRNA-based vaccine that encodes for S protein of SARS-CoV-2 (Mulligan et al., 2020). Another interesting mRNA vaccine candidate utilizing a nanomaterial, specifically a lipid-enabled and unlocked nucleic acid-modified RNA (LUNAR) nanoparticle-based delivery system, is ARCT-021, which is being developed using the STARR™ technology for self-replicating RNA, to prolong its otherwise short half-life, which boosts the expression of SRS-CoV-2 S protein (Arcturus Therapeutics, 2020a). LUNAR is considered a safe, effective and reproducible lipid nanoparticle for mRNA delivery and it includes four lipids: cholesterol, a PEGylated commercial lipid, and a phospholipid 1,2-distearoyl-sn-glycero-3-phosphocholine, in addition to a special ionizable lipid produced by Arcturus Therapeutics (ATX) (Ramaswamy et al., 2017).

In 2014, promising findings emerged from a study aimed at synthesizing SARS-CoV and MERS-CoV spikes-like nanoparticles. Combined with adjuvants, these nanoparticles were injected in mice, where they enhanced the immune response and the neutralizing antibodies count (Coleman et al., 2014). Based on these findings and the genetic similarity between those viruses and SARS-CoV-2, Hashemzadeh et al. suggested that this strategy could be effective against SARS-CoV-2 too (Hashemzadeh et al., 2020). Furthermore, two current vaccine candidates are using coronavirus-like particles (CoVLPs). First, Medicago's vaccine candidate has been proposed based on producing CoVLPs derived from *Nicotiana benthamiana* plant-based S protein, with the adjuvants being Dynavax's CpG 1018™ and GlaxoSmithKline's pandemic adjuvant technology, separately (Medicago Begins Phase I, 2020). Second, AdaptVac/ExpreS^{2}ion's vaccine candidate composed of CoVLP-based S2 protein is derived from insect cell expression systems (ExpreS2ion's joint venture AdaptVac, 2020). Recently, Nie et al. have shown that based on its ability to be inserted into the gaps of virion glycoproteins, the short spikes (5–10 nm size) are fixed on nanostructures and can preferentially attach to influenza A virus (IAV) virions relative to smooth nanoparticles (Nie et al., 2020). They also demonstrated that using nanostructures coated with the erythrocyte membrane to target the IAV virion can inhibit the virus infection by blocking the binding of the virion to the host cell surface and thus reduced the virus replication rate by more than 99.9% (Nie et al., 2020). Therefore, such types of nanoinhibitors hold a great potential against SARS-CoV-2.

Further, Raghuwanshi et al. loaded specific plasmid DNA onto biotinylated chitosan nanoparticles, which were designed to target the nasal resident DCs as the nasal immunization route against the N protein of SARS-CoV in mice (Raghuwanshi et al., 2012). Also, Sekimuka et al. used gold nanoparticle (AuNPs) adjuvants in conjunction with the recombinant S protein, not only as an antigen carrier, but also as an effective adjuvant in the immunization of mice (Sekimukai et al., 2020). However, although this vaccine candidate (AuNP-adjuvanted S protein) induced antigen-specific IgG response against SARS-CoV, it was unable to enhance the effectiveness of the vaccine or to decrease eosinophilic infiltration due to the strong allergic inflammatory responses (Sekimukai et al., 2020). Overall, by confirming the efficiency of nanomedicine in the development and delivery of low-dose DNA vaccines that enhance immunogenicity, these studies combined have presented baselines for the further understanding of noninvasive immunization strategies against SARS viruses. Such understanding of fundamental concepts governing the interaction between nanoparticles and SARS viruses is foreseen as the grounds from which new technologies for preventing the infection with SARS-CoV will be made possible (Uskoković, 2020).

