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REVIEW

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Unleashing the potential of cell membrane-based nanoparticles for COVID-19 treatment and vaccination

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ABSTRACT

Introduction: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a particular coronavirus strain responsible for the coronavirus disease 2019 (COVID-19), accounting for more than 3.1 million deaths worldwide. Several health-related strategies have been successfully developed to contain the rapidly-spreading virus across the globe, toward reduction of both disease burden and infection rates. Particularly, attention has been focused on either the development of novel drugs and vaccines, or by adapting already-existing drugs for COVID-19 treatment, mobilizing huge efforts to block disease progression and to overcome the shortage of effective measures available at this point.

Areas covered: This perspective covers the breakthrough of multifunctional biomimetic cell membrane-based nanoparticles as next-generation nanosystems for cutting-edge COVID-19 therapeutics and vaccination, specifically cell membrane-derived nanovesicles and cell membrane-coated nanoparticles, both tailorable cell membrane-based nanosystems enriched with the surface repertoire of native cell membranes, toward maximized biointerfacing, immune evasion, cell targeting and cell-mimicking properties.

Expert opinion: Nano-based approaches have received widespread interest regarding enhanced antigen delivery, prolonged blood circulation half-life and controlled release of drugs. Cell membrane-based nanoparticles comprise interesting antiviral multifunctional nanoplatforms for blocking SARS-CoV-2 binding to host cells, reducing inflammation through cytokine neutralization and improving drug delivery toward COVID-19 treatment.

1. Introduction

Severe acute respiratory syndrome-related corona-virus (SARS-CoV-2) is the novel virus termed as the causative agent of the COVID-19 disease outbreaks [1,2]. More than 150 million cases are reported as of April 30, 2021, with above 3.1 million deaths across the globe. The pandemic is still expanding, and the challenges are still increasing with the emergence of new waves in many countries [3–5]. This difficult situation demands the deployment of all possible management options available. The biggest challenge of 2021 and beyond is to develop effective therapeutic or vaccine candidates. Several options, including nanotechnology tools, are on the table and being explored to counter the pathology associated with this virus [6]. The role of nanomedicine (i.e. usage of nanotechnology for medical applications) against nanosized viruses (80–160 nm) is crucial, and nano-based approaches have attracted special attention for developing versatile nano-based diagnostics, therapeutics, and vaccines to tackle COVID-19 as reviewed elsewhere [7–15]. A typical nanomedicine strategy is to develop nanocarriers – such as nanoparticles – to increase the efficacy of newly designed or repurposed therapeutic molecules, including antivirals, small molecules, as well as antigens [6,16,17]. Also recently, biomimetic strategies including antigen or nucleic acid vaccination have shown interesting results and emerged as strong contenders for a universal COVID-19 vaccine, achieving particular success the recently-approved messenger RNA-encapsulating lipid nanoparticles [6,18]. However, additional strategies are also sought after as those may bring novel insights in how to counteract the pandemic. One of these strategies involve the use of nano-engineered biomimetic systems either armed with or mimicking the biofunctionality of cellular components – which endow them with the capability of replicating and modulating cellular processes and biological cues – still underexplored for COVID-19 applications. Particularly, the incorporation of such

Article highlights

- COVID-19 is an ongoing disease provoked by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2);
- Novel prophylactic and therapeutic measures are urgently needed for COVID-19 management;
- Nanoparticles have been receiving particular attention for COVID-19 treatment and vaccination;
- Cell membrane-based nanoparticles acanreproduce the surface repertoire and biofunctionality of native cell membranes;
- Cell membrane nanovesicles and cell membrane-coated nanoparticles represent the two main classes of cell membrane-based nanoparticles;
- Cell membrane-based nanoparticles are promising multifunctional nano-based approaches for multivalent COVID-19 treatment and vaccination.

This box summarizes key points contained in the article.

bioderived or bioinspired components can be achieved by unleashing the potential of cell membranes as complex, fully-replicable and multivalent biological components for (1) coating nanoparticle cores, by assembling cutting-edge cell membrane-coated nanoparticles; or by (2) functioning as cell membrane-derived nanovesicles devoid of nanoparticle core, known as cell membrane nanovesicles. These cell membrane-based nanoparticles are a relatively new class of materials merging distinct cell membrane biofunctionalities with the versatility of nanoparticles, creating thus far innovative nanoplatforms showing a vast array of applications within the biomedical field. The purpose of a cell membrane-derived surface is to act as a biological cloak encasing the interior contents, protecting them from premature clearance, degradation or release, and acting as a multi-addressable, multivalent and tailorable interface to mimic and boost biological interactions. Cell membrane-based nanoparticles are already showing some exciting results in COVID-19 management [19–21]. In this review, the authors will comment on the recent advances and future prospects of cell membrane-based nanoparticles for harnessing COVID-19, focusing on the potentialities of recently developed cell membrane-coated and cell membrane nanovesicle-based COVID-19 therapies and providing a roadmap of possible future applications of this technology for COVID-19 management. Additionally, the review will build on previously reported biomedical advances regarding cell membrane bioengineering and surface functionalization toward full unleashing of the potential of cell membrane-based nanoparticles for multifunctional, biomimetic and innovative COVID-19 therapeutics and vaccination.

1.1. SARS-CoV-2 structure and pathology

SARS-CoV-2 is a positive-sense enveloped RNA virus with a single stranded RNA genome of approximately 34 kilobases and a nucleocapsid of helical symmetry [22]. This 80–160 nm-sized virus presents a roughly spherical or moderately pleiomorphic morphology, with a condensed mass of nucleic acid and nucleocapsid protein underneath a well-defined lipid bilayer envelope (Figure 1). The S protein (spike glycoprotein) enables the attachment of the viral particle to host cells and membrane fusion, hence promoting the entry of SARS-CoV-2 into the host cells [23–29]. The angiotensin-converting enzyme 2 (ACE2) is the key receptor for entry of SARS-CoV-2 into the host cells. Cellular proteases (human airway trypsin-like protease (HAT), cathepsins and transmembrane protease serine 2 (TMPRSS2)) control the viral entry process by splitting the spike protein and initiating further penetration mechanisms [30].

The interaction between the ACE2 and SARS-CoV-2 is facilitated by polar interactions [31–33]. Some of the major therapeutic targets identified include interaction sites of viral S protein with ACE2, TMPRSS2, viral proteases (3CLpro and PLpro) and RNA polymerase (RdRp) [34–40]. Structures involved in SARS-CoV-2 binding (either for infection *via* ACE2 or neutralization *via* convalescent serum antibody) were solved at unprecedented speed, and such evidence accelerates both vaccine and therapeutic developments. For example, *in silico* immunoinformatic studies leveraging SARS-CoV-2 homology to SARS-CoV provided a shortlist of candidates for vaccine epitope design even prior to downstream SARS-CoV-2 convalescent serum neutralization studies (reviewed in [41]). The pathological framework of SARS-CoV-2 infection is not only limited to its transmission inside the host cell, as host's
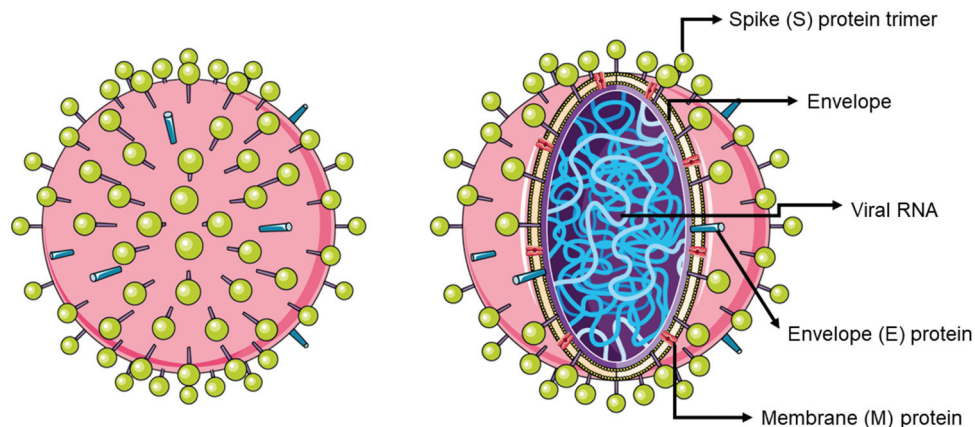

Figure 1. Schematic illustration of severe acute respiratory syndrome coronavirus 2 structure.

immune system response against it is also very crucial. A dysfunctional immune response initiated after SARS-CoV-2 infection may also result in the worsening of the condition both locally as well as systemically [42–45]. Active replication of the virus results in the release of damage-associated molecular patterns, which further triggers the localized flux of pro-inflammatory cytokines, chemokines and subsequently attract immune cells to the site of infection [46–48]. Excessive infiltration of immune cells results in the pro-inflammatory cytokine storm, provoking pulmonary edema, pneumonia, and severe lung damage. Multiple organs may also become severely affected by this widespread inflammation and antibody-dependent enhancement (ADE) by non-neutralizing antibodies produced by B-cells [48].

1.2. Nanotechnology direction for SARS-CoV-2 treatment and vaccination

Current COVID-19 therapy mostly resort to the use of antivirals (to inhibit the multiplication of virus) and immune modulators (to manage the response of immune system to counter the virus). In the absence of an exclusive antiviral treatment against SARS-CoV-2 infection, its management is still a great challenge [6]. In parallel, the scientific community is using high-throughput drug discovery platforms to develop new small molecules, repurpose existing drugs and designing formulations for these candidates [49–55]. Input of nanotechnology becomes vital here to develop creative strategies to maximize the efficacy of currently available therapeutics.

Nanomedicine strategies can circumvent various disadvantages and potentiate the therapeutic benefits of repurposed antiviral molecules by increasing bioavailability, localizing the delivery to the infection sites (viral reservoir sites such as ACE 2 expressing cells, domains of viral S protein, cathepsin-binding sites), decreasing off-targeted effects, and weakening the resistance development mechanisms [56,57]. Nanocarriers can deliver a range of small molecules, biologicals (RNA interference, antibodies, proteins, antigens), peptides, and combined therapeutics as well [6,58–60]. Nanocarriers also ensure the physical prevention of the biological molecules against the premature degradation in harsh biological environments, whilst evading the immune recognition and minimizing renal and/or hepatic clearance [6,61]. Sustained release of nanoparticle´s loaded compounds (e.g. antiviral molecules) can also prevent the viral rebound and improve the overall therapeutic management. In addition to payload and antigen delivery via nanocarriers, nano-based antiviral strategies with possible applications to harness COVID-19 include development of virucidal nanomaterials and harnessing 'nanodecoy' abilities of nanocarriers toward virus immobilization and cytokine neutralization [58] (Figure 2).

SARS-CoV-2 infection is evolving continuously and some of the viral mutants are escalating the healthcare challenges. COVID-19 vaccines are introduced as a parallel strategy to reduce the morbidity and mortality worldwide. Current COVID-19 vaccines are based on both replicating and non-replicating platforms. One of the biggest challenges associated with the development of COVID-19
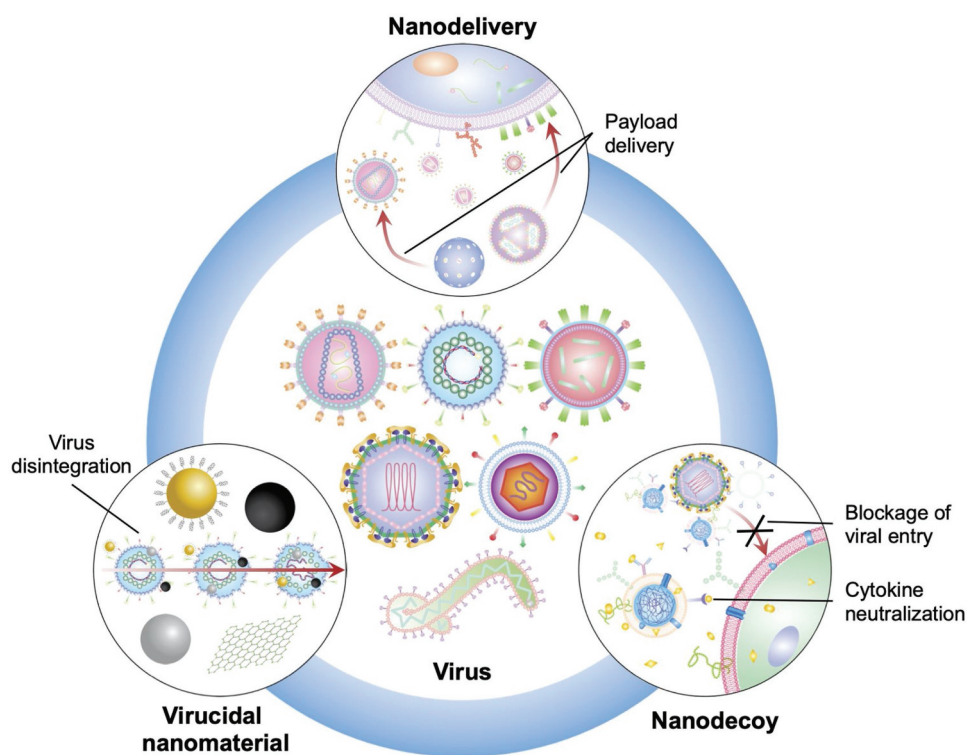

Figure 2. Nanotechnology approaches to treating viral diseases. Nanotechnology can improve antiviral therapy through various means: (1) nanoparticles can protect and deliver therapeutic cargoes specifically to viruses or infected cells and increase bioavailability; (2) some nanomaterials have virucidal properties that enable them to disrupt and alter viral structure; (3) nanodecoys can interact directly with viruses to neutralize their infectivity, or they can be used to soak up inflammatory cytokines and mitigate hyperinflammation. Reproduced with permission from reference [58], Copyright 2021, Elsevier.

vaccine is to assure its safety while maintaining efficacy in the global heterogeneous population [6,41]. The input of nanotechnology in vaccine development is exciting the scientific world on many fronts. Various nanovaccines are under consideration to develop a safe and effective immune response against potential targets like the viral S protein [62,63]. Along with the safe and effective delivery of the antigens, nanotechnology can assist a successful vaccine development by allowing a better control over antigenic release and display, cellular presentation and uptake, and targeting both adaptive (T cells, B cells) and innate (macrophages, monocytes, neutrophils) immune systems. For example, polymersomes, which are artificial polymer-based vesicles enclosing an aqueous core, were used to display at the surface spike protein receptor-binding domain (RBD) resulting in strong humoral neutralizing response to SARS-CoV-2 as well as robust cellular immunity [64]. Also in this context, nanomaterials possessing intrinsic adjuvant properties are of utmost importance to optimize the safety and efficacy parameters. These vaccine adjuvant nanocarriers can play a key role to design effective prophylaxis against SARS-CoV-2 infection [6,18]. Once COVID-19 is associated with inflammatory stages characterized by cytokine overproduction and a so-called cytokine storm, strategies to neutralize inflammatory cytokine production and reduce inflammation recurring to nanotechnology are also receiving special attention [65].

