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Toward the prevention of coronavirus infection: what role can polymers play?

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Abstract
Severe acute respiratory syndrome–associated coronavirus 2 has caused a global public health crisis with high rates of infection and mortality. Treatment and prevention approaches include vaccine development, the design of small-molecule antiviral drugs, and macromolecular neutralizing antibodies. Polymers have been designed for effective virus inhibition and as antiviral drug delivery carriers. This review summarizes recent progress and provides a perspective on polymer-based approaches for the treatment and prevention of coronavirus infection. These polymer-based partners include polyanion/polycations, dendritic polymers, macromolecular prodrugs, and polymeric drug delivery systems that have the potential to significantly improve the efficacy of antiviral therapeutics.

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1. Introduction
Severe acute respiratory syndrome–associated coronavirus 2 (SARS-CoV-2) belongs to the β family of coronaviruses and infects humans by the fusion of viral and cell membranes, facilitated by binding between the SARS-CoV-2-related spike (S) protein and angiotensin-converting enzyme 2 (ACE2) [1–3]. The β coronavirus family is also responsible for the common cold, severe acute respiratory syndrome coronavirus (SARS-CoV), and Middle East respiratory syndrome–associated coronavirus (MERS-CoV) [4,5]. Strategies to reduce coronavirus infection include wearing masks [6–10], small-molecule drugs [11,12], vaccines, neutralizing antibodies [13–15], RNA interference therapy [16,17], and other mitigation factors [18]. These treatment methods span in vitro prevention to in vivo treatment, including blocking the spread of the virus, inhibiting the translation of viral RNA in host cells, activating the immune system and inhibiting the expression of the S protein gene. Some of these interventions, however, would benefit from a polymer ‘modulator’ to improve efficacy.

There has been some work in literature that describes disinfection as well as antimicrobial materials [19–24]. Recently, polymer materials have demonstrated antiviral capabilities. As shown in Fig. 1, polymers can prevent or inhibit the spread of a virus by (1) providing a semipermeable barrier (e.g. mask or face-shield), (2) interfering with binding to the glycoprotein surface of host cells, (3) augmenting small molecular antiviral drug therapies, (4) enhancing the response of the immune system as a vaccine adjuvant, or (5) as a vehicle for other therapeutic molecules to improve the water solubility or stability of antiviral therapeutics.

2. Polymer-based in Vitro prevention strategy
Coronavirus disease 2019 is spread by droplets or contact, and a proven strategy for preventing this spread is daily use of personal
Polymeric approaches for the prevention or treatment of coronavirus. (i) Integrating functional polymers into personal protective equipment (PPE) can prevent the entrance of virus into the respiratory system. (ii) Cellular binding of viral particles at the alveoli can be inhibited using polyanion and polycation against viral S protein or angiotensin-converting enzyme 2 (ACE2) receptors. (iii) Polymers could also be used to deliver antivirus drugs. (iv) Polymers could also be useful when being covalently combined with small-molecule drugs to form macromolecular prodrugs. (v) Polymer-based vaccines or vaccine adjuvants can be used to prevent virus infection or even to boost the immune response during infection [23]. SARS-CoV-2, Severe acute respiratory syndrome—associated coronavirus 2.

Protective equipment [6,26]. Masks, gloves, and protective clothing are made from various polymers, such as polystyrene, polypropylene, polyethylene, polyvinyl chloride, polyethylene terephthalate etc. [17]. During outbreaks of severe acute respiratory syndrome (SARS), masks and isolation gowns are effective in protecting health care workers from the risk of infection [27]. As a typical example, common medical masks are usually composed of three layers of non-woven fabrics, which are divided into an outer layer (for insulating the sprayed liquid), an inner layer (for moisture absorption), and the middle filter layer (the core part, as a barrier to block viral particles). The core filter layer of the mask is generally made from electret-treated polypropylene melt-blown non-woven fabric, which can reach 95% filterability. Melt-blown, non-woven fabrics have a much higher filtration efficiency than fabrics of cotton, polyester, nylon, or silk. The polypropylene is triboelectrically charged to enhance filtration efficiency. Polypropylene is more hydrophobic and so repels moisture in the air, providing a protective environment [28]. In another case, the effect of polytetrafluoroethylene/polyurethane membranes in chemical protective clothing was evaluated. Excellent isolation performance against poliovirus was demonstrated, and a possible protective mechanism against the SARS virus was inferred [29]. This ultra-high filtration efficiency has proved to be an effective block to the intrusion of coronavirus.