5.2. Nanomedicine in therapeutic formulations

As far as the use of nanomaterials as facilitators of treatment modalities against COVID-19 are concerned, several studies have reported on a greater efficacy of antiviral medications when they were delivered by specific nano-carriers. For example, after the promising results of using dexamethasone in patients infected with COVID-19, Lammers et al. have proposed to improve the efficacy of this drug as a safe anti-inflammatory against COVID-19 complications by nano-formulating it

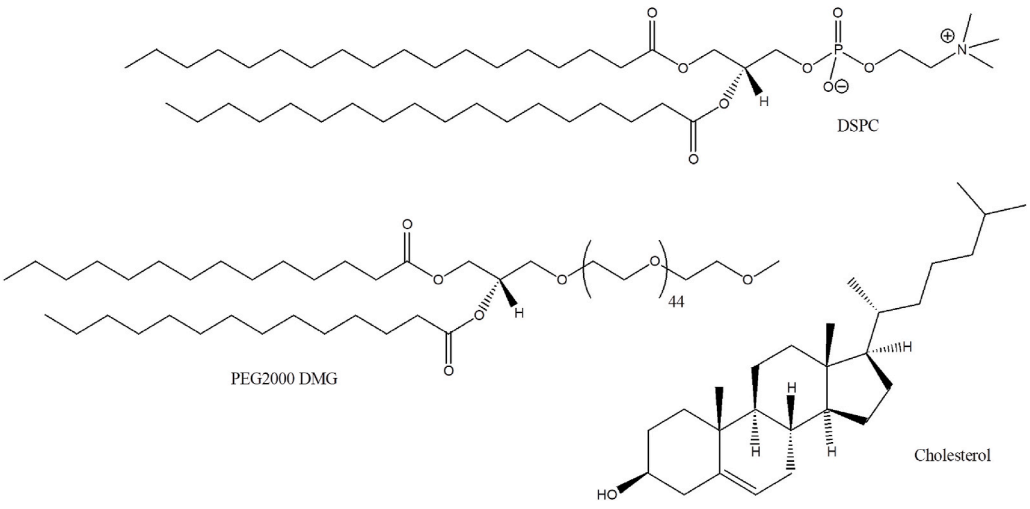

Fig. 4. Commercial lipids used to encapsulate mRNA-1273 vaccine candidate from Moderna Inc.

(Lammers et al., 2020). Due to the severity of COVID-19 could be affected by the commensal microbiome and dietary patterns, researchers also highlighted the potential role of nanomedicine in designing intelligent drugs and functional foods that could target problematic bacterial strains in the gut as a form of auxiliary therapy for COVID-19 (Kalantar-Zadeh et al., 2020). Another one of the hypothesized approaches pertains to the use of nanostructured lipid carriers (NLCs) for the intra-pulmonary delivery of salinomycin (SAL) in patients infected with SARS-CoV-2 (Pindiprolu et al., 2020). SAL is a potential antiviral drug whose mechanism of action is based on a pH-dependent process that prevents the membrane fusion with SARS-CoV-2 and thus the virus entry into the host cells (Jang et al., 2018; Ko et al., 2020). Owing to its small size with good tolerability for drug delivery, along with the ability to be aerosolized into droplets that adhere to the mucosal surface of the lungs and get retained there for prolonged periods of time (Pindiprolu et al., 2020), NLCs are considered prospective for improvement of the therapeutic potentials of SAL against SARS-CoV-2.

Researchers have also proposed several nanomedicine-based approaches to deactivate SARS-CoV-2 or inhibit its binding with the ACE2 receptor on the host cells (Nasrollahzadeh et al., 2020). A study by Zhang et al., for example, successfully utilized two types of cellular nanosponges synthesized from the plasma membrane of the human cells (macrophages and type II alveolar epithelial cells) as an antiviral therapeutic agent that can neutralize SARS-CoV-2 *in-vitro* (Zhang et al., 2020b). The main idea behind this study was that these nanosponges could display the same protein receptor (e.g., ACE2) as that expressed on the host cells and required by SARS-CoV-2 for binding and the cell entry (Zhang et al., 2020b). Therefore, these nanosponges were able to bind to SARS-CoV-2 and neutralize it, and thus block the virus entry into the host cells.