Apart from these conventional nanomedicine strategies, biomimetic nanosystems have emerged as an alternative option against such threatening pathogens. Advantages associated with these biomimetic nanosystems in terms of their surface functionalization, tailorability, biocompatibility, and reproducibility make them a versatile nanomedicine candidate. With optimized biophysiochemical properties, these nanosystems possess a great potential both for therapeutic and vaccine delivery [66–70]. Furthermore, the therapeutic or vaccine efficacy may also be benefited by their nature-inspired design and an intrinsic activity attributed to these biomimetic nanosystems.

1.3. Basic biomimetic strategies for treatment and vaccination

The complexity of biological systems and the richness of the interactions established in biological environments have inspired the design of novel structures able to mimic the functionalities of biological components toward the maximization of biointerfacing and manipulation of biological cues [71]. This can be achieved for distinct strategies: through surface functionalization of nanocarriers with selective targeting ligands [72]; by mimicking endogenous particles (e.g. lipoproteins [73]) and vesicles (extracellular vesicles [74]); by mimicking cell membranes natural structure, for example, recurring to synthetic constituents [75]; or by coating nanocarriers with extracted cell membrane coatings from source cells [76]. Biomimetic nanocarriers display enhanced biocompatibility, biodegradability, specificity as well as minimal toxicity, and allow for improved immune response avoidance. Such bioinspired nanocarriers may also possess intrinsic activity to

potentate the respective therapy or vaccine approach against infectious diseases. Such attributes have made biomimetic nanocarriers a very interesting approach toward enhanced delivery of therapeutics, as well as vaccines with applications in a wide range of diseases [77].

Biomimetic nanotechnology approaches have been employed for SARS-CoV-2 vaccine design and therapy development, holding great promise, as these approaches operate on the same size scale as that of the pathogens [21]. For instance, mesenchymal stem cell-derived exosomes could be a valuable tool for reducing lung infection and alleviate COVID-19-related symptoms, in addition to posing as safe and fully-biocompatible nanovesicles toward targeted payload delivery to cells [78]. Besides the contemporary vaccines, i.e. inactivated and live-attenuated vaccines, the majority of vaccination approaches either under development, under clinical testing and already approved are based on novel biomimetic nanotechnologies, such as messenger RNA-laden lipid nanoparticles including approved Pfizer-BioNTech's BNT162b2 and Moderna's mRNA-1273, in which antigen-encoding messenger RNA is delivered into cells' cytoplasm and promote expression of a SARS-CoV-2 antigen, further displayed at the surface of host cells and enabling recognition by immune cells and immune response [79–81]; lipid-based [82] and protein-based [83] nanoparticles exposing SARS-CoV-2 antigens; or adenoviral vectors encoding the SARS-CoV-2 spike protein [84–86]. Other approaches focus on subunit vaccines self-assembled into virus-like particles (VLPs) as reviewed in [41,87], bacteria-based expression of SARS-CoV-2 membrane and nucleocapsid proteins [88]. Given that the respiratory mucosa is the first main barrier for preventing SARS-CoV-2 invasion, another interesting strategy is to develop nanoparticles mimicking SARS-CoV-2 structure and activity to elicit anti-COVID-19 mucosal immunity in the respiratory tract (Figure 3a) [89]. Here, virosome-mimicking nano-enabled bionic vaccine was composed of synthetic double-stranded RNA poly(I:C) as immune adjuvant and simulating viral RNA, pulmonary surfactant-based liposomes mimicking viral capsid and SARS-CoV-2 receptor-binding domains (RBDs) acting as the viral spike, assembling a complex biomimetic inhalable nanovaccine sized around 154 nm (similar to SARS-CoV-2) and aimed at nasal administration (Figure 3(b,c)). The nanovaccine was able to induce significant mucosal immunity through production of secretory immunoglobulin A (sIgA) by the respiratory mucosa, resulting in potent SARS-CoV-2 neutralization and blocking host cell invasion. Additionally, the nanovaccines could stimulate CD4+ T cells differentiation (Figure 3(d-g)), thus promoting humoral activation and enhanced secretion of neutralizing antibodies, as well as B cell activation in the spleen (Figure 3(h,i)). Importantly, the nanovaccine showed remarkable immune protection and mucosal immunity performance as compared to the groups subjected to intramuscular and intraperitoneal injection, including higher sIgA titers and duration of protection (Figure 3(j-m)) [89].

While vaccines are undergoing clinical testing, there is an urgent need for therapeutics, especially as new waves of infection have already emerged globally. Moreover, non-vaccine therapeutics also may serve to benefit those whose immune systems approach senescence. Therapeutic
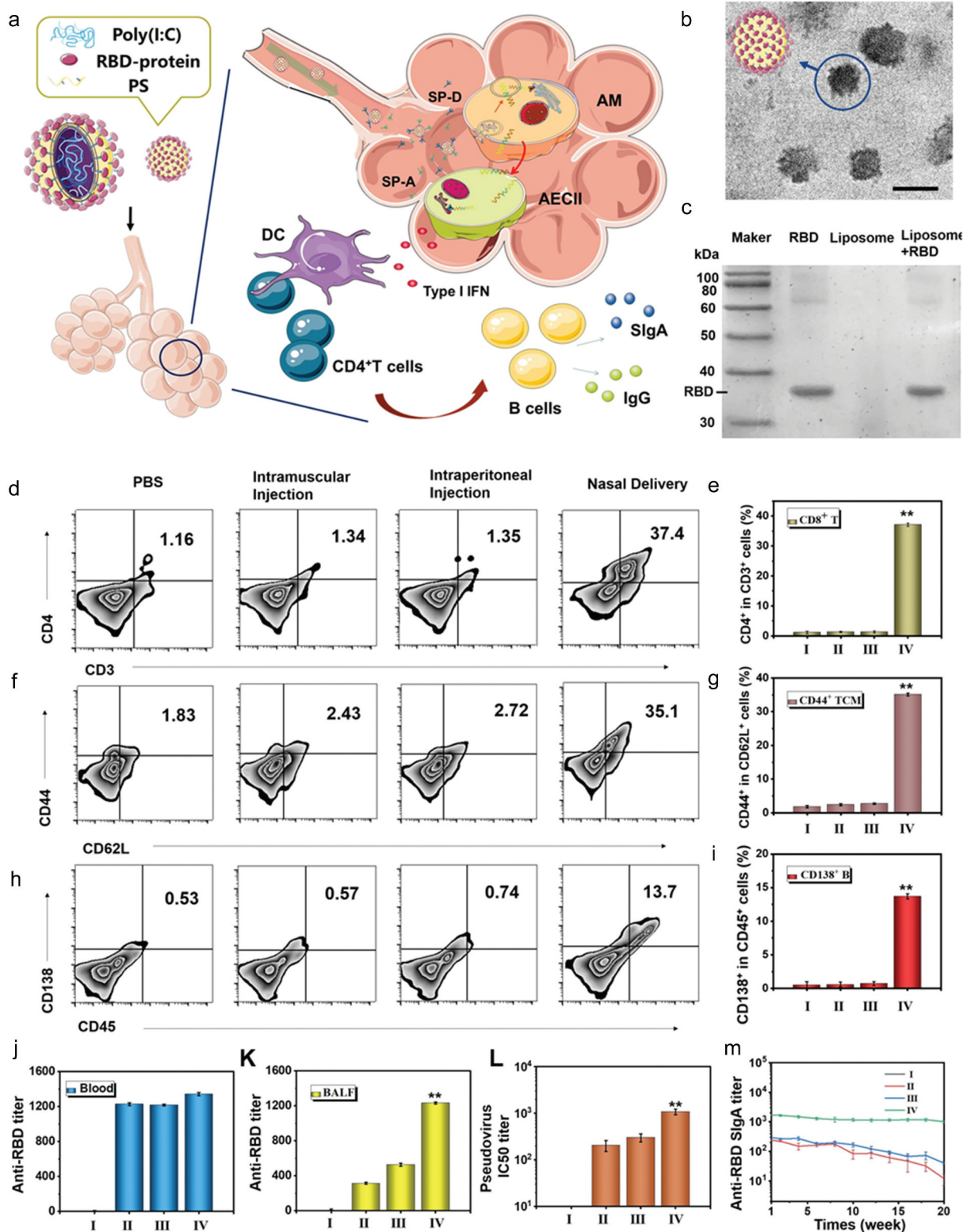
Figure 3. General overview of the bionic-virus nanovaccine and immune protection conferred by different administration routes. (a) Schematic diagram of inhalable bionic-virus nanovaccine activating cellular immunity and humoral immunity of respiratory mucosa. (b) TEM images of bionic-virus particles. Scale bars, 200 nm. (c) Coomassie blue staining results of RBD protein. (d) Representative flow cytometric analysis images of $CD4^+CD3^+$ T cells in BALF. (e) Relative quantification of $CD4^+CD3^+$ T cells in BALF. (f) Representative flow cytometric analysis images of $CD44^+CD62L^+$ TCM cells in BALF. (g) Relative quantification of $CD44^+CD62L^+$ TCM cells in BALF. (h) Representative flow cytometric analysis images of $CD138^+CD45^+$ B cells in spleen. (i) Relative quantification of $CD138^+CD45^+$ B cells in spleen. (j) Anti-RBD IgG titer. (k) Anti-RBD sIgA titer. (l) PsV IC_{50} inhibition titer of BALF. (m) Anti-RBD sIgA titer of mice during the five months evaluation period. (I: PBS, II: Intramuscular Injection, III: Intraperitoneal Injection, IV: Nasal Delivery). Adapted with permission from reference [89]. Copyright 2021, Elsevier.

intervention or even prophylaxis may come in the form of neutralizing antibodies [90], however cold-chain requirements and risk for antibody-dependent enhance (ADE) of infection bear translational challenges [91]. Other SARS-CoV-2 spike protein binders in the development pipeline include ACE2-inspired *de novo* design peptides [92,93] and nanobodies (a

single monomeric variable domain antibody) [94]. A particularly powerful decoy strategy is the multivalent presentation of such capture agents on a nanocarrier. This has been demonstrated recently using biomimetic virus-like particles (VLPs) with a multivalent sialic acid array to capture and neutralize influenza A-virus [68]. This biomimetic strategy can be easily adopted to SARS-CoV-2 treatment:a synthetic, highly-branched derivative of heparin was reported to improve antiviral activity against SARS-CoV-2 [95]. An alternative strategy to multivalent display is multi-expression. In this context, lipid nanoparticles containing mRNA encoding hACE2 led to decoy expression and SARS-CoV-2 neutralization [96].

2. Cell membrane-based nanoparticles basics for COVID-19 treatment and vaccination

2.1. General overview

Inspired by the attributes of nanomaterials, of which nanoparticles have been explored the most, and the multivalent interactions performed by cells in a biological environment, cell membrane-
based nanoparticles have been receiving special attention to improve bio-interfacing and mimicking features of native nanocarriers.

Cell membranes can be extracted from distinct biological sources and (1) wrapped around nanocarrier cores by multiple possible combinations, resulting in cell membrane-coated nanoparticles, or (2) used as biomimetic cell membrane-
derived nanovesicles composed of cell membrane-derived lipid bilayer surrounding an aqueous core. Considering the first case, the decorated nanoparticles have been adapted so far for distinct therapeutic destinations, according to the inherited and transferable functionalities conveyed by the surface repertoire of each cell membrane. Various cell membranes, such as red blood cells (RBCs), platelets, immune cells, cancer cells and bacterial membranes, have been reported [97]. Distinct cellular origins of cell membranes provide different array of biofunctionalities, namely (1) cancer cell membrane coatings for enhanced cancer therapies, owing to homotypic targeting of source cancer cells [98,99] and immune system stimulation by collective surface antigens of the membranes [100]; (2) RBC membrane coatings, for extended blood circulation profile, blood stability and immune escape, with applications in cancer therapy, acute liver failure [101] and diabetes management [102]; (3) immune cell membrane coatings, for improved cancer biodistribution and accumulation, such as neutrophil membrane coatings, aimed at anti-inflammatory therapies, by acting as deep tissue penetrating decoys capable of neutralizing inflammatory mediators and alleviating rheumatoid arthritis [103]; Leukocyte membrane coatings, for atherosclerosis treatment, to improve intimal foam cells targeting and migration properties [104], or expanding interaction with damaged endothelium and surroundings by platelet membrane coatings [105] (Figure 4).