3. Polymeric structures with direct coronavirus binding

Polymers can directly interfere with the interactions of a virus with the host cell. The high molecular weight and multivalent binding of specifically designed polymers can sterically shield the viral surface or competitively inhibit virus—host cell interactions [30]. The next section summarizes recent advances in this field by category of polymer.

3.1. Synthetic polymers

3.1.1. Polyelectrolytes

The surface of a virus is rich in amino acid residues. For example, the envelope protein gp120 of HIV is rich in positively charged arginine and lysine. Polyanions therefore can electrostatically bind to the gp120 protein and prevent HIV from interacting with the host cell’s surface. Similarly, SARS-CoV or SARS-CoV-2 has a spike (S) glycoprotein, which binds to the ACE2 protein as an important step in host epithelial cell invasion. SARS-CoV-2 has the D480 → S456 mutation relative to SARS-CoV, which removes some negatively charged amino acids in the former, leading to an even stronger electrostatic interaction between ACE2 on epithelial cell membranes and SARS-CoV-2 (as shown in Fig. 2A) [31]. Disrupting this strong electrostatic interaction will inhibit the virus from entering the host cell, and polyanions and polycations can potentially disrupt the binding between the virus and host cell.

Polyanions are the largest class of biomaterials that have been investigated for the blocking of viral adsorption and infection. As early as the 1960s, poly(methacrylic acid) (PMAA) was demonstrated to inhibit the infectivity of enveloped vesicular stomatitis, Simbis, and vaccinia viruses [32,33]. More and more polyanions were subsequently shown to exhibit antiviral activity. Poly(propylacrylic acid), poly(vinylbenzoic acid) (PVBzA), poly(vinylphosphonic acid) (PVPA), and poly(2-acrylamidoethyl) phosphate have exhibited an inhibitory effect on the SARS virus. PVPA has the strongest inhibitory effect on SARS. However, PVBzA, a carbobylexyl, exhibits broad-spectrum antiviral activity in antivirally infected, with a lesser inhibitory effect on enveloped viruses (as shown in Fig. 2B) [34]. Polyanions target the receptor-binding domain of the coronavirus S protein that binds to the ACE2 receptor of potential host cells in bats or humans. Polycations may also act as antiviral agents through electrostatic interaction with negatively charged cell membranes or lipid-encapsulated virus envelopes, thereby preventing viruses from adsorbing to the cell surface or directly inactivating virus particles. Poly(1-amidoamine)s (PAMAMs), phosphonium-type cationic polyacrylamide, poly(ethylene imine) (PEI), and their derivatives have significant inhibitory effects on influenza virus and herpes simplex virus (HSV) [35–41]. Polycations interact with negatively charged cell membranes or with lipid-encapsulated virus envelopes. For example, the envelope of HSV contains glycoproteins with anionic amino acid side chains, and cationic PEI serves as an effective HSV inhibitor by interacting with HSV glycoproteins [46]. Moreover, PEI with glycosyl modification bound to TIM-1/TIM-3 receptors, thereby inhibiting viral infection. More interestingly, this glycosyl PEI derivative could also (1) neutralize the pH of the cell nucleus and prevent virus replication, (2) reduced the toxicity of PEI, and (3)
improved selectivity and helped overcome drug resistance. Glycosyl-modified PEI imparted extraordinary resistance to infection by RNA, DNA, and enveloped or non-enveloped viruses (as shown in Fig. 2C) [42]. ACE2 receptors have a negative electrostatic potential and could also be a potential target of polycations to prevent virus binding. The previously mentioned PEI with glycosyl modification has unique potential in anticoronavirus.