In a study that used the porcine epidemic diarrhea virus (PEDV) as a SARS-CoV model in conjunction with cultured Vero cells, the antiviral properties of stable cationic carbon dots (CCM-CDs) as a nanomaterial for the delivery of curcumin was assessed (Ting et al., 2018). The results suggested that CCM-CDs suppressed the synthesis and budding of viral negative-strand RNA, changed the structure of viral surface proteins which leads to inhibition of the viral entry into the host cells, and suppressed the accumulation of reactive oxygen species (ROS) by PEDV (Ting et al., 2018). High levels of ROS can be generated in the host cells due to viral infection, and the excessive levels of ROS can lead to biphasic activation of cellular apoptotic signaling pathways (mitogen-activated protein kinase (MEK) and extracellular signal-regulated kinase (ERK)). Activation of these pathways increases the virus expansion and the DNA damage, and it also stimulates the production of pro-inflammatory cytokines and the activation of interferon-stimulating genes (ISGs) (Hung et al., 2016; Lin et al., 2016; Ting et al., 2018; Wong et al., 2016), all of which adversely affects the host cell fate. Another similar study on the use of PEDV as a model for SARS-CoV showed that glutathione-capped silver sulfide (Ag_2S) nanoclusters (NCs) can also directly suppress the synthesis and budding of viral negative-strand RNA, which may inhibit the virus replication (Du et al., 2018). However, the authors reported that Ag_2S–NCs positively regulate the expression of pro-inflammation cytokines and the generation of ISGs, and thus they suggested that Ag_2S–NCs activate antiviral innate immunity (Du et al., 2018). Altogether, these findings refer to the large potential of inorganic nanostructures, such as CCM-CDs and Ag_2S–NCs, in the inhibition of SARS-CoV-2 replication, proliferation and infection.

Moreover, Chen et al. used graphene oxide (GO) sheets with silver NPs (GO-AgNPs) to inhibit feline CoV (FCoV), which may be of relevance for SARS-CoV-2 therapies (Chen et al., 2016). This study showed that GO-AgNPs inhibited 25% of FCoV infection in *Felis catus* whole fetus-4 (fcwf-4) cultured cells through the attachment of GO to FCoV lipid tails, which resulted in the aggregation entailing the binding of AgNPs to the sulfhydryl (thiol) group of E protein and the subsequent rupture (Chen et al., 2016). Considering the pervasive clinical use of AgNPs as inorganic antimicrobial agents, it is foreseeable that this material, along with GO, will be at the frontier of the efforts to create therapeutic platforms based on materials with intrinsic inhibitory properties with respect to SARS-CoV-2 (Ahmed et al., 2020).

Ansari et al. have discussed the potential of using nanoformulation-based drug delivery to improve the efficacy of repurposed antiviral drugs against COVID-19 infection (Ansari et al., 2020). The authors emphasized the potential role of lipid-based nanoparticles conjugated with cell-penetrating peptides for the delivery of drugs or vaccines against COVID-19. This type of nano-systems has displayed several attractive features due to its bioavailability, cellular permeability, uptake propensity and stability of the loaded therapeutic agent, along with the ability to be tailored for a kinetically precise and sustained drug release (Ansari et al., 2020). In addition to the direct potential of mesenchymal stem cell (MSC) transplantation to cure patients infected with COVID-19 (Leng et al., 2020), Pinky et al. discussed the advantages of exosomes derived from MSCs, as compared with other synthetic nano-vesicles (Pinky et al., 2020). Specifically, the MSCs-derived exosomes are said to be safe and highly biocompatible, without causing considerable levels of immunogenicity. They are also effective for cell targeting and thus could play a promising role as nano-based drug delivery systems towards fighting COVID-19 (Pinky et al., 2020).

Weiss et al. recently presented a promising future perspective based on using nanomaterials against COVID-19, focusing in detail on the antiviral activities of several metal NPs, including Ag and copper (Cu) (Weiss et al., 2020). The antiviral properties of AgNPs were extensively assessed against a variety of viruses, including human immunodeficiency virus (HIV), herpes simplex virus (HSV), and the hepatitis B virus (HBV), and it is conceivable that the same antiviral mechanism of action attributable to the ROS and the toxicity of Ag^+ ions released by AgNPs (Weiss et al., 2020) would apply to SARS-CoV. In short, it was hypothesized that these ionic species might interact with the virus surface proteins causing the virus damage and/or accumulate in the host cell and further interact with specific enzymes, leading to inhibition of virus replication (De Gusseme et al., 2010; Joe et al., 2016; Zodrow et al., 2009). Furthermore, based on similar mechanisms of action (Han et al., 2005), previous reports showed the potential antiviral activity of Cu nanoparticles against HuCoV-229E, SARS-CoV and SARS-CoV-2 (Han et al., 2005; van Doremalen et al., 2020; Warnes et al., 2015). Correspondingly, the authors suggested that AgNPs, CuNPs and CuONPs may express disinfectant properties against SARS-CoV-2.