Altogether, these results have shown the versatility of cell membrane-coated nanoparticles, building on the multifunctional cell membrane shells and the diversity of the
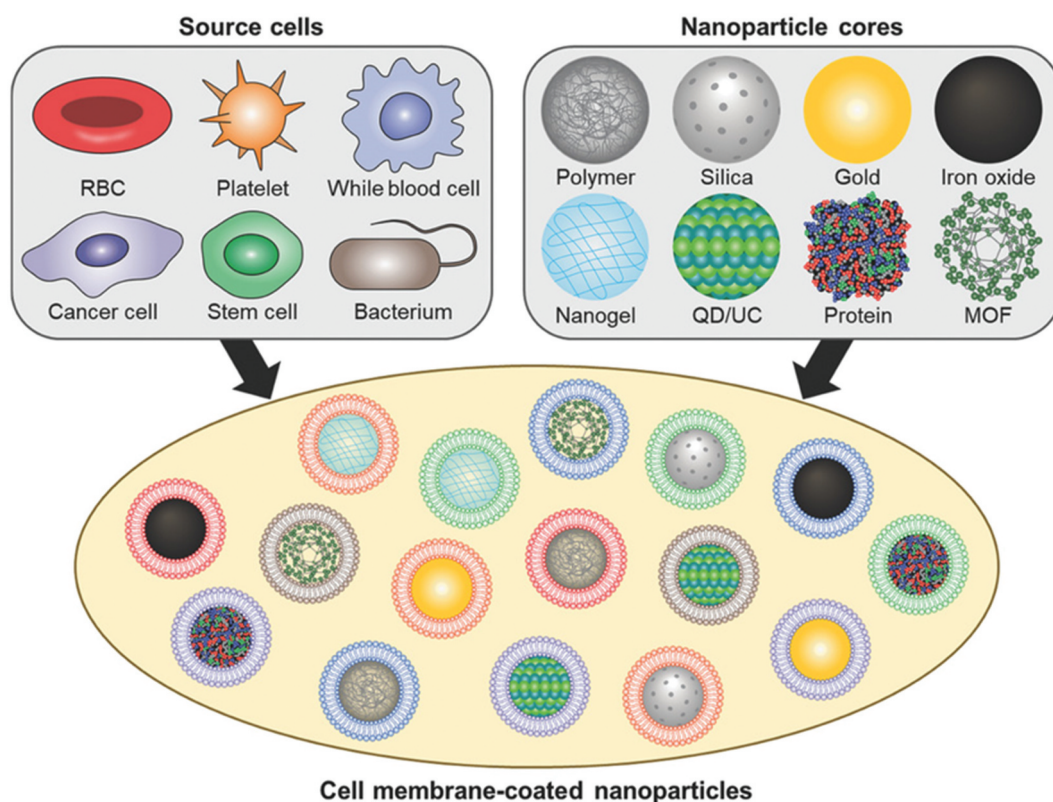

Figure 4. Schematic illustration of cell membrane-coated nanoparticles. A variety of cell types have been used as sources of membranes to coat over nanoparticles. Each cell membrane type can utilize unique properties to provide functionalities to nanoparticulate cores, the material of which can be varied depending on the desired application. Reproduced with permission from reference [76]. Copyright 2018, Wiley-VCH.

nanoparticle cores carrying active molecules, which have evidenced hitherto improved performance in treating several diseases. The composition of cell membranes can be enriched through functionalization with targeting ligands or antigens for maximized biofunctionality either *via* lipid-insertion methods in which the ligand is coupled to a lipid for intercalating into the lipid bilayer of cell membrane nanovesicles, or by cell engineering (Figure 5) [106].

So far, several classes of ligands from sugars (Figure 5), aptamers (Figure 5), peptides (Figure 5), cell-penetrating moieties (Figure 5), proteins (including enzymes and antibodies) (Figure 5) and small molecular weight molecules (Figure 5A) have been actively explored for surface functionalization of cell membrane-based nanoparticles, including cell membrane-coated ones [107–114] (Table 1).

Modulation of the lipid bilayer composition of the cell membrane nanovesicles can be achieved *via* hybrid approaches, either through (1) fusion with other cell membrane nanovesicles bearing distinct provenience assembling hybrid cell membrane vesicles (Figures 5–7); by (2) producing liposomes enriched with membrane-extracted constituents (Figures 5–8); or by (3) fusing liposome lipid bilayer with cell membrane nanovesicles (Figures 5–9). In the first case, single cell membrane nanovesicles can fuse together under an extrusion process and combine the surface repertoire and inherent bifunctionalities of distinct cell membrane sources [119]. This strategy has been mainly used for cancer-targeted therapies so far. The second approach consists of intercalating native cell membrane-extracted proteins into the lipid bilayer of liposomes, through mixing lipidic building blocks with extracted protein content, as reported for leukocyte cell membrane-based biomimetic liposomes [120,121]. A distinct study reported biomimetic liposomes based on RBC membrane vesicles functionalized with *Escherichia coli (E. coli)* membrane endotoxin-targeting polymyxin B (PMB)-lipid conjugates for concerted detoxification [122]. These RBC-based liposomes exhibited dual function, namely *E. coli*-anchoring abilities upon PMB binding to membrane endotoxins and exotoxin-absorbing abilities conferred by the lipid bilayer of RBC membrane nanovesicles, thus able to neutralize both endotoxin and exotoxin production, as *in vivo* studies showed. Lastly, fusion of exosomes – lipid bilayer nanovesicles secreted by almost all cells – with liposomes through freeze-thaw method assembling exosome-liposome hybrids has been reported, shedding light into advanced functionalization of cell membrane-derived nanovesicles [123].

The highly problematic issues of antimicrobial resistance, emergence of new infectious diseases and the current COVID-19 pandemic have resulted in an urgent and vital need for new medical therapies and interventions to counteract this biological war we have found ourselves faced with. As stated before, nano-based therapeutic approaches are known to broadly leverage the performance of several conventional therapeutics by conferring protection to encapsulated active molecules from harsh *in vivo* environment, and improving pharmacokinetics [58]. This enables payload controlled release and long term therapeutic effect, as well as providing stimuli-responsiveness and tissue-targeting features toward maximized therapeutics [76,124].

Inspired by such advances, the potential of cell membrane coatings can be applied to harness infectious diseases such as COVID-19 and maximize therapeutic efficacy on account of the suitability of the nanoparticle cores and multifunctionality of the cell membrane coat to build advanced nano-based biomimetic platforms toward infection management, as discussed next.
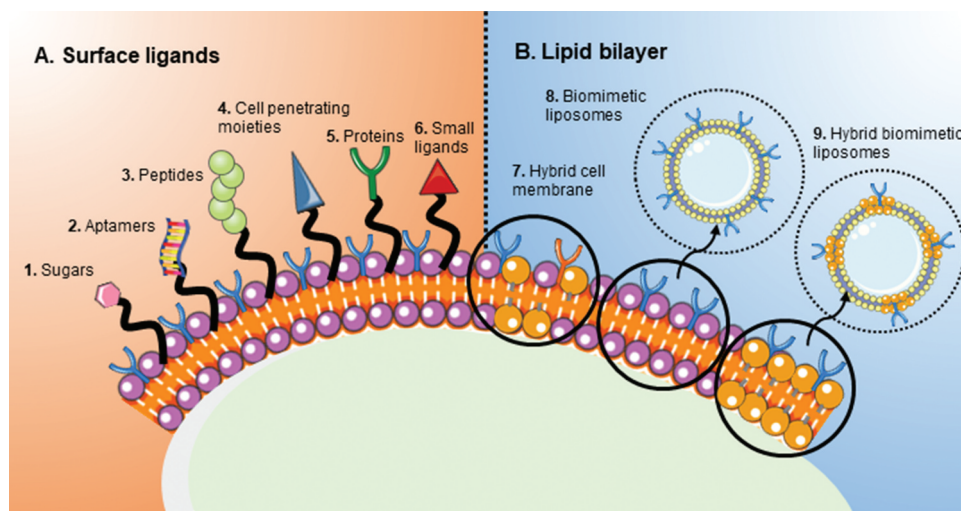

Figure 5 Surface functionalization and lipid bilayer composition modulation of cell membranes. The surface and lipid bilayer content of either cell membrane nanovesicles or cell membrane-coated nanoparticles can be modified to a desired finality. This includes surface functionalization with targeting ligands of different natures (A. 1–6) and lipid bilayer engineering by fusion of two distinct cell membrane nanovesicles (B. 7) assembling a multifunctional hybrid cell membrane nanovesicle; enriching synthetic liposomes with cell membrane-extracted components (B. 8); and fusion cell membrane nanovesicle with a synthetic liposome or endogenous extracellular vesicles (B. 9). Similar to the single cell membrane nanovesicles, the nanovesicles obtained in 7–9 can be used to coat nanoparticle cores yielding cell membrane-coated nanoparticles, or used as biomimetic nanovesicles *per se* toward multiple applications, and enriched with targeting ligands (1–6).

Table 1. Overview of ligand-targeted cell membrane-based nanoparticles.

Nanoparticle core	Type of membrane	Targeting	Function	Disease	Ref.
PLGA NPs	RBC	Mannose	↑ lymph node targeting	Cancer	[107]
Upconverting NPs	RBC	Folic acid	↑ tumor targeting *via* folate receptors	Cancer	[108]
Immunomagnetic NPs	RBC	Anti-EpCAM antibody	↑ tumor targeting *via* EpCAM molecules	Cancer	[109]
PHis-grafted black phosphorus NPs	RBC	YSA peptide	↑ tumor targeting *via* Ephrin A2 receptors	Cancer	[110]
Metal-organic frameworks	RBC	cRGD peptide	↑ tumor targeting *via* integrin αvβ3 receptors	Cancer	[115]
PLGA NPs	RBC	Hyaluronidase	↑ tumor diffusion of the NPs	Cancer	[116]
Magnetic nanoclusters	Leukocyte	apolipoprotein A-I mimetic 4 F peptide	↑ Atherosclerotic plaque targeting	Atherosclerosis	[104]
Magnetosomes	Macrophage	Antibodies	↑ tumor targeting	Cancer	[111]
Solid Lipid NPs	Macrophage	RVG29 and TPP	↑ targeting to neuronal mitochondria	Alzheimer's Disease	[117]
Copper sulfide NPs	Macrophage	RGD peptide	↑ tumor targeting *via* integrin αvβ3 receptors	Cancer	[112]
PLGA NPs	Platelet	TRAIL protein	↑ tumor targeting *via* TRAIL receptors	Cancer	[113]
Melanin NPs	Platelet	RGD peptide	↑ tumor targeting *via* integrin αvβ3 receptors	Cancer	[114]
-	RBC	Aptamer	↑ tumor targeting	Cancer	[118]

Abbreviations: PLGA, poly (lactic-co-glycolic acid); NPs, nanoparticles; RBC, red blood cell; EpCAM, Epithelial cell adhesion molecule; Phis, Poly-L-Histidine; cRGD, cyclic arginylglycylaspartic acid; RGD, Arginylglycylaspartic acid; RVG, rabies virus glycoprotein; TPP, triphenylphosphine cation.

2.2. Applications to infectious diseases

In infectious diseases, the range and complexity of pathological frameworks means they all progress *via* different routes and mechanisms. However, interaction at the interface between the host cell membrane and disease-specific pathogens always occurs, and hence this is an area of great interest in infection control. Cell membrane-coated nanoparticles have been shown to possess efficacy against bacterial and viral infections, above explored.

2.2.1. Bacterial infections

Recently, cell membrane-coated nanoparticles have been reported to counteract bacterial toxins due to the toxin's ability to adhere to cellular membranes and promote toxin neutralization and detoxification [125]. Particularly, RBC membrane-coated nanoparticles were effective in neutralizing the pore-forming toxin (PFT) staphylococcal alpha-hemolysin (α-toxin), acting as a toxin-absorbing nanosponge on account of the binding properties of PFT to their natural membrane substrates [126]. Further studies using nanodecoys coated with bacterial outer membranes of the pathogenic bacteria using *H. pylori* have been shown to act as anti-adhesion agents competitively binding at the mmembrane-bindingsites required for pathogen interaction and virulence [127]. In addition, cell membrane-coated nanoparticles can be loaded with antigens, toxoids or other immunostimulatory factors [124], as biomimetic toxoid nanovaccines for effective vaccination strategies. These include α-hemolysin (Hla) detainment in RBC membranes wrapped around poly(lactic-co-glycolic acid) (PLGA) polymeric nanocores, showing superior immunoprotective properties in methicillin-resistant *Staphylococcus aureus* (MRSA) mice models of skin infection [128]; multivalent nanotoxoids containing virulent proteins entrapped in RBC membrane-coated nanoparticles, effectively protecting against bacterial infection *in vivo* (Figure 6(a-c)) [129]; and PFTs-containing RBC membrane-coated nanotoxoids for immunization against PFT-producing bacteria [130].

Gram-negative bacteria are known to produce outer membrane vesicles (OMVs), lipid bilayer-enclosed nanovesicles with enriched surface repertoire composed of bacterial antigens – capable of modulating host immune response; and adhesins – allowing binding to target cells, among other recognition molecules [131]. Studies have examined the use of these secreted vesicles as a form of cloaking mechanism. It is thought that exploitation of cell membrane-coated nanoparticles does not explicitly impact the immunomodulatory roles of the membrane proteins, but instead that the extracellular vesicles are enriched with membrane-associated proteins which hold a critical role in bacteria–host interaction [132]. By taking advantage of host cell-targeting and attachment abilities of OMVs, *Helicobacter pylori*-derived OMVs were coated onto PLGA NPs and competed with *Helicobacter pylori* for binding to the gastric epithelium (Figure 6(e)) [127]. The OMV membrane was able to maintain surface virulence factors and adhesins present on the bacterial membrane source. The OMV-coated NPs showed strong anti-adhesion properties evidenced by the reduced *Helicobacter pylori* binding to gastric cells.