Although PVBzA and PEI both exhibit a broad-spectrum antiviral effect, which helps reduces drug resistance, their limitation is potential toxicity that has not been assessed, and large-scale clinical still needs to be conducted.

3.1.2. Dendritic polymers

Dendritic or highly branched polymers possess greater solubilities, larger surface areas, and tunable shapes, including the possibility of hydrophobic cavities, relative than their linear counterparts. These structural features can impart enhanced antimicrobial or antiviral activity, resulting from ultrastrong interaction

![Diagram](image1)

**Fig. 2.** (A) Electrostatic potential maps (in kT/e) SARS-CoV-2 and ACE2 shown in a cartoon view [31]. (B) The structure of PVBzA, PPAA, PVPA, and PAEP and antiviral activities of 14 polyanions [34]. (C) Synthesis and characterization of PEI-man [42]. (A) Synthetic scheme and chemical structure of mannose-functionalized carbonate-modified PEI polymers. (b) Antiviral activity (EC50), cytotoxicity (CC50), selectivity index (SI, CC50/EC50), and pH neutralization capacity of unmodified and mannose-functionalized PEI polymers. Prevention of DENV-2 infection in human primary peripheral blood mononuclear cells (PBMCs) (c) and macrophages (d) by PEI-man. ACE2, angiotensin-converting enzyme 2; PEI, poly(-ethylene imine); PPAA, poly(propylacrylic acid); PVPA, poly(vinylphosphonic acid); PVBzA, poly(vinylbenzoic acid); SARS-CoV-2, severe acute respiratory syndrome-associated coronavirus 2.

**Fig. 3.** (A) Sulfide nanogels (simulating HS) to shield virus particles (rigid nanogel [R-NG] and flexible nanogel [F-NG]) [46]. (B) Schematic representation of flexible and rigid dPGS-based nanogels. Using linPG and dPG as cross-linkers, respectively, they were prepared by strain-promoted azide–alkyne ring addition reaction via reverse nanoprecipitation technique. The scheme shows the structure of dPG and the models of rigid and flexible nanogels [46]. (C) The terminal groups of the PAMAM dendrimers used were sodium carboxylate, primary amine, hydroxyl, and succinic acid. PAMAM, polyamidoamine [44].
with viruses [43]. Kandeel et al. have reported three anionic dendritic polymers, including hydroxyl, carboxyl, and succinic acid-terminated PAMAM dendrimers, and cationic dendritic polymers containing primary amine end groups. These dendrimers inhibited MERS-CoV, with the G(1.5)-16COONa (carboxyl derivative) and G(5)-128SA (succinic acid derivative) exhibiting the best performances (as shown in Fig. 3C) [44]. Nanogels based on dendritic polyglycerol sulfate, an analog of heparan sulfate (HS), have proved to be non-toxic with broad-spectrum antiviral activity, inhibiting viruses from binding to the cell surface. HS is a co-receptor for SARS-CoV-2 mediating entry to host cells [45]. Non-toxic and broad-spectrum dendritic nanogels could therefore be potential components of a coronavirus therapy (as shown in Fig. 3A and B) [46].

![Fig. 4. (A) Structures of modified CDs and relative effective concentrations of inhibition of HSV-2 growth [52]. (B) Structures of HTCC and HM-HTCC and inhibition of HCoV-NL63 and MHV replication in vitro [54]. CD, cyclodextrin; HSV, herpes simplex virus; HTCC, N-(2-hydroxypropyl)-3-trimethylammonium chitosan chloride; HCoV-NL63, human coronavirus strain; MHV, murine hepatitis virus.](image)