Moreover, among the emerging materials which have been discussed by Weiss et al. to be utilized in the future fight against COVID-19 are graphene derivatives and photocatalytic NPs (Weiss et al., 2020). Studies have reported that GO, reduced GO (rGO), and sulfated GO sheets showed antiviral effects against orthopoxvirus, HSV, PEDV, enterovirus-A71 (EV-A71), and influenza A virus (H9N2). While the antiviral activity was attributed to the viral binding and shielding potential of these sheets due to their sharp edges and binding promoted by the electrostatic attraction between the negative surface charge of GO and the positive charge of the nucleocapsid shell of the viral particles (Sametband et al., 2014; Song et al., 2015; Ye et al., 2015). Furthermore, regardless of the paucity of research on the antiviral effect of titanium dioxide (TiO_2), the most described photocatalytic NPs in the literature, a study showed that a titanium apatite filter (PTAF) could inactivate SARS-CoV when exposed to the UV light for 6 h, which was hypothesized to have caused damage to the S protein, resulting in diminished virus infectivity (Han et al., 2004). Therefore, it is indisputable that nano-formulations of the materials mentioned in this section could play promising roles in the context of drug design and vaccine development against COVID-19.

6. Future directions based on polymersomes

Lacking a universal vaccine along with the increase in the number of cases opens the door for virus inhibitors to be recognized as powerful tools to suppress virus infection. On the other hand, in addition to a long

time and high costs that are still required to reach the targeted safe and effective vaccine against COVID-19, the recently emerged reinfection dilemma has threatened the efforts and hopes for the ongoing COVID-19 vaccine trials. Since the nanomedicine field has shown a variety of promising therapeutic applications against COVID-19, and previously against various viral infections and diseases, it is worth to emphasize that learning from the past can be an effective route towards therapeutics against COVID-19. Here we propose a novel approach based on using polymersomes (polymer-like liposomes) as potential nano-objects with a significant imprint in the field of nanomedicine. Despite their immense potential, they have not been employed in the fight against COVID-19 so far.

Polymersomes are some of the most efficient nanomaterials for use as drug delivery systems with a special surface functionalization (Discher et al., 1999; Tuguntaev et al., 2016). They are artificial vesicles composed of amphiphilic block or grafted copolymers, and they emerged thanks to their high colloidal stability, strong membrane properties, as well as easy ligand conjugation with high biocompatibility (Ferji et al., 2015, 2018; Guan et al., 2015). Fig. 5 shows common amphiphilic block copolymers that are used to formulate polymersomes (Barnier Quer et al., 2011; Chun et al., 2018; Galan-Navarro et al., 2017; Scott et al., 2012). Polymersomes were designed to mimic the cell structure with an aqueous cavity, and they showed a high capacity for drug loading, especially as a co-delivery system upon loading hydrophobic and hydrophilic drugs in their exterior layers and cores, respectively (Kim et al., 2013; Li et al., 2016). Polymersomes have recently been exploited not only as vehicles for the delivery of various therapeutic compounds (Chun et al., 2018), but also based on their potential to regulate ROS (Kim et al., 2017). Owing to their immunogenic properties (Webster et al., 2013), polymersomes could play a vital role in improving subunit vaccines and therapeutics delivery against COVID-19 infection.

In a previous study, for example, polymersomes were loaded with influenza hemagglutinin (HA) antigens and then used as an immune adjuvant (Barnier Quer et al., 2011). Notably, a superior increase of serum IgG and hemagglutination inhibition titers were reported upon immunization with polymersome-loaded HA relative to free HA, without causing any cellular toxicity (Barnier Quer et al., 2011). Therefore, polymersomes successfully enhanced the immunogenicity of HA, which indicated their potential not only as a delivery system, but also as an adjuvant for subunit vaccines. Furthermore, researchers have shown that loading specific protein antigens into the polymersome core can boost the antigen presentation by DCs *in-vitro* (Scott et al., 2012). While polymersomes enhanced strong T cell immunity to protein antigens and induce the activation of antigen-specific $CD4^+$ T cells (Stano et al., 2013), it has also been reported that polymersomes can regulate intracellular ROS levels when used as a delivery system for antiviral therapeutics against H1N1 infection *in-vitro* (Kim et al., 2017). Their ability to reduce the ROS generation, which is normally increased during viral infection, could be one of the promising approaches in inhibiting viral replication, cell death, production of pro-inflammatory cytokines, and activation ISGs in the host (Drew et al., 2012; Hung et al., 2016; Lin et al., 2016; Reshi et al., 2014; Svegliati et al., 2005; Ting et al., 2018; Vlahos et al., 2012; Wong et al., 2016). As a result, polymersomes can play a vital role as ROS regulators that can assist in the suppression of SARS-CoV-2 propagation and disease severity, as well as increase the cell survival rate.