Another report showed efficient internalization by *Staphylococcus aureus* – infected macrophages of nanoparticles loaded with triclosan-ciprofloxacin amphiphilic conjugates, further coated with macrophage cell membranes with intrinsic pathogen-targeting abilities [133]. This strategy is interesting because the establishment of secondary bacterial niches in macrophages may enable bacterial survival and result in therapeutic inefficiency. The macrophage cell membrane coating could improve the antimicrobial effect of the triclosan-ciprofloxacin conjugates and lead to efficient *in vivo* eradication of intracellular Staphylococcus aureus infection.

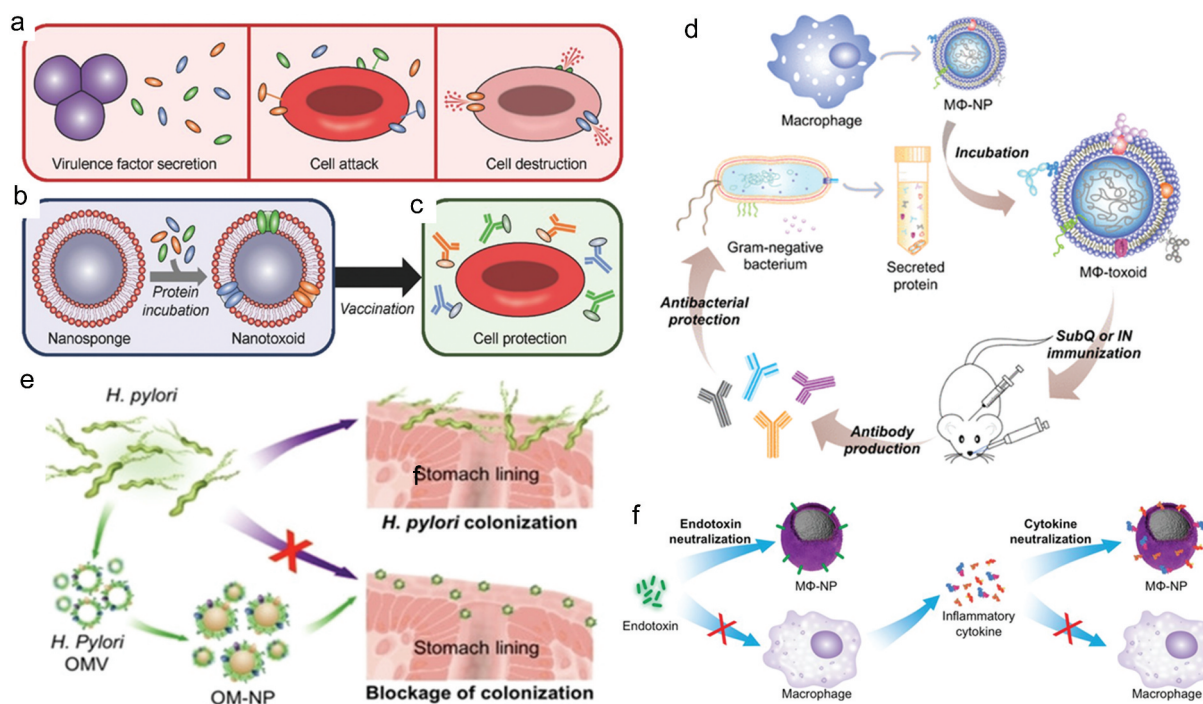Recently, macrophage cell membrane-coated PLGA NPs showed affinity to virulence factors secreted by *Pseudomonas*

Figure 6. Applications of cell membrane-coated nanoparticles to fight bacterial infections. (a) Pathogens secrete virulence factors, which are capable of inserting into target cells and causing their destruction. (b) Using nanosponges prepared with the membrane of target cells and incubating the particles with a bacterial supernatant-derived protein fraction, it is possible to generate a nanotoxoid carrying pathogen-specific virulence factors. (c) After vaccination using the nanotoxoid, antibodies against the incorporated virulence factors are elicited and can prevent their toxic effects, leaving the intended targets unharmed. Adapted with permission from [129]. Copyright 2017, Wiley-VCH (d) Schematic illustration of multiantigenic nanotoxoids against Gram-negative bacterial infection. Macrophage-mimicking nanoparticles (MΦ-NPs) are fabricated by coating the plasma membrane of macrophages onto polymeric nanoparticle cores. These particles can then be used in the generation of multiantigenic nanotoxoids through the capture and neutralization of secretions from Gram-negative bacteria. When vaccinated either by the subcutaneous (subQ) or intranasal (IN) route, mice receiving macrophage nanotoxoids (MΦ-toxoids) generate potent antibacterial immunity that can be used to protect against subsequent bacterial challenge. Adapted with permission from [134]. Copyright 2019, American Chemical Society. (e) Schematic representation of using OM-NPs to inhibit H. pylori adhesion on the stomach lining. OM-NPs were prepared by coating polymeric cores made from PLGA with H. pylori outer membranes containing adhesins critical for bacterial colonization. By mimicking the adhesion of H. pylori onto gastric epithelium, OM-NPs occupy the binding sites and hence inhibit the colonization of the bacteria. Adapted with permission from [127]. Copyright 2019, Wiley-VCH. (f) Schematic representation of using MΦ-NPs to neutralize endotoxins and proinflammatory cytokines as a two-step process for sepsis management. Adapted with permission from [136]. Copyright 2017, United States National Academy of Sciences.

aeruginosa as they were capable to capture, neutralize and display a variety of *Pseudomonas aeruginosa* antigens at the cell membrane's surface, inducing potent immune reaction (Figure 6(d)) [134]. These nanotoxoids could function as multiantigenic antivirulence nanoplatforms for potent immunization against bacterial infection. Additionally, macrophage membrane-coated magnetic composite nanoparticles were able to display antibacterial and anti-inflammatory properties by binding to bacteria and neutralization of toxins and inflammatory cytokines in bone infection [135] and sepsis [136] (Figure 6(f)).

2.2.2. Viral infections

Cell membrane-coated and cell membrane-based nanovesicles can act as nanodecoys able to trap and inactivate the pathogens of their infectious properties [67]. Several studies have explored their potential and have since demonstrated efficacy against diseases such as HIV (Figure 7(a)) [137], Zika virus (Figure 7(b)) [70], and Hepatitis B virus [138]. Here, the pathogen can bind to its natural target cell disguised as a target cell membrane-coated nanoparticle, which results in its immobilization, therefore disabling its ability to bind with the host target cells and, ultimately, removing its virulence. Other

studies reported a similar phenomenon in HIV models, using plasma of CD4$^+$ T cells to cloaking polymeric nanoparticles [137,139]. Cell membrane-coated nanoparticles can also be used as multivalent nanovaccine platforms for antigen delivery to antigen-presenting cells (APCs). Ligands such as mannose can improve targeting of nanoparticles to APCs for instance by interacting with mannose receptors. In a recent study, mannose-modified RBC-derived membranes was used to coat plasmid DNA(pDNA)-loaded chitosan cores and improve transfection efficiency of antigen-encoding pDNA to APCs and elicit potent immune responses against fish viral disease (Figure 7(c)) with prophylactic effects (Figure 7 (d)) [140].

2.3. Applications to COVID-19 therapeutics & vaccination

The diversity of source cells and correspondent cell membranes have since inspired breakthrough developments toward management of a plethora of diseases, such as cancer, inflammation and infection [67,76,141]. According to the desired application, specific cell membrane coatings may be preferred on account of their bminterfacing properties. For
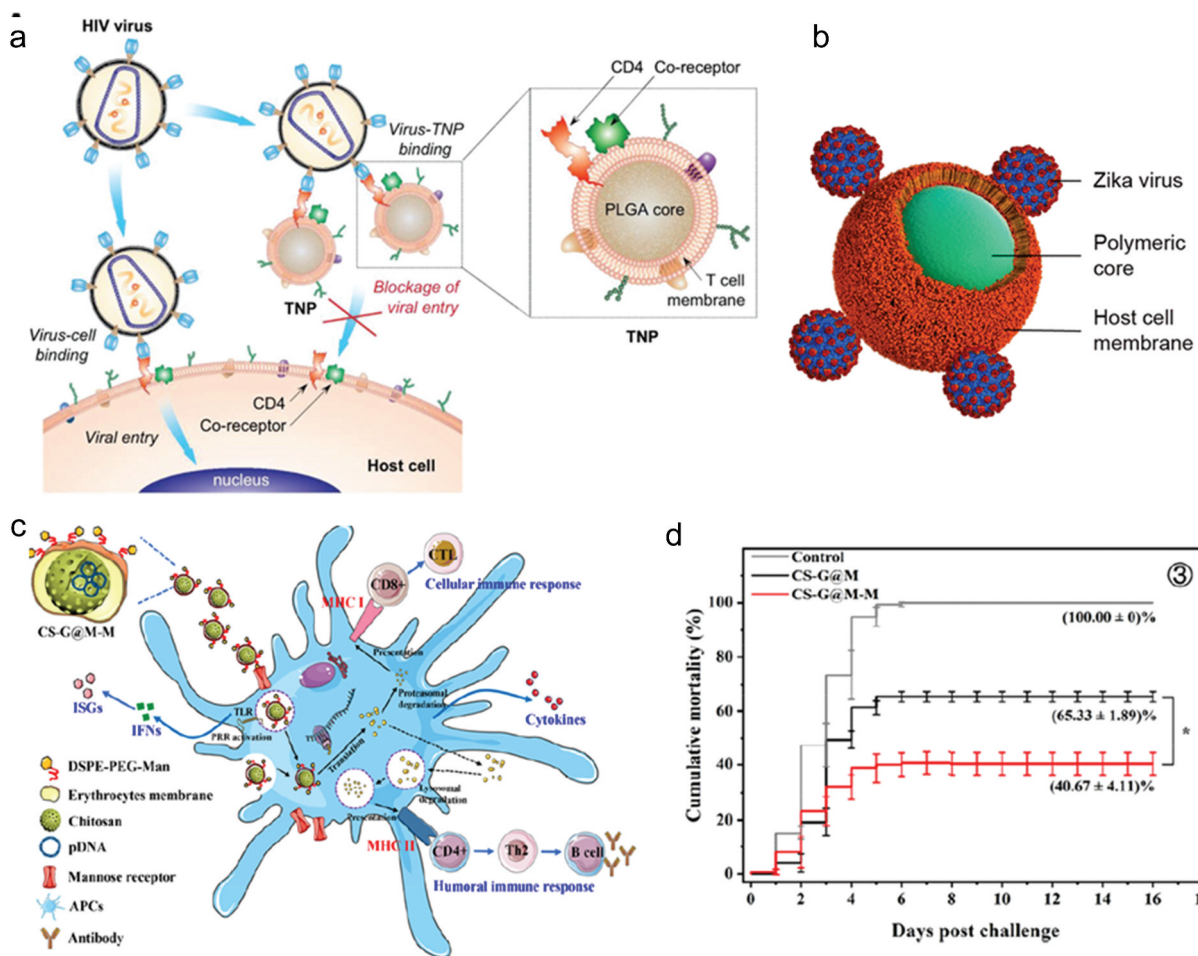
Figure 7. Applications of cell membrane-coated nanoparticles to fight viral infections. (a) Schematic representation of T-cell-membrane-coated nanoparticles (denoted as 'TNPs') designed for attenuating HIV infectivity. TNPs were constructed by wrapping polymeric cores with natural CD4 + T cell membranes, which contain key antigens including CD4 receptor and CCR5 or CXCR4 coreceptors for viral targeting. By replicating the surface antigen profile of source T cells, TNPs can act as decoys to bind with T cell targeted viruses and subsequently block viral entry into and infection of the target cells. Adapted with permission from [137]. Copyright 2018, Wiley-VCH. (b) Schematic illustration of the host cell membrane-coated nanoparticles as nanodecoys for ZIKA virus adsorption. Adapted with permission from [70]. Copyright 2018, American Chemical Society. (c) Schematic illustration of the red blood cell-coated chitosan nanoparticles for plasmid DNA delivery to antigen-presenting cells. (d) Prophylactic effects of the constructed nanovaccine in zebrafish, 70 days after vaccination. P values were calculated by log-rank (Mantel–Cox) test (*P < 0.05, **P < 0.01). Adapted with permission from [140]. Copyright 2020, American Chemical Society.

example, while cancer cell membrane coatings may be preferred to target cancer cells *via* a homotypic targeting mechanism and enable enhanced cancer-targeted therapies [142,143], immune cells such as macrophages and neutrophils may be equally preferred for targeting cancer [144–147] and manage inflammation and infection [103,133,135,148–150]. Hence, in the case of COVID-19, certain cells with intrinsic biofunctionalities may emerge as preferential source of cell membranes for coating nanoparticles, namely: (1) RBCs, providing prolonged blood circulation and immune evasion of payload-loaded nanoparticle cores (Figure 8(a)) [151]; (2) immune cells as inflammation and infection mediators, such as macrophages [135,147] and neutrophils [150], due to their innate recruitment to diseased tissues and intrinsic targeting ability for accumulation at inflammatory sites, and dendritic cells for lymph node targeting [152] (Figure 8(b)); additionally, they may act as nanodecoys for SARS-CoV-2 immobilization and as inflammatory cytokine-absorbing nanosponges [19,65]; (3) host epithelial cells, such as epithelial lung cells, as preferred targeted cells by SARS-CoV-2 and acting as nanodecoys

mediating SARS-CoV-2 immobilization and neutralization, diverting SARS-CoV-2 from its natural targets (Figure 8(c)); (4) platelets, owing to their mechanical flexibility and innate tropism to inflamed endothelium, injured tissue and vasculature (Figure 8(d)) [153,154].