![Fig. 5. (A) Mechanism of macromolecular prodrugs inhibiting viruses [59]. (B) Ribavirin acrylate monomer is synthesized via a chemotaxis pathway (top). RAFT controlled the copolymerization of RBV acrylate with N-vinylpyrrolidone (NVP) to provide a macromolecular precursor for RBV (bottom). Phthalimidomethyl-O-ethyl xanthate was used as an RAFT agent [56]. (C) Synthesis of ribavirin (RBV) methacrylate and macromolecular prodrugs for RBV based on HPMA [57]. (D) Proposed synthesis of macromolecular prodrugs of RBV. The polymerizable acrylate of RBV was synthesized by a chemoenzymatic method using N435/CAL-B in dioxane (i) for RAFT polymerization and AA as a co-monomer to obtain a macromolecular precursor (ii). The synthesized polymer released the original RBV on hydrolysis (iii) [58]. (E) Structures of polyanionic macromolecular prodrugs of ribavirin based on these polymers, whereby RBV is conjugated to the polymer via an ester linkage or a disulfide linkage to achieve ultrafast intracellular drug release [59].](image)
Table 1
Summary of polymers for vaccine carriers and adjuvants.

| Polymers                  | Compounds                  | Virus                                      | Animal model                      | Effect                                                                 | Advantage                                                                                                                                                                                                 | References |
|---------------------------|----------------------------|--------------------------------------------|-----------------------------------|------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| PLGA                      | CpG ODN 2007               | Infectious bronchitis virus (IBV)          | Chickens                          | Improved innate and long-term immunostimulatory effects in vivo and in vitro Coordinated delivery of antigen and adjuvant in vivo and in vivo; significantly enhances antigen-specific humoral and cellular responses | Degradability, renewable, non-toxic, and completely biodegradable and recognized by the Food and Drug Administration (FDA)                                                                             | [67]       |
| PLGA                      | STING agonists             | Middle East respiratory syndrome coronavirus (MERS-CoV) | C57BL/6 mice                      | Improved innate and long-term immunostimulatory effects in vivo and in vitro Coordinated delivery of antigen and adjuvant in vivo and in vivo; significantly enhances antigen-specific humoral and cellular responses | Degradability, renewable, non-toxic, and completely biodegradable and recognized by the Food and Drug Administration (FDA)                                                                             | [68]       |
| PLGA                      | PEDV killed vaccine antigens (KAg) | Porcine epidemic diarrhea virus (PEDV) | Pregnant sows and suckling piglets | Induced systemic and mucosal immunity; efficiently protected suckling piglets against challenge with PEDV | Degradability, renewable, non-toxic, and completely biodegradable and recognized by the Food and Drug Administration (FDA)                                                                             | [69]       |
| PLGA                      | Inactivated PRRSV vaccine (NP-KAg) | Porcine reproductive and respiratory syndrome virus (PRRSV) | Piglets                           | Reduce greatly the required vaccine dose; the entrapped antigen was released at a much slower rate and triggers a robust effect and memory immune response | Degradability, renewable, non-toxic, and completely biodegradable and recognized by the Food and Drug Administration (FDA)                                                                             | [70]       |
| PLGA                      | DNA vaccines               | Newcastle disease virus (NDV)              | Chickens                          | Induces stronger immune responses, and achieve sustained release       | Degradability, renewable, non-toxic, and completely biodegradable and recognized by the Food and Drug Administration (FDA)                                                                             | [71]       |
| PLGA                      | Killed PRRSV vaccine (Nano-KAg) | PRRSV                                      | Pigs                              | The potential to generate anti-PRRSV immune response and in better clearance of virema | Degradability, renewable, non-toxic, and completely biodegradable and recognized by the Food and Drug Administration (FDA)                                                                             | [72]       |
| PEG-PLGA                  | Diphyllin                  | Feline coronaviruses (FCoVs)               | Mice                              | Higher safety and increased inhibitory activity against FIPV           | Degradability, renewable, non-toxic, and completely biodegradable and recognized by the Food and Drug Administration (FDA)                                                                             | [73]       |
| O-2'-HACC                 | Live Newcastle disease vaccine | NDV                                        | Chickens                          | Long release, low toxicity, high safety                               | High antimicrobial activity, low toxicity, and a high safety level; N-2-HACC was more cost-effective than O-2'-HACC, and N-2-HACC has superior water solubility and more suitable size than chitosan and O-2'-HACC | [74]       |
| N-2-HACC-CMC              | NDV/La Sota + IBV/H120     | NDV and IBV                                | Chickens                          | Induces greater IgG and IgA antibody potency; significantly promotes lymphocyte proliferation and induces higher levels of cytokines | Degradability, renewable, non-toxic, and completely biodegradable and recognized by the Food and Drug Administration (FDA)                                                                             | [75]       |
|                           | NDV F gene plasmid DNA with C3d6 molecular adjuvant | NDV                                         | Chickens                          | Increased production of anti-NDV IgG and IgA antibodies; significantly stimulated lymphocyte proliferation, triggering higher levels of IL-2, IL-4, and IFN-γ | Degradability, renewable, non-toxic, and completely biodegradable and recognized by the Food and Drug Administration (FDA)                                                                             | [76]       |
| HACC and SCS              | As vaccine adjuvants to prepare NDV-loaded nanoparticles | NDV                                        | Chickens                          | Qualified levels of humoral immunity (HI > 5) and higher levels of cellular immunity compared with the commercial oil emulsion vaccine; these nanoparticles provide 100% protection against virulent NDV | Degradability, renewable, non-toxic, and completely biodegradable and recognized by the Food and Drug Administration (FDA)                                                                             | [77]       |
| Chitosan                  | Inactivated NDV vaccine    | NDV                                        | Chickens                          | Adjuvant effects of Chitosan, CS particles efficiently changed mucosal and humoral immunity and protective activity | Degradability, renewable, non-toxic, and completely biodegradable and recognized by the Food and Drug Administration (FDA)                                                                             | [78]       |
|                           | Live NDV vaccine           | NDV                                        | Chickens                          | Induced greater protection of immunized specific pathogen              | Degradability, renewable, non-toxic, and completely biodegradable and recognized by the Food and Drug Administration (FDA)                                                                             | [79]       |
|                           | NDV F gene deoxyribonucleic acid (DNA) vaccine | NDV                                         | Pathogen-free chickens            | Induced significantly higher mucosal and humoral immune responses; protect the plasmid DNA from degradation and help the | Degradability, renewable, non-toxic, and completely biodegradable and recognized by the Food and Drug Administration (FDA)                                                                             | [80]       |