In a study on Lassa virus (LASV) infected mice, recombinant LASV E protein was encapsulated inside oxidation-sensitive polymersomes as nanocarriers that induced intracellular drug transfer (Galan-Navarro et al., 2017). The results showed that immunization with polymersome-loaded LASV E protein, compared to the treatment with free LASV E protein, preferentially activated the humoral immune response. LASV E protein loaded polymersome immunization elevated

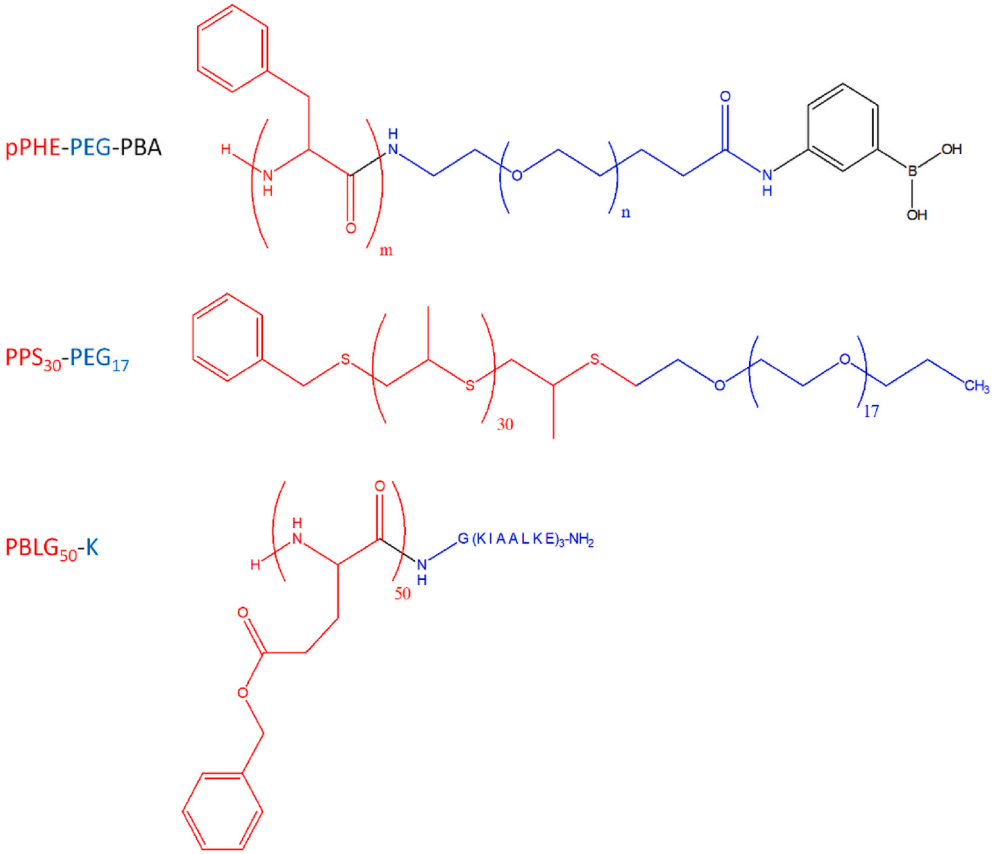

Fig. 5. Amphiphilic block copolymers used to formulate polymersomes.

the antibody production with a higher binding affinity to the E protein of LASV virion, and also increased the production of IgG-secreting B cells and antiviral $CD4^+$ T cells (Galan-Navarro et al., 2017). Another study used polymersomes to encapsulate two antivirals (favipiravir in the exterior layer and mir-323a in the core) for use *in-vitro* against H1N1 infection (Chun et al., 2018). The surface density of polymersomes was controlled by functionalization via specific copolymers to maximize cellular uptake (Chun et al., 2018). This study showed promising synergistic effects upon using these functional polymersomes against H1N1 infection. Together, these studies indicate the potential efficiency of polymersome-based delivery systems in improving the transfection of antiviral therapeutics and vaccine substances against COVID-19, which has not been studied yet nor proposed.