Also similar to other diseases, the extracted cell membranes are used to produce cell membrane nanovesicles which can then be employed to coat nanoparticle cores yielding so-called cell membrane-coated nanoparticles, or used without further modification as cell membrane nanovesicles. So far, only host epithelial cell membrane-coated nanoparticles [19], macrophage cell membrane-coated nanoparticles [19], hybrid cell membrane nanovesicles [20] and leukocyte cell membrane vesicles [155] have been applied to COVID-19 management, particularly COVID-19 therapeutics, further discussed.

2.3.1. Cell membrane-based nanovesicles
The virulence of SARS-CoV-2 is reliant on its interaction with protein receptors on the target cells upon entering the body. Hence, this interaction between pathogen and membrane is
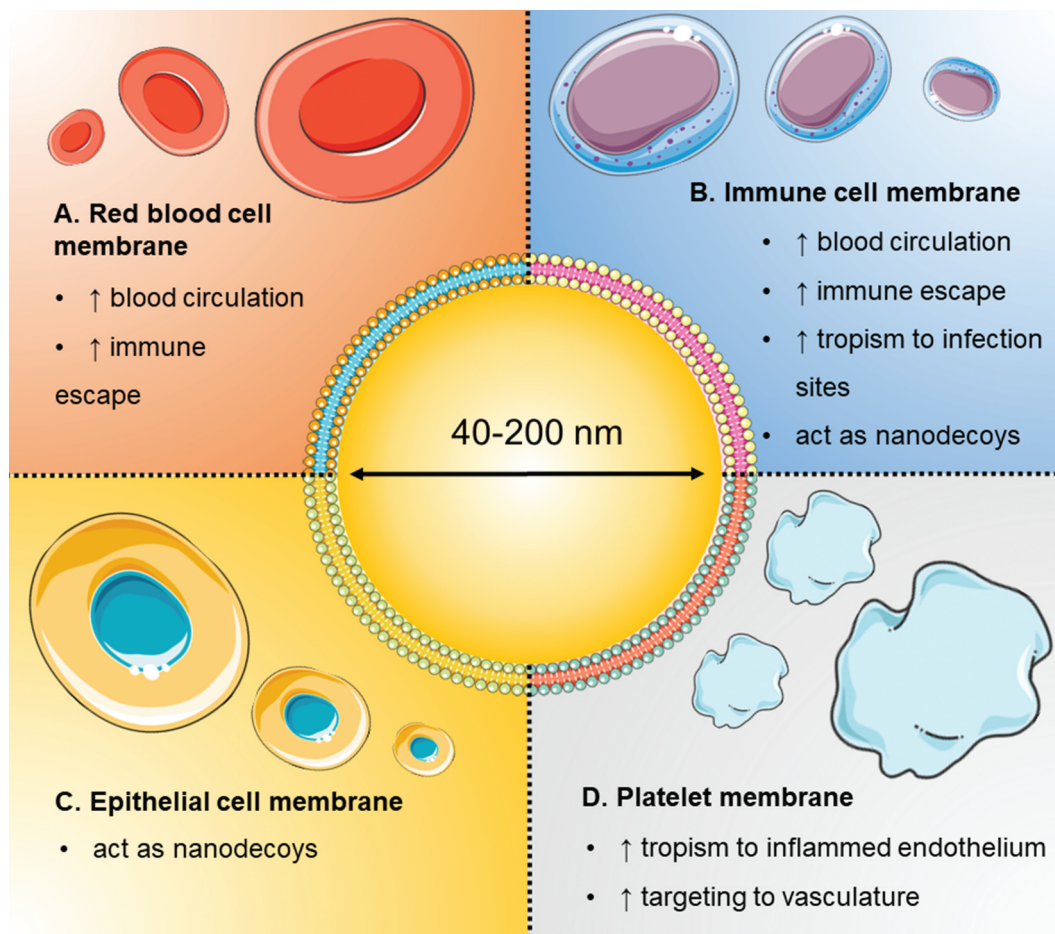
Figure 8. Distinct cell types as cell membrane sources toward development of cell membrane-coated nanoparticles for COVID-19 management. (A) Red blood cell membrane coatings; (B) Immune cell membrane coatings, such as macrophage and neutrophil cell membrane coatings; (C) Host epithelial cell membrane coatings; (D) Platelet cell membrane coatings. These cell membranes can also be used to form cell membrane nanovesicles enclosing the same cell attributes.

mechanistically similar to that of the more well-defined infectious diseases, and conventional therapeutic approaches can also be applied in this situation. In this regard, a recent strategy encompassed the preparation of cell membrane-based nanovesicles as nanodecoys which can act as virus-trapping cell-like structures for virus immobilization and cytokine neutralization [20]. Briefly, 293 T genetically-engineered human embryonic kidney 293 T cells were genetically engineered to expose ACE2 protein. Then, ACE2-attached cell membrane vesicles were extracted and fused with cytokine receptors-enriched human myeloid mononuclear THP-1 cell membrane vesicles, originated from precursor human myeloid mononuclear THP-1 cells (Figure 9(a-c)). The prepared cellular nanodecoys inherited native biological features, orientation and structure of source cells and showed combined SARS-CoV-2 immobilization and inflammatory cytokines (interleukin-6 (IL-6) and granulocyte–macrophage colony-stimulating factor (GM-CSF)) neutralization. *In vivo* suppression of acute pneumonia was additionally shown in acute lung inflammation mice models (Figure 9(d-f)) [20], suggesting interesting potentialities toward nanodecoy-assisted COVID-19 therapeutics. These cell membrane-derived nanovesicles successfully show the multifunctionality of biomimetic nanosystems *via* SARS-CoV-2 binding and immobilization combined with cytokine

neutralization upon interaction with membrane-exposed cytokine receptors.

Other similar study reported ACE2-rich human embryonic kidney-293 T cells membrane-derived nanovesicles able to bind SARS-CoV-2 spike in means of biocompetitive inhibition and neutralize the virus, blocking its entry to the cytoplasm of host cells, namely renal tubular epithelial cells [156].

Another study showed leukocyte-derived vesicles – leukosomes – (LKs) loaded with corticosteroid dexamethasone effectively improved pharmacokinetics of dexamethasone and attenuated SARS-CoV-2-triggered inflammatory response in a mice model of lipopolysaccharide (LPS)-induced endotoxemia [155]. The dexamethasone-loaded LKs were obtained from mouse macrophage J774 cell lines and consisted of macrophage cell membrane-based vesicles bearing an aqueous core enabling dexamethasone solubilization and an outer macrophage cell membrane-derived shell. When compared to free dexamethasone, the dexamethasone-loaded LKs could substantially suppress *in vivo* pro-inflammatory cytokines production and improve overall survival of mice models. The LKs *per se* are endowed with anti-inflammatory properties, namely augmenting anti-inflammatory cytokine levels
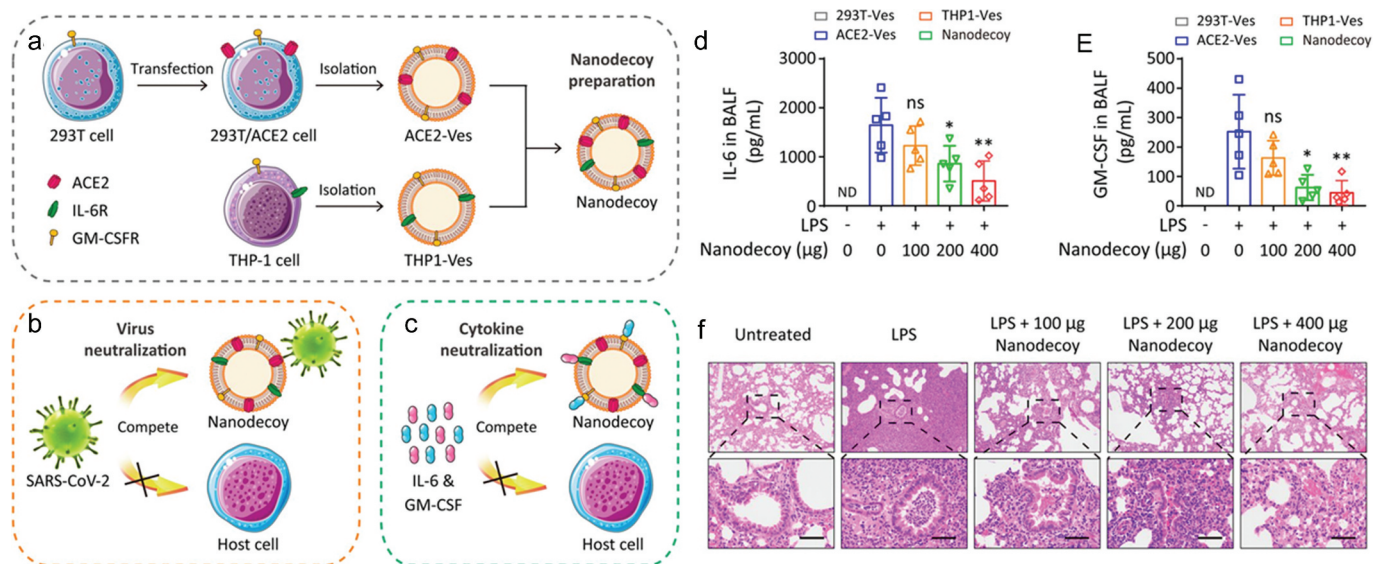
Figure 9. Schematic illustration of nanodecoys against COVID-19, namely SARS-CoV-2 and cytokine neutralization. (a) Preparation of nanodecoys by fusing cellular membrane nanovesicles derived from genetically edited 293 T/ACE2 and THP-1 cells. The nanodecoys, displaying abundant ACE2 and cytokine receptors, compete with host cells and protect them from COVID-19 by neutralizing (b) SARS-CoV-2, and (c) inflammatory cytokines, such as IL-6 and GM-CSF. (d-f) Nanodecoys suppress acute pneumonia *in vivo*. (d) IL-6 and (e) GM-CSF in the BALF after indicated treatments. ND indicates not detectable. (f) H&E-stained lung tissue sections after indicated treatments. (Scale bars, 50 μm.) Data points represent mean ± SD (n = 5). As compared with the group of LPS (+) and Nanodecoy (0), ns, *, and ** indicate no statistical difference, $P < 0.05$, and $P < 0.01$, respectively. Reproduced with permission from reference [20], Copyright Springer Nature (2020). COVID-19: coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; ACE2: Angiotensin-converting enzyme 2; IL-6: Interleukin-6; GM-CSF: Granulocyte-macrophage colony-stimulating factor.

(interleukin 10 and transforming growth factor beta (TGF-β)) and reducing pro-inflammatory ones (interleukin 6, interleukin 1b and transforming growth factor alpha (TNF-α)) [149].

2.3.2. Cell membrane-coated nanoparticles

Once a nanoparticle core is able to provide additional stability in biological environments when compared to sole cell membrane vesicles, a similar strategy was employed this time with polymeric nanoparticle cores. In this study, nanosponges composed of human-cell-derived membranes, which are sourced from cells that are naturally targeted by SARS-CoV-2, were wrapped around PLGA cores. The hypothesis of the study was that upon adherence to the nanosponges, SARS-CoV-2 is immobilized and disabled, and, therefore, it can no longer bind to its cell targets [19]. Nanosponges were either based on human lung epithelial type II or human macrophage cell membranes. The report showed that although both nanosponges exhibited activity against COVID-19, the macrophage-based nanosponges may have greater potential as a therapy. This is attributed not only to their ability to disable the viral efficacy, by reducing the viral load in the body, but also to their added ability to address the severe and sudden inflammatory response at later stages of COVID-19, due to the macrophages' intrinsic immunological functions [19] (Figure 10). Importantly, these nanosponges may not only maintain their therapeutic potential upon SARS-CoV-2 mutation but also have a transferable application to other viral diseases as long as the target cells remain the same, which constitute two major advantages when compared to conventional COVID-19 therapeutics. Regarding preclinical safety, no haemotoxicity or abnormal immune cell infiltration were detected after intra-tracheal administration of the nanosponges in mice.

The viral spike protein responsible for the pathogenesis of COVID-19 can be divided into S1 and S2 subunits after degradation, where the S1 subunit is responsible for recognizing host receptors, and S2 subunit mediates viral fusion into the cytoplasm [157]. The S1 binds to ACE2 gaining entry into the cells [157,158] . In order to block the virus entry, cell membrane-coated nanoparticles based on the membrane of human embryonic kidney-239 T cells overexpressing human ACE2 (HEK-293 T-hACE2) have been developed to competitively bind the S1 proteins, thus blocking SARS-CoV-2 binding onto the cell membrane and subsequent entry into its targeted cells. The study showed that these biomimetic nanocarriers adsorbed the SARS-CoV-2 S pseudovirons onto their surface as expected, and indeed blocked viral entry into the cytoplasm, thus disabling virulence [157].

The experimental studies described in this section so far encompass the application of cell membrane-coated or cell membrane-based nanoparticles as decoys for virus immobilization and inflammation reversal (Figure 11(a)). However, other strategies could be possible undertaken toward COVID-19 treatment by enhancing antiviral drug delivery and pharmacokinetics by performing drug loading directly to the membrane or into the nanoparticle cores, similarly to studies reported so far in a wide range of diseases (Figure 11(c)) [76].