(continued on next page)
Polymers can serve as delivery systems and adjuvants for vaccines; they can protect the integrity of encapsulated antigen to inhibit degradation and retain antigenicity comparable to that of vaccines administered by injection, which means that patients can be vaccinated orally; meanwhile, it can induce humoral and cell-mediated immune response and mucosal immunity strongly, improving the safety and effectiveness of vaccines. A suitable polymeric structure can simultaneously controllably release the drug and protect the integrity of the encapsulated antigen to inhibit degradation, thereby significantly improving the therapeutic index of the drug.

3.2. Natural polymers

Natural polymers have also been extensively studied as potential antiviral agents [47,48]. Polysaccharides such as carrageenan from seaweed have good antiviral activity after sulfation or sulfonation. Cyclodextrins (CDs) and derivatives such as methyl-CD have shown in Fig. 4A) [52]. Chitosan is a natural polycationic polymer with a broad spectrum of antiviral effects and possessed high biocompatibility (as shown in Fig. 5B) [56–58]. Ribavirin can accumulate in red blood cells, causing hemolytic anemia. It is therefore only clinically available to hospitalized patients with severe respiratory syncytial virus (RSV) or anti–hepatitis C virus (HCV) infections. Ribavirin polyion complex macromolecular prodrug (PAMP) has been used as a broad-spectrum antiviral drug against HIV, HCV, RSV, influenza, measles, mumps, dengue fever, and Ebola virus. PAMP’s antiviral effect is associated with its ability to inhibit virion binding to the host cell receptor because of both the polyanion component and the inhibitory effect of the nucleoside analog (as shown in Fig. 5E) [59]. A prodrug made of PMAA and ribavirin linked with a disulfide bond achieved rapid intracellular release compared with other macromolecular prodrugs [60].