We recently proposed a novel therapeutic approach for cancer based on nano-objects that have the capacity to target specific immune checkpoints along with the inhibition of DNA demethylation (Al-Hatamleh et al., 2019b). Here we hypothesize that there could be benefits arising from the readjustment of this approach involving the use of polymersomes as promising nanocarrier-based systems against COVID-19. Based on the unique characteristics of polymersomes, it is possible to functionalize them and turn them into effective delivery systems for therapeutic substances or antibodies that block the pro-inflammatory cytokines or their cellular receptors. Owing to their potential for co-delivery of both hydrophobic and hydrophilic drugs, polymersomes are able to be loaded with DNA demethylation inhibitors along with cytokines blockers to cause a stronger blockage. Using specific DNA demethylation inhibitors such as histone deacetylase (HDAC) inhibitors, histone methyltransferase (HMT) inhibitors, and dimethyltryptamine (DMT) inhibitors, might lead to epigenetic alteration and result in a decreased expression of genes encoding cytokines (e.g., *IL-6, TNF, IL-10*) and their respective receptors (i.e., *IL-6 receptor, TNF receptors 1 and 2, and IL-10 receptor*), and thus downregulate those cytokines. Thus, the synergistic effects of cytokine blockers and DNA demethylation inhibitors loaded into polymersomes would be a promising approach in fighting COVID-19 by suppression of the cytokine storm in patients.

More specifically, this approach can be tested first against IL-6, the most important member in the cytokine storm (Zhang et al., 2020a), but also against other cytokines in the advanced stages of the research. In the early days of the COVID-19 pandemic, researchers from Wuhan, China noted that levels of IL-6 were higher in critical cases than in severe and mild cases (Chen et al., 2020a). This report was confirmed later by