Manipulating immune responses *via* a vaccine approach to battle COVID-19 has also been receiving growing attention. Inspiration from previous studies within the biomedical field covering cell membrane-coated nanoparticles as nanovaccines draw promising potentialities for further application to COVID-19 vaccination. In this case, immunization *via* SARS-CoV-2-derived antigens-coupling onto cell membranes could be
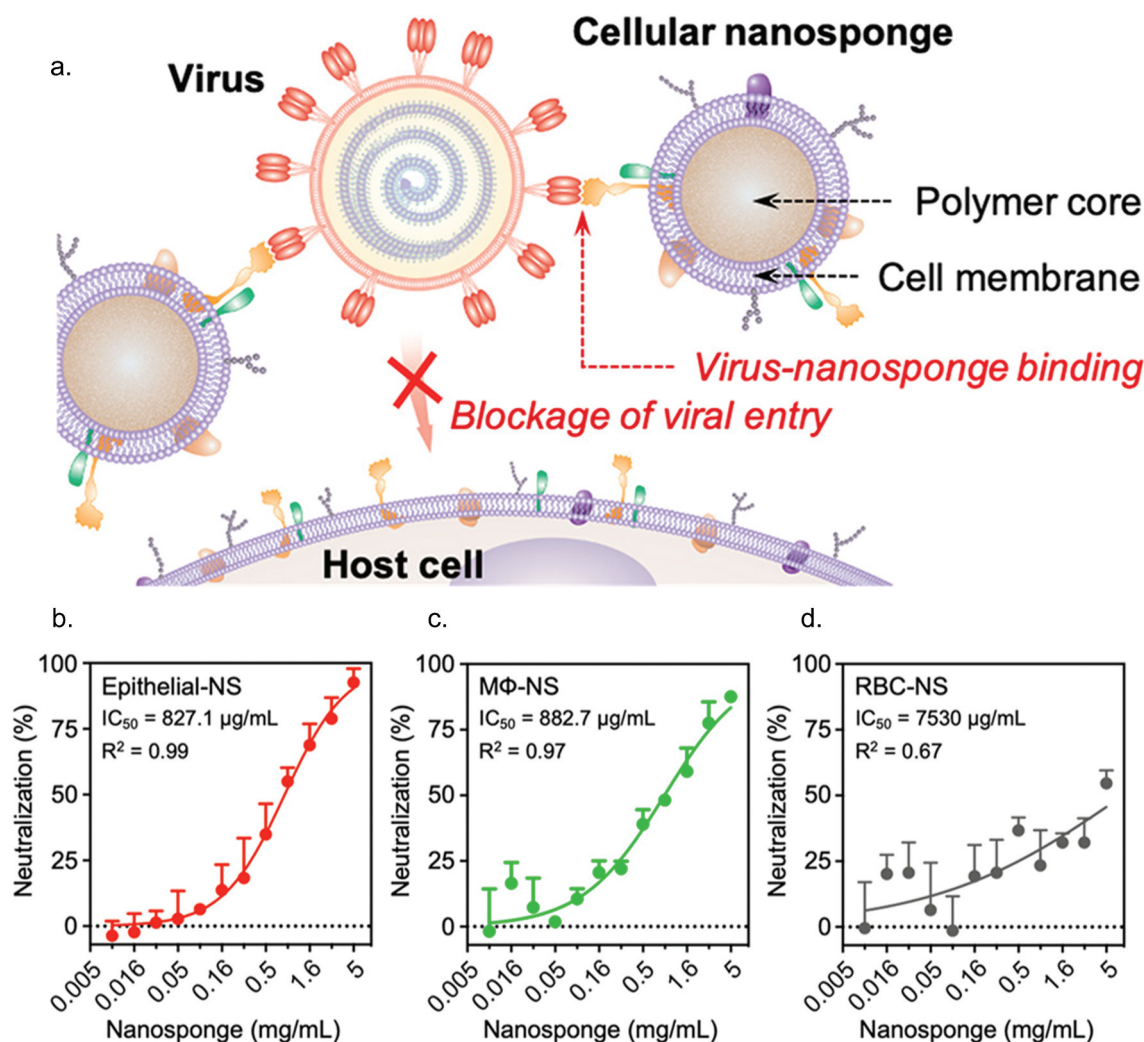
Figure 10. Cellular nanosponges for SARS-CoV-2 neutralization and inhibition of its infectivity. (a) Schematic mechanism of cellular nanosponges inhibiting SARS-CoV-2 infectivity. The nanosponges were constructed by wrapping polymeric nanoparticle cores with natural cell membranes from target cells, namely lung epithelial cells and macrophages (MΦs). The resulting coated nanosponges (denoted 'Epithelial-NS' and 'MΦ-NS', respectively) inherit the surface antigen profiles of the source cells and serve as decoys to bind with SARS-CoV-2. Such binding interaction blocks viral entry and inhibits viral infectivity. The neutralization against SARS-CoV-2 infection by (b) Epithelial-NS, (c) MΦ-NS, and (d) nanosponges made from red blood cell membranes (RBC-NS, used as a control) was tested using live SARS-CoV-2 viruses on Vero E6 cells. The IC_{50} values for Epithelial-NS and MΦ-NS were found to be 827.1 and 882.7 μg/mL (membrane protein concentration), respectively. In all data sets, $n = 3$. Data are presented as mean ± standard deviation. Horizontal dashed lines mark the zero levels. IC_{50} values were derived from the variable slope model using GraphPad Prism 8 ™. Adapted with permission from reference [19], copyright American Chemical Society (2020).

of utmost relevance to boost vaccine development for COVID-19 prevention, building on integrated nano-based and biomimetic strategies, as reported for other infectious diseases. Immunoadjuvants can also be added to expand immune responses, loaded either in the nanoparticle core, or installed in the cell membrane, see for instance (Figure 11(b)). Another possibly strategy may consist of tuning targetability of cell membrane-coated nanoparticles by attaching targeting ligands to direct nanoparticles to particular tissues and cells and increase target specificity (Figure 11).

2.4. Safety

Elucidating the *in vivo* safety of nanoparticles regardless of the biomedical applications is of paramount relevance as it may provide relevant cues on *in vivo* behavior and potential deleterious impact of nanoparticles in biological systems [159]. Hence, new data is urgently needed to improve the potentialities,

safety and clinical translation of nano-based systems to counter back COVID-19 infection, a subject receiving particular attention in current times [160]. Toxicity assessment of cell membrane-based nanoparticles is still at an early stage, particularly when referring to COVID-19 applications, due to the low amount of studies reported so far and lack of emphasis on toxicological profile owing to the novelty of this technology (Table 2).

While the biomimetic facet of cell membrane-based nanosystems are known to improve their biocompatibility toward biological systems due to their endogenous cell-derived constituents which are the ultimate source of contact with the majority of *in vivo* environment – either functioning as cell membrane coatings to nanoparticle cores or as cell membrane nanovesicles bearing an aqueous core – it is not exactly clear the potential long-term impact of these nanosystems in humans. The sum of evidence so far has pointed toward their relatively safe profile [19,156]; however, *in vitro* and *in vivo* models and the
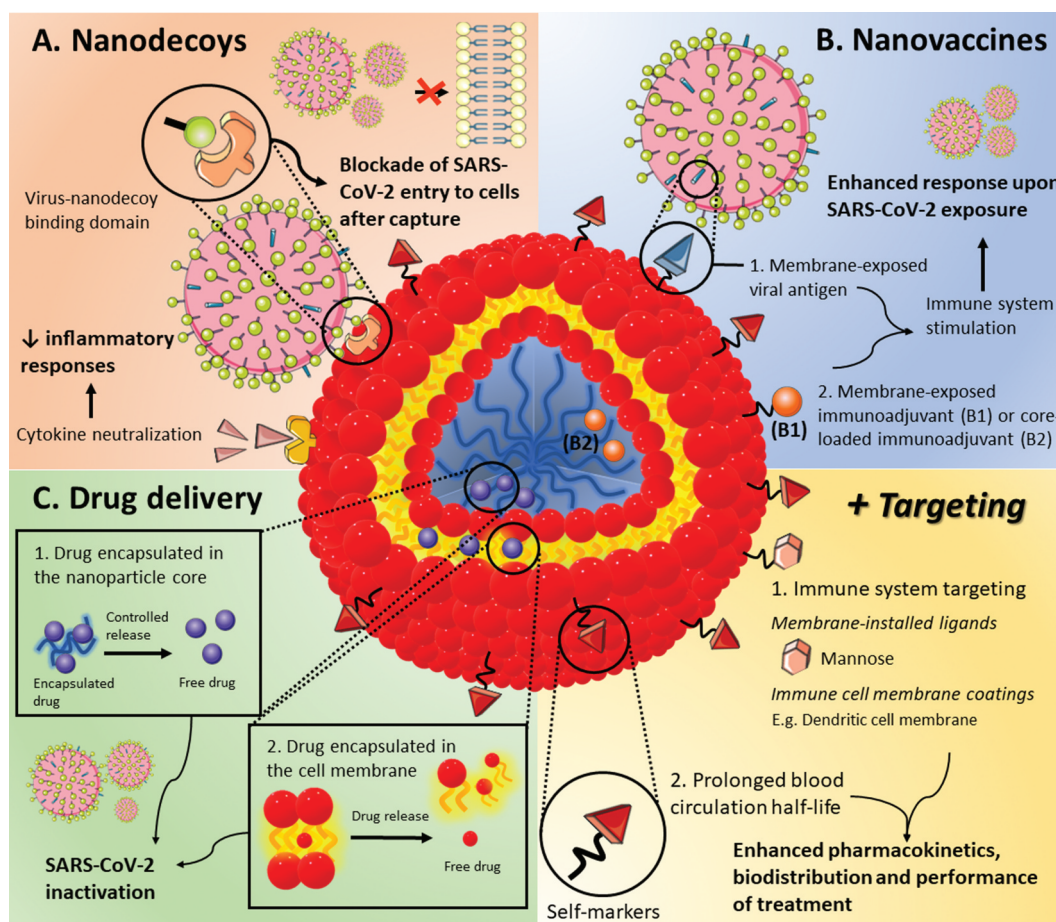
Figure 11. Potential applications of cell membrane-coated nanoparticles as biomimetic and multifunctional systems for COVID-19 therapeutics and vaccination. (A) Nanodecoys composed of SARS-CoV-2 target cells' membrane provide a strategy to divert SARS-CoV-2 from its target cells and diminishing its infectivity. Nanodecoys are also able to reduce inflammatory processes *via* cytokine neutralization (B) SARS-CoV-2 vaccination can be composed of SARS-CoV-2 antigens coupled into or onto the cell membrane to achieve maximum exposition and delivery, as well as potentially benefiting from immunoadjuvant-mediated enhanced immune responses. (C) Both hydrophilic and hydrophobic drugs can be loaded in the nanoparticle core, and cell membranes provide also a reservoir for hydrophobic drug incorporation on account of their lipidic nature. Alone or in combination, these strategies may undergo substantial improvements by fine-tuning targeting affinity of cell membrane coatings by either ligand-coupled active targeting strategies, inherited surface self-markers (e.g. CD47 in the case of red blood cells) and immune cell membrane coatings.

experience settings are distinct, which can difficult further comparability of results. Undoubtedly, more data specifically concerning the safety of these nanosystems is urgently needed.

3. Conclusion

The bioinspired technology, and wealth of choice in bioinspired membrane-coated nanocarriers, coupled with the pre-existing promise from other applications makes cell membrane-based nanoparticles a potentially real frontrunner in the development of new therapeutic and vaccination/prophylaxis approaches toward COVID-19 management. These innovative nanosystems have been described so far to block SARS-CoV-2 entry and replication in host cells and to reduce inflammation by cytokine capture, thus able to attenuate cytokine storm; and function as drug delivery nanosystems bearing high antiviral efficacy. Despite cell membrane-based nanoparticles have been widely explored toward several biomedical applications, the amount of data available on *in vivo* studies and regarding

in vivo safety is still scarce, particularly when considering potential anti-COVID-19 applications.

Nevertheless, as more delivery technologies are developed and translated, the pathway will open wider, and it is certain that membrane-cloaked nanosponges and nanodecoys will play a pivotal role in these future biomedical interventions and therapies. Due to the lockdown of many laboratories globally, and still to this day, progress into the use of these technologies is hindered, but it is being expected that further information, as to their potential as well as translation, will be realized for application in COVID-19 cases within the coming years.

4. Expert opinion

The COVID-19 pandemic has reshaped the present times calling for urgent and effective health and socio-sanitary responses to counteract this deadly outbreak. As the pandemic expands across the globe, enhanced research efforts across multidisciplinary fields are helping to rapidly gain more information on how the SARS-CoV-2 resulting in COVID-19

Table 2. Safety aspects of recently-developed cell membrane-based nanoparticles for COVID-19 management.