5.1. Polymers as vaccine carriers and adjuvants

Polymers can serve as delivery systems and adjuvants for improving the safety and effectiveness of vaccines. A suitable excipient can increase the accumulation of vaccine at a disease site and elevate an immune response. Polymeric structures can improve the safety and effectiveness of a vaccine as well as protecting the integrity of encapsulated antigen to inhibit degradation. Polymeric encapsulation can facilitate mucosal administration, rather than injection, resulting in higher patient compliance. Polymers can also be designed with a low immunogenic risk, good biocompatibility, a large specific surface area, biodegradability, and a reduction in the therapeutic dose required [61–66]. Several natural and synthetic polymers have been used for preparing nanoparticle vaccine delivery vehicles (Table 1).

Table 1 (continued)

| Polymers                  | Compounds                        | Virus          | Animal model | Effect                                                                 | Advantage                                                                                       | References |
|--------------------------|----------------------------------|----------------|--------------|------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|------------|
| Chitosan (CS)-coated poly(lactic-co-glycolic) acid (PLGA) | DNA (the F gene) of NDV           | NDV            | Chickens     | expression of the plasmid DNA encapsulated                             | Produce higher mucosal immunity titers by taking vaccine orally; meanwhile, it can induce humoral and cell-mediated immune response and mucosal immunity strongly | [81]       |
| Polymethylenimine (PEI)  | SARS DNA vaccine                 | Severe acute respiratory syndrome (SARS-CoV) | BALB/c mice  | PEI/pci-S nanoparticles                                                   | Induce antigen-specific humoral and cellular immune responses                              | [83]       |
| pci-S/PEI                | SARS DNA vaccine                 | SARS-CoV       | BALB/c mice  | PEI/pci-S nanoparticles                                                   | Induce antigen-specific humoral and cellular immune responses                              | [84]       |

5. Polymeric delivery systems for antivirus applications

5.1. Polymers as vaccine carriers and adjuvants

Polymers can serve as delivery systems and adjuvants for improving the safety and effectiveness of vaccines. A suitable excipient can increase the accumulation of vaccine at a disease site and elevate an immune response. Polymeric structures can improve the safety and effectiveness of a vaccine as well as protecting the integrity of encapsulated antigen to inhibit degradation. Polymeric encapsulation can facilitate mucosal administration, rather than injection, resulting in higher patient compliance. Polymeric structures can improve the safety and effectiveness of a vaccine as well as protecting the integrity of encapsulated antigen to inhibit degradation. Polymeric encapsulation can facilitate mucosal administration, rather than injection, resulting in higher patient compliance. Polymeric structures can be designed with a low immunogenic risk, good biocompatibility, a large specific surface area, biodegradability, and a reduction in the therapeutic dose required [61–66]. Several natural and synthetic polymers have been used for preparing nanoparticle vaccine delivery vehicles (Table 1).
CDs have also been used as delivery systems and adjuvants in virus-induced disease treatments. For example, a common influenza vaccine containing 30% 2-hydroxylpropyl-beta-CD (HP-beta-CD) as adjuvant generated increased antibody production against virus infection in mice [85]. Survival rates in infected mice reached 100%. In the presence of thiomersal and alum, CD was found to minimize the degradation of IPV (inactivated polio vaccine or virus) and reduce the loss of D antigen titer of mixed IPV (as shown in Fig. 6B) [86,87].