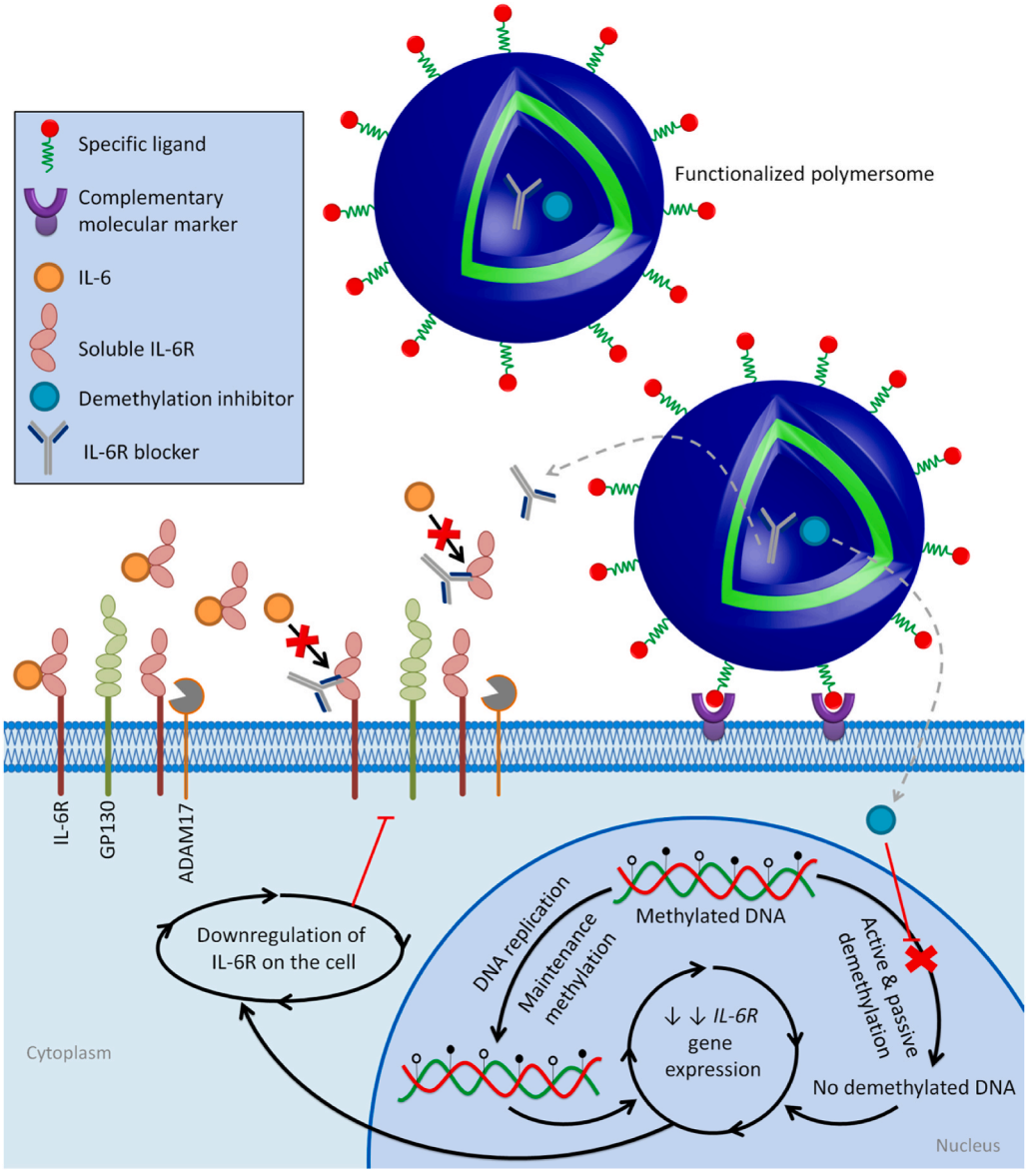

Fig. 6. Potential cellular and molecular mechanism of actions of polymersomes loaded with IL-6 receptor (IL-6R) blockers and DNA demethylation inhibitors against COVID-19 infection. Polymersomes will be synthesized, loaded with IL-6 receptor blockers and DNA demethylation inhibitors, and then functionalized with specific ligands to target cells expressing IL-6. IL-6 receptor blockers (e.g., a monoclonal antibody-based drug) would block the IL-6 receptor signaling pathway, while demethylation inhibitors might lead to epigenetic alteration, resulting in decreased expression of *IL-6 receptor* gene, thus downregulating IL-6 receptor in the targeted cell. Therefore, co-administration of these two therapeutics might cause effective synergistic effects to calm down the cytokine storm, which results mainly from the interaction of IL-6 and its receptor. The ADAMs (A disintegrin and metalloproteinases) are a family of transmembrane proteins that responsible for cleaving membrane-bound IL-6 receptor, resulting in soluble IL-6 receptor. Glycoprotein 130 (gp130) is a receptor for IL-6/sIL-6 receptor complex.

another similar study showing significantly higher levels of IL-6 among severe cases compared to mild cases (Gao et al., 2020). Interestingly, a retrospective study on data related to COVID-19 cases (68 mortality and 82 recovered cases) showed that IL-6 levels were significantly higher in died cases compared to the survivors (Ruan et al., 2020). Therefore, employing IL-6 inhibitors in the treatment of COVID-19 is considered as a promising immunotherapeutic approach to control the infection. Some clinical trials are being conducted to repurpose the existing IL-6 inhibitors including anti-IL-6 antibodies (e.g., clazakizumab and siltuximab) and anti-IL-6 receptor antibodies (e.g., tocilizumab and sarilumab) against COVID-19 (Atal and Fatima, 2020). Overall, based on the above literature survey, we hypothesize that loading IL-6 receptor blockers along with DNA demethylation inhibitors into functionalized polymersomes might be a promising approach in fighting COVID-19 (Fig. 6).

Polymersomes could have specific advantages over other nanomaterial-based delivery systems (e.g., liposomes) for development of therapeutics and vaccines against COVID-19. A variety of highly reproducible and scalable production methods are used to produce polymersomes with low polydispersity, and the process became achievable within about 1 h (Poschenrieder et al., 2017). The ability of polymersomes to encapsulate hydrophobic, hydrophilic and amphiphilic molecules makes them more suited for *in-vivo* studies compared to many other nanomaterials (Zhang and Zhang, 2017). Despite their similar amphiphilic nature, the bilayer thickness of polymersomes (5–50 nm) is greater compared with the bilayer of liposomes (3–5 nm), which causes more robust and impermeable wall (Rideau et al., 2018). Thus, polymersomes have considerably higher membrane stability than liposomes (Poschenrieder et al., 2017), which widely used nowadays in development of COVID-19 vaccines. The higher stability and versatility of polymersomes gives them advantages towards more sustained and controlled release, and the improved metabolic stability of the loaded therapeutic agent (Zhang and Zhang, 2017; Gurunathan et al., 2020). Furthermore, the immunogenicity of polymersomes can be reduced (stealthiness) if a dense PEG brush is used on the surface with relatively long PEG polymers, meanwhile their biological stability would be increased (Zhang and Zhang, 2017). Therefore, the use of a proper polymersome-based delivery system can help in reducing therapeutic doses, along with maintaining a constant concentration of drug in the targeted site or circulation for longer time. These factors support polymersomes to be applicable and universal carrier-systems for medical applications, more specifically in the fighting against COVID-19.

In addition to the potential polymersome-based system which is hypothesized above, polymersomes could have promising roles with other repurposed drugs that have regulatory effects on the immunity of COVID-19 patients, especially for severe cases. Among these drugs, anticoagulant treatments (e.g., heparin and nafamostat), that also could inhibit the cytokine storm and increase the percentage of lymphocytes (Shi et al., 2020; Tang et al., 2020; Yamamoto et al., 2020), as well as some other immune-based therapies (e.g., interferon alfa-2B) which also expected to have similar effects, but are still awaiting experimental evaluation (Khan et al., 2020). Also, other types of drugs are repurposed and currently being studied, such as antihypertensive drugs and non-steroidal anti-inflammatory drugs, but no scientific evidence proving the effectiveness of any drug or therapeutic compound against COVID-19 has been demonstrated so far.

Moreover, the potential roles of polymersome-based delivery systems are not limited to boosting immunity and suppressing cytokine storm in COVID-19 patients. Polymersomes can be functionalized to deliver several types of repurposed drugs that showed potential antiviral effects against SARS-CoV-2, including antimalarial drugs (e.g., chloroquine), antimalarial and antibiotic combinations (e.g., hydroxychloroquine and azithromycin), antiviral drugs (e.g., camostat, bromhexine, favipiravir, remdesivir and lopinavir), and antihelmintics/antiparasitic agents (e.g., nitazoxanide and ivermectin) (Khan et al., 2020; Rajoli et al., 2020; Santos et al., 2020). However, the clinical effectiveness of these drugs has not yet been fully evaluated, while several clinical trials are still underway (Singh et al., 2020). Future studies may also investigate potential polymersome-formulations for combination therapy (using repurposed drugs) to COVID-19 infection.

7. Conclusion

The current global public health emergency caused by COVID-19 requires continued and urgent efforts by scientists to stop the spreading or at least reduce the number of deaths caused by the SARS-CoV-2 virus. Despite the large number of reports that address COVID-19 infection and fighting strategies, there is no approved solution to contain the pandemic. Since nanomedicine applications had promising roles in the development of vaccines and therapeutics against COVID-19, gathering the recent findings and suggesting promising approaches in a comprehensive review could be helpful for researchers and readers who are interested in this topic, and this exactly has been the goal of this review. On the other hand, various vaccine candidates and therapeutic substances were proposed against COVID-19 on the basis of nanomaterials. None of them have utilized polymersomes, despite their definite potentials against a variety of diseases, including viral infections, as shown by previous studies. Therefore, in addition to addressing various aspects of COVID-19 vaccine and therapeutic development, this review has provided a future perspective on the use of polymersomes to suppress the cytokine storm and reduce the severity of COVID-19 infection.

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CRediT authorship contribution statement

M.A.I. Al-Hatamleh: Conceptualization, Data curation, Data analysis and/or interpretation, Writing- Original draft preparation, Visualization, Writing- Review and Editing. R. Mohamud: Conceptualization, Supervision, Writing - Review and Editing. M.M. Hatmal, W. Alshaer, E. N.S.E.A. Rahman, M.H. Mohd-Zahid, D.M. Alhaj-Qasem, C.Y. Yean, I.Z. Alias, J. Jaafar, K. Ferji, J.L. Six, V. Uskoković, H. Yabu: Writing- Review and Editing.

Ethical approval

Not required.

Declaration of competing interest

The authors have no conflict of interest.

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