5.2. Delivery systems for antiviral drugs

Many polymers have been used for antiviral drug delivery, including natural polysaccharides, poly(ethylene glycol) (PEG) and
PEI derivatives, and emerging dendrites. Polymeric delivery vehicles reduce the side effects of encapsulated drugs, increase their water solubility, and improve efficiency. Natural polysaccharides (e.g., CD or chitosan) are popular for the delivery of antiviral drugs, such as nitazoxanide [76], ribavirin [88], camostat mesylate [89,90], lopinavir, and ritonavir [91], which all exhibit inhibitory effects on coronavirus. Polymeric structures are also helpful for the delivery of therapeutic small interfering RNA (siRNA), improving stability, pharmacokinetics, and cellular uptake [92]. siRNA can be physically encapsulated in nanoparticles made of PEG [93,94] or poly(lactic acid–history polymer co-glycolic acetic acid) (PLGA) [95]. This stability is enhanced by the electrostatic interaction between the negatively charged phosphates of the siRNA and the positively charged groups on polymer chain such linear poly(ethylene imine) (LPEI) and branched poly(ethylene imine) (BPEI) [96,97]. With more folding options, BPEI exhibited stronger siRNA loading ability than LPEI, indicating the importance of branched polymeric structures. Inspired by this discovery, researchers have synthesized highly branched architectures of natural polymer such as CD and chitosan. CD-based, self-assembled polymer nanoparticles improve siRNA delivery [98,99]. Likewise, higher molecular weight chitosan provided better complexation ability and increase stability of siRNA polyelectrolyte complexes (polyplex) [100,101]. Dendritic macromolecules have also been used as non-viral vectors for siRNA delivery-based virus treatments [102,103]. siRNA could effectively and specifically inhibit gene expression of S protein in SARS-CoV-infected cells, and so, a RNAi strategy might have potential for SARS-CoV inhibition [104–106]. Conti et al. have reported that poly(amide)-based dendrimer nanocarriers as an aerosol based siRNA delivery system could effectively transfect lung epithelial cells for coronavirus treatment [107,108]. Ciliated cells of the human lung are the main site of SARS-CoV-2 infection. siRNA delivery systems based on dendritic macromolecules might therefore have potential as a treatment for SARS-CoV-2–induced pneumonia (Fig. 7).

6. Conclusions and future perspectives

SARS-CoV-2 has caused a global public health crisis with high rates of infection and mortality. In conventional treatment programs, there are disadvantages such as time consuming and high cost. There is also an added worry that the next pandemic may be even more dangerous. Thoughts around a superinfectious Disease X needing ultra-low virus dose to infect and working on the combination of the aerosol transmission as well as the asymptomatic infection. This will be a disastrous recipe that will make a pandemic of a Disease X very difficult to control. As an emerging field of antiviral properties, polymers have inestimable prospects. Polymers will play an important role in the fight against coronavirus infections, from providing better semipermeable barriers to air-

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**Fig. 7.** (A) Schematic diagram of the targeted nanoparticles. Polyethylene glycol (PEG) molecules were endowed with adamantane (AD) to form inclusion complexes with surface CDs, which decorated the nanoparticle surface with PEG for steric stabilization and PEG-TF for targeting [99]. (B) 7C1 Synthesis scheme. 7C1 nanoparticles were mixed with C14PEG2000 and siRNA in a high-throughput microfluidic chamber [97]. (C, a) Synthesis program for siRNA-PLGA conjugates via cleavable disulﬁde linkers. (b) Schematic illustration of the preparation of surface crosslinked siRNA-PLGA–conjugated microbubbles with cationic LPEI and their efficient intracellular uptake by polyelectrolyte charge interaction [95]. (D) Preparation of mannitol microparticles loaded with dendripexes [107].
borne particles to important partners in chemotherapeutic treatments. Polymer vaccine adjuvants provide improved humoral immunity and administration routes. Polymer nanocarriers of small-molecule antiviral drugs assist local or sustained delivery and assist to overcome poor aqueous solubility and drug resistance. Last, but not least, polymeric structures with targeted gene delivery ability have the potential to silence or disturb the activity of coronaviruses. Polyanions/polyacids, dendritic polymers, macromolecular prodrugs, and polymer drug delivery systems have a bright future in this respect. The current evidence shows that its advantages are irrereplaceable in conventional treatment programs. There will be new polymer discoveries, some enabled by new technologies or new scientific capabilities and knowledge, which did not exist before. It is hoped that the development of polymers will advance rapidly in the future and move toward clinical treatment as soon as possible. We hope that this summary of recent advances in polymer bioscience will stimulate more discoveries to meet an increasing demand for polymers. Polymeric nanocarriers of small-borne particles to important partners in chemotherapeutic treatment routes. Polymeric nanocarriers of small-borne particles to important partners in chemotherapeutic treatment.

Authors’ contributions

C.W., Y.W., and X.L. proposed the ideas; X.J., Z.L, and D.J.Y. searched the references and wrote the article; all the authors have critically revised the scientific content of this article and approved the final version.

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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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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