Carrier	Membrane	Size	Model test	Administration	Toxicity studies	Ref
Cell membrane nanovesicles	ACE-2-rich kidney-239 T cells and human macrophage (THP-1) cells	100 nm	*In vitro*: THP-1 cells, Vero-E6 cells *In vivo*: adult ICR mice treated with LPS *via* nebulization	Inhalation of HBSS containing 100, 200, and 400 µg of nanodecoys	-	[20]
Cell membrane nanovesicles	ACE-2-rich kidney-293 T cells	100 nm	*In vitro*: HK-2 cells, HEK-293 T-ACE2 cells *In vivo*: pseudovirion-based mouse infection model	Intravenous injection (2.5 mg mL^{-1}, 200 µL)	*In vitro*: HUVECs (100, 200, 300, 400, and 500 µg mL−1) • no impact on cell viability till 500 µg mL^{-1} ———————————— *In vivo*: intravenous injection of ACE2-NPs (25 mg kg^{-1}) • Rapid blood elimination (3 h); • Distribution lungs and liver; • No pathological changes.	[156]
Macrophage cell membrane nanovesicles (*Leukosomes*)	Mouse macrophage J774 cells	120 nm	*In vitro*: Balb/c mouse pulmonary vein endothelial cells *In vivo*: LPS-induced endotoxemia murine model	Intravenous injection (5 mg/Kg of dexamethasone)	-	[149]
Cell membrane-coated nanoparticles	human lung epithelial type II cells and human macrophage (THP-1) cells	100 nm	*In vitro*: virus-containing Vero E6 cells *In vivo*: C57BL/6NHsd mice	-	*In vivo*: Intratracheal administration (300 µg of membrane-coated nanoparticles) • Standard immune infiltration; • Absence of lesions and tissue damage; • Blood parameters normal.	[19]

Abbreviations: ACE-2: Acetilcolinesterase-2; THP-1: human monocytic cell line; HBSS: Hank's balanced salt solution.

works. Together with several approaches that have been underlined to better understand SARS-CoV-2 nature and infectivity, the current anti-COVID-19 therapeutic or prophylactic arsenal consists of small drugs, antibody-based compounds and vaccines.

Nano-based approaches constitute an effective and stimulating avenue to improve therapeutic effect and vaccination (prophylactic or therapeutic) potency of conventional strategies delineated for COVID-19 management, by improving pharmacokinetics, pharmacodynamics and safety. Multivalence benefits of nano-based delivery systems may augment neutralization potency as compared to monovalent binders, and improve vaccination as well. Further, unlike some biologics, biomimetic nanotechnologies can be manufactured at speed and scale – which constitutes an assertive goal when there is global demand. In this regard, more sophisticated and multifunctional strategies have been receiving increasing importance to maximize efficacy of COVID-19 prophylaxis and treatment, inspired by the biological interactions and cellular components. In this regard, cll membrane-based nanoparticles have received substantial attention recently as biofunctional, multivalent, tunable and biocompatible systems capable of acting as virus-neutralizing nanodecoys and with promising future potential for building refined nanovaccines, as well as refined drug delivery systems bearing ultra-targeting features for ideal site-specific action. When experimental or theoretical structural information is combined with biomimetic nanotechnologies, the timeline to develop first-line, *target-specific*

vaccines or therapeutics to emerging infectious disease is unmatched in potential.

Cell membrane-based nanoparticles strategies on fighting SARS-CoV-2 have relied so far on a nanodecoy-based approach in which the virus recognizes and binds to host cell membranes either coating a nanoparticle core or in the form of nanovesicles, followed by virus immobilization and/or neutralization and blocking its infectivity. These strategies are interesting once they function as multifunctional *cellular traps* by disguising nanoparticles as natural SARS-CoV-2 target cells thus mimicking its biological responses.

Despite cell membrane-based nanoparticles are known to preserve the biofunctionality of the parent cells, additional functionalization with targeting ligands may impart maximized biomimicry, and magnify their tissue targeting properties. Several methods have been described so far including the broadly used lipid insertion method, as well as metabolic engineering and genetic modification methods. Membrane hybridization by fusing to cell membranes form distinct cell sources can endow cell membrane coatings with additional functionalities and expand their versatility [106]. Targeting capabilities of the nanoparticles to various cellular and subcellular sites can be used to improve the overall therapeutic efficacy and reduce the chances of resistance development.

Mannose-targeted cell membrane coated nanoparticles, for instance, have been explored to target antigen presenting cells expressing mannose receptors. Besides enhancing antigen delivery to the lymph node by a nano-based

strategy, the additional functionalization with mannose increased dendritic cell targeting, contributing to maximized antigen processing, immune system activation and enhanced anticancer [107] or antiviral [140] performance. In the light of these reports, a similar technological strategy could possibly be carried out for SARS-CoV-2 long-term immunization (Figure 11).

According to the aforementioned, of considerable interest is the provenience of cell membranes and respective intrinsic cell membrane biofunctionalities transferred onto nanoparticle cores. While RBC membrane coatings have been the most studied so far, other membrane types endowed with lymph node targeting features hold particular relevance, as recently reported with dendritic cell membrane coatings able to strengthen cellular immunity for cancer immunotherapy purposes [161]. This strategy could potentially refine the scope of vaccines for COVID-19 prevention, which could pass by coating nanoparticle cores with dendritic cell membranes for achieving improved lymph node targeting and maximize interaction of antigen/toxoid with antigen-presenting cells (APCs).

Similar to outer membrane vesicles (OMVs) as natural bacteria's lipid bilayer-mimetics in terms of composition and function, perhaps an approach involving SARS-CoV-2 envelope-derived nanovesicles – virosomes – could be of interest to design multivalent antigen-displaying biomimetic nanoplatforms for COVID-19 vaccination and prophylaxis [162]. These nanovesicles may undergo successful surface functionalization through hybridization with bifunctional cell membrane vesicles to assemble hybrid membrane-based nanovesicles which can be used isolated or as a coat to nanoparticle cores.

As with all nanomedicines, however, caution must be paid when proceeding, as regulatory frameworks are not sufficiently adapted in order to define the long-term effects of nanoparticles, which hinders their ability to become rapidly translated to meet the demands of the pandemic. Key issues to be surpassed include the variability of the cell membrane sources, the amount of available material and complex characterization procedures which can be hopefully – and partially – overcome through simpler standardized production and characterization protocols together with the generation of more knowledge regarding *in vivo* stability and safety of these nanosystems. Moreover, the lack of *in vivo* studies so far calls for new data for better conclusions regarding the short- and long-term potential of cell membrane-based technology for COVID-19 management, and is a reflex of its novelty.

A key issue regarding cell membrane-based nanovaccines for COVID-19 prophylaxis is also the durability and adaptability toward potential viral mutations, as reported to other vaccines [163].

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Declaration of interest

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Du Toit A. Outbreak of a novel coronavirus. Nat Rev Microbiol. 2020;18(3):123-123.
2. Wu M, Mei T, Lin C, et al. Melanoma cell membrane biomimetic versatile CuS nanoprobes for homologous targeting photoacoustic imaging and photothermal chemotherapy. ACS Appl Mater Interfaces. 2020;12(14):16031–16039.
3. WHO. Coronavirus disease 2019 (COVID-19) Situation Report-68; 2020 [cited 2020 Apr 6]; Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200328-sitrep-68-covid-19.pdf?sfvrsn=384bc74c_2.
4. Callaway E. Time to use the p-word? Coronavirus enters dangerous new phase. Nature. 2020.
5. Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. ActaBiomed. 2020;91(1):157–160.
6. Chauhan G, Madou MJ, Kalra S, et al., Nanotechnology for COVID-19: therapeutics and vaccine research. ACS Nano. 14(7): 7760–7782. 2020.
   • A great review on nano-based approaches for COVID-19 therapeutics and vaccination.
7. Talebian S, Conde J. Why go NANO on COVID-19 Pandemic? Matter. 2020;3(3):598–601.
8. Jones GW, Monopoli MP, Campagnolo L, et al. No small matter: a perspective on nanotechnology-enabled solutions to fight COVID-19. Nanomed (Lond). 2020;15(24):2411–2427.
9. Tang Z, Kong N, Zhang X, et al. A materials-science perspective on tackling COVID-19. Nat Rev Mater. 2020;5(11):847–860.
10. Tang Z, Zhang X, Shu Y, et al. Insights from nanotechnology in COVID-19 treatment. Nano Today. 2021;36:101019.
11. Pushparajah D, Jimenez S, Wong S, et al. Advances in gene-based vaccine platforms to address the COVID-19 pandemic. Adv Drug Deliv Rev. 2021
12. Pilaquinga F, Morey J, Torres M, et al. Silver nanoparticles as a potential treatment against SARS-CoV-2: a review. WIREs Nanomed Nanobiotechnol. 2021;n/a(n/a):e1707.
13. Rana MM. Polymer-based nano-therapies to combat COVID-19 related respiratory injury: progress, prospects, and challenges. J Biomater Sci Polym Ed. 2021;1–33. doi:10.1080/09205063.2021.1909412
14. Abduljauwad SN, Habib T, Ahmed H-U-R. Nano-clays as potential pseudo-antibodies for COVID-19. Nanoscale Res Lett. 2020;15(1):173.
15. Serrano-Aroca Á, Takayama K, Tuñón-Molina A, et al. Carbon-based nanomaterials: promising antiviral agents to combat COVID-19 in

the microbial-resistant era. ACS Nano. 2021. doi:10.1021/acsnano.1c00629.

16. Kostarelos K. Nanoscale nights of COVID-19. Nat Nanotechnol. 2020;15(5):343–344.

17. Mitchell MJ, Billingsley M, Haley R, et al. Engineering precision nanoparticles for drug delivery. Nat Rev Drug Discov. 2020

18. Chung YH, Beiss V, Fiering SN, et al. COVID-19 vaccine frontrunners and their nanotechnology design. ACS Nano. 2020;14 (10):12522–12537.

19. Zhang Q, Honko A, Zhou J, et al., Cellular nanosponges inhibit SARS-CoV-2 infectivity. Nano Lett. 20(7): 5570–5574. 2020.
•• The first report of a cell membrane-based nanosystem for COVID-19 management.

20. Rao L, Xia S, Xu W, et al., Decoy nanoparticles protect against COVID-19 by concurrently adsorbing viruses and inflammatory cytokines. Proc Natl Acad Sci U S A. 2020;117(44):27141–27147.
•• Interesting report on cell membrane-based nanosystems for COVID-19 management.

21. Witika B, Makoni P, Mweetwa L, et al. Nano-biomimetic drug delivery vehicles: potential approaches for COVID-19 treatment. Molecules. 2020;25(24):5952.

22. Zhou P, Yang X-L, Wang X-G, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270–273.

23. Masters PS. The molecular biology of coronaviruses. Adv Virus Res. 2006;66:193–292.

24. Liu DX, Fung TS, Chong KK-L, et al. Accessory proteins of SARS-CoV and other coronaviruses. Antiviral Res. 2014;109:97–109.

25. Mortola E, Roy P. Efficient assembly and release of SARS coronavirus-like particles by a heterologous expression system. FEBS Lett. 2004;576(1–2):174–178.

26. Wang C, Zheng X, Gai W, et al. MERS-CoV virus-like particles produced in insect cells induce specific humoural and cellular immnity in rhesus macaques. Oncotarget. 2017;8(8):12686–12694.

27. De Haan CA, Rottier PJ. Molecular interactions in the assembly of coronaviruses. Adv Virus Res. 2005;64:165–230.

28. Tooze J, Tooze S, Warren G. Replication of coronavirus MHV-A59 in sac- cells: determination of the first site of budding of progeny virions. Eur J Cell Biol. 1984;33(2):281–293.

29. Neuman BW, Kiss G, Kunding AH, et al. A structural analysis of M protein in coronavirus assembly and morphology. J Struct Biol. 2011;174(1):11–22.

30. Bertram S, Glowacka I, Muller MA, et al. Cleavage and activation of the severe acute respiratory syndrome coronavirus spike protein by human airway trypsin-like protease. J Virol. 2011;85 (24):13363–13372.

31. Song W, Gui M, Wang X, et al. Cryo-EM structure of the SARS coronavirus spike glycoprotein in complex with its host cell receptor ACE2. PLoS Pathog. 2018;14(8):e1007236.

32. Li F, Li W, Farzan M, et al. Structure of SARS coronavirus spike receptor-binding domain complexed with receptor. Science. 2005;309(5742):1864–1868.

33. Yan R, Zhang Y, Li Y, et al. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. Science. 2020;367 (6485):1444–1448.

34. Zhang L, Lin D, Sun X, et al. Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved alpha-ketoamide inhibitors. Science. 2020;368(6489):409–412.

35. Wec AZ, Wrapp D, Herbert AS. Broad sarbecovirus neutralizing antibodies define a key site of vulnerability on the SARS-CoV-2 spike protein. bioRxiv. 2004:2020. 01.31.929695. doi:10.1101/2020.05.15.096511

36. Baez-Santos YM, St John SE, Mesecar AD. The SARS-coronavirus papain-like protease: structure, function and inhibition by designed antiviral compounds. Antiviral Res. 2015;115:21–38.

37. Iwata-Yoshikawa N, Okamura T, Shimizu Y, et al. TMPRSS2 contributes to virus spread and immunopathology in the airways of murine models after coronavirus infection. J Virol. 2019;93(6): e01815-18.

38. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181(2):271–280. e8.

39. Lung J, Lin Y-S, Yang Y-H, et al. The potential chemical structure of anti-SARS-CoV-2 RNA-dependent RNA polymerase. J Med Virol. 2020;92(6):693–697.

40. Du L, He Y, Zhou Y, et al. The spike protein of SARS-CoV–a target for vaccine and therapeutic development. Nat Rev Microbiol. 2009;7(3):226–236.

41. Shin MD, Shukla S, Chung YH, et al., COVID-19 vaccine development and a potential nanomaterial path forward. Nat Nanotechnol. 15(8): 646–655. 2020.
• Interesting review on nano-based approaches towards COVID-19 vaccination.

42. Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020;579(7798):265–269.

43. Chiappelli F, Khakshooy A, Greenberg G. CoViD-19 Immunopathology and Immunotherapy. Bioinformation. 2020;16 (3):219–222.

44. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan. China Lancet. 2020;395 (10223):497–506.

45. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020;8(4):420–422.

46. Li G, Fan Y, Lai Y, et al. Coronavirus infections and immune responses. J Med Virol. 2020;92(4):424–432.

47. De Wit E, Van Doremalen N, Falzarano D, et al. SARS and MERS: recent insights into emerging coronaviruses. Nat Rev Microbiol. 2016;14(8):523–534.

48. Tay MZ, Poh CM, Rénia L, et al. The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol. 2020;20 (6):363–374.

49. Tian X, Li C, Huang A, et al. Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-specific human monoclonal antibody. Emerg Microbes Infect. 2020;9(1):382–385.

50. Shin YW, Chang K-H, Hong G-W, et al. Selection of vaccinia virus-neutralizing antibody from a phage-display human-antibody library. J Microbiol Biotechnol. 2019;29(4):651–657.

51. Casadevall A, Pirofski LA, Racaniello V. The Ebola epidemic crystallizes the potential of passive antibody therapy for infectious diseases. PLoS Pathog. 2015;11(4):e1004717.

52. Reynolds A, Leake D, Boese Q, et al. Rational siRNA design for RNA interference. Nat Biotechnol. 2004;22(3):326–330.

53. Wu CJ, Huang H-W, Liu C-Y, et al. Inhibition of SARS-CoV replication by siRNA. Antiviral Res. 2005;65(1):45–48.

54. Barik S. RNAi applications to defeat respiratory viral infections, in RNA interference and viruses: current innovations and future trends. RNAi Interference and Viruses: Current Innovations and Future Trends. Caister Academic Press. 2010.

55. Tian D, Liu Y, Liang C, et al. An update review of emerging small-molecule therapeutic options for COVID-19. Biomed Pharmacother. 2021;137:111313.

56. Kobayashi K, Wei J, Iida R, et al. Surface engineering of nanoparticles for therapeutic applications. Polym J. 2014;46(8):460–468.

57. Petros RA, DeSimone JM. Strategies in the design of nanoparticles for therapeutic applications. Nat Rev Drug Discov. 2010;9 (8):615–627.

58. Zhou J, Krishnan N, Jiang Y, et al. Nanotechnology for virus treatment. Nano Today. 2021;36:101031.
• Great review on nano-based approaches for virus treatment.

59. Pereira-Silva M, Jarak I, Alvarez-Lorenzo C, et al. Micelleplexes as nucleic acid delivery systems for cancer-targeted therapies. J Control Release. 2020;323:442–462.

60. Santos AC, Pereira I, Pereira-Silva M, et al. Nanocarriers for resveratrol delivery: impact on stability and solubility concerns. Trends Food Sci Technol. 2019;91:483–497.

61. Luo C, Sun J, Sun B, et al. Prodrug-based nanoparticulate drug delivery strategies for cancer therapy. Trends Pharmacol Sci. 2014;35(11):556–566.

62. Machhi J, Shahjin F, Das S, et al. Nanocarrier vaccines for SARS-CoV-2. Adv Drug Deliv Rev. 2021

63. Park KS, Sun X, Aikins M, et al. Non-viral COVID-19 vaccine delivery systems. Adv Drug Deliv Rev. 2020;169:137–151.

64. Volpatti LR, Wallace R, Cao S, et al. Polymersomes decorated with SARS-CoV-2 spike protein receptor binding domain elicit robust humoral and cellular immunity. bioRxiv. 2021;438884

65. Meng Q-F, Tian R, Long H, et al. Capturing cytokines with advanced materials: a potential strategy to tackle COVID-19 cytokine storm. Adv Mater. 2021;n/a(n/a):2100012.

66. Loczechin A, Séron K, Barras A, et al. Functional carbon quantum dots as medical countermeasures to human coronavirus. ACS Appl Mater Interfaces. 2019;11(46):42964–42974.

67. Rao L, Tian R, Chen X. Cell-membrane-mimicking nanodecoys against infectious diseases. ACS Nano. 2020;14(3):2569–2574.
   • Great review on cell membrane-based approaches for virus treatment.

68. Lauster D, Klenk S, Ludwig K, et al. Phage capsid nanoparticles with defined ligand arrangement block influenza virus entry. Nat Nanotechnol. 2020;15(5):373–379.

69. Magee WE, Miller OV. Liposomes containing antiviral antibody can protect cells from virus infection. Nature. 1972;235(5337):339–341.

70. Rao L, Wang W, Meng Q-F, et al. A biomimetic nanodecoy traps zika virus to prevent viral infection and fetal microcephaly development. Nano Lett. 2019;19(4):2215–2222.

71. Valcourt DM, Harris J, Riley RS, et al. Advances in targeted nanotherapeutics: from bioconjugation to biomimicry. Nano Res. 2018;11(10):4999–5016.

72. Tan T, Wang Y, Wang J, et al. Targeting peptide-decorated biomimetic lipoproteins improve deep penetration and cancer cells accessibility in solid tumor. Acta Pharm Sin B. 2020;10(3):529–545.

73. Tan T, Hu H, Wang H, et al. Bioinspired lipoproteins-mediated photothermia remodels tumor stroma to improve cancer cell accessibility of second nanoparticles. Nat Commun. 2019;10(1):3322.

74. Yong T, Zhang X, Bie N, et al. Tumor exosome-based nanoparticles are efficient drug carriers for chemotherapy. Nat Commun. 2019;10(1):3838.

75. Lu Q, Yi M, Zhang M, et al. Folate-conjugated cell membrane mimetic polymer micelles for tumor-cell-targeted delivery of doxorubicin. Langmuir. 2019;35(2):504–512.

76. Fang RH, Kroll AV, Gao W, et al., Cell membrane coating nanotechnology. Adv Mater. 30(23): e1706759. 2018.
   • Great review on cell membrane-based nanosystems.

77. Sabu C, Rejo C, Kotta S, et al. Bioinspired and biomimetic systems for advanced drug and gene delivery. J Control Release. 2018;287:142–155.

78. Pinky, Gupta S, Krishnakumar V, et al. Mesenchymal stem cell derived exosomes: a nano platform for therapeutics and drug delivery in combating COVID-19. Stem Cell Rev Rep. 2021;17(1):33–43.

79. Topol EJ. Messenger RNA vaccines against SARS-CoV-2. Cell. 2021;184(6):1401.

80. Khurana A, Allawadhi P, Khurana I, et al. Role of nanotechnology behind the success of mRNA vaccines for COVID-19. Nano Today. 2021;38:101142.

81. Schoenmaker L, Witzigmann D, Kulkarni JA, et al. mRNA-lipid nanoparticle COVID-19 vaccines: structure and stability. Int J Pharm. 2021;601:120586.

82. Park KS, Bazzill JD, Son S, et al. Lipid-based vaccine nanoparticles for induction of humoral immune responses against HIV-1 and SARS-CoV-2. J Control Release. 2021;330:529–539.

83. He L, Lin X, Wang Y, et al. Single-component, self-assembling, protein nanoparticles presenting the receptor binding domain and stabilized spike as SARS-CoV-2 vaccine candidates. Sci Adv. 2021;7(12)

84. Hassan AO, Feldmann F, Zhao H, et al. A single intranasal dose of chimpanzee adenovirus-vectored vaccine protects against SARS-CoV-2 infection in rhesus macaques. bioRxiv. 2021. 428251

85. Kim E, Weisel FJ, Balmert SC, et al. A single subcutaneous or intranasal immunization with adenovirus-based SARS-CoV-2 vaccine induces robust humoral and cellular immune responses in mice. Eur J Immunol. 2021. DOI:10.1002/eji.202149167.

86. Feng L, Wang Q, Shan C, et al. An adenovirus-vectored COVID-19 vaccine confers protection from SARS-COV-2 challenge in rhesus macaques. Nat Commun. 2020;11(1):4207.

87. Huang L, Rong Y, Pan Q, et al. SARS-CoV-2 vaccine research and development: conventional vaccines and biomimetic nanotechnology strategies. Asian J Pharm Sci. 2020. DOI:10.1016/j.ajps.2020.08.001.

88. Jia Q, Bielefeldt-Ohmann H, Maison RM, et al. Replicating bacterium-vectored vaccine expressing SARS-CoV-2 membrane and nucleocapsid proteins protects against severe COVID-19-like disease in hamsters. NPJ Vaccines. 2021;6(1):47.

89. Zheng B, Peng W, Guo M, et al. Inhalable nanovaccine with biomimetic coronavirus structure to trigger mucosal immunity of respiratory tract against COVID-19. Chem Eng J. 2021;418:129392.

90. Rogers TF, Zhao F, Huang D, et al. Isolation of potent SARS-CoV-2 neutralizing antibodies and protection from disease in a small animal model. Science. 2020;369(6506):956–963.

91. Li W, Drelich A, Martinez D, et al. Potent neutralization of SARS-CoV-2 in vitro and in an animal model by a human monoclonal antibody. bioRxiv. 2020:093088

92. Cao L, Goreshnik I, Coventry B, et al. De novo design of picomolar SARS-CoV-2 miniprotein inhibitors. Science. 2020;370(6515):426–431.

93. Panda SK, Sen Gupta PS, Biswal S, et al. ACE-2-derived biomimetic peptides for the inhibition of spike protein of SARS-CoV-2. J Proteome Res. 2021;20(2):1296–1303.

94. Hanke L, Vidakovics Perez L, Sheward DJ, et al. An alpaca nanobody neutralizes SARS-CoV-2 by blocking receptor interaction. Nat Commun. 2020;11(1):4420.

95. Kwon PS, Oh H, Kwon S-J, et al. Sulfated polysaccharides effectively inhibit SARS-CoV-2 in vitro. Cell Discov. 2020;6(1):50.

96. Kim J, Mukherjee A, Nelson D, et al. Rapid generation of circulating and mucosal decoy ACE2 using mRNA nanotherapeutics for the potential treatment of SARS-CoV-2. bioRxiv. 2020:205583

97. Xuan M, Shao J, Li J. Cell membrane-covered nanoparticles as biomaterials. Natl Sci Rev. 2019;6(3):551–561.

98. Zhang D, Ye Z, Wei L, et al. Cell membrane-coated porphyrin metal–organic frameworks for cancer cell targeting and O2-evolving photodynamic therapy. ACS Appl Mater Interfaces. 2019;11(43):39594–39602.

99. Pereira-Silva M, Santos A, Conde J, et al. Biomimetic cancer cell membrane-coated nanosystems as next-generation cancer therapies. Expert Opin Drug Deliv. 2020;17(11):1515–1518.

100. Gan J, Du G, He C, et al. Tumor cell membrane enveloped aluminum phosphate nanoparticles for enhanced cancer vaccination. J Control Release. 2020;326:297–309.

101. Liang H, Huang K, Su T, et al. Mesenchymal stem cell/red blood cell-inspired nanoparticle therapy in mice with carbon tetrachloride-induced acute liver failure. ACS Nano. 2018;12(7):6536–6544.

102. Fu Y, Liu W, Wang L-Y, et al. Erythrocyte-membrane-camouflaged nanoplatform for intravenous glucose-responsive insulin delivery. Adv Funct Mater. 2018;28(41):1802250.

103. Zhang Q, Dehaini D, Zhang Y, et al. Neutrophil membrane-coated nanoparticles inhibit synovial inflammation and alleviate joint damage in inflammatory arthritis. Nat Nanotechnol. 2018;13(12):1182–1190.

104. Wu G, Wei W, Zhang J, et al. A self-driven bioinspired nanovehicle by leukocyte membrane-hitchhiking for early detection and treatment of atherosclerosis. Biomaterials. 2020;250:119963.

105. Wei X, Ying M, Dehaini D, et al. Nanoparticle functionalization with platelet membrane enables multifactored biological targeting and detection of atherosclerosis. ACS Nano. 2018;12(1):109–116.

106. Ai X, Wang S, Duan Y, et al. Emerging approaches to functionalizing cell membrane-coated nanoparticles. Biochemistry. 2020;60(13):941–955.

107. Guo Y, Wang D, Song Q, et al. Erythrocyte membrane-enveloped polymeric nanoparticles as nanovaccine for induction of antitumor immunity against melanoma. ACS Nano. 2015;9 (7):6918–6933.

108. Li M, Fang H, Liu Q, et al. Red blood cell membrane-coated upconversion nanoparticles for pretargeted multimodality imaging of triple-negative breast cancer. Biomater Sci. 2020;8(7):1802–1814.

109. Meng QF, Cheng Y-X, Huang Q, et al. Biomimetic immunomagnetic nanoparticles with minimal nonspecific biomolecule adsorption for enhanced isolation of circulating tumor cells. ACS Appl Mater Interfaces. 2019;11(32):28732–28739.

110. Ou W, Byeon JH, Soe ZC, et al. Tailored black phosphorus for erythrocyte membrane nanocloaking with interleukin-1αsiRNA and paclitaxel for targeted, durable, and mild combination cancer therapy. Theranostics. 2019;9(23):6780–6796.

111. Xiong K, Wei W, Jin Y, et al. Biomimetic immuno-magnetosomes for high-performance enrichment of circulating tumor cells. Adv Mater. 2016;28(36):7929–7935.

112. Poudel K, Banstola A, Gautam M, et al. Macrophage-membrane-camouflaged disintegrable and excretable nanoconstruct for deep tumor penetration. ACS Appl Mater Interfaces. 2020;12 (51):56767–56781.

113. Hu Q, Sun W, Qian C, et al. Anticancer platelet-mimicking nanovehicles. Adv Mater. 2015;27(44):7043–7050.

114. Jing L, Qu H, Wu D, et al. Platelet-camouflaged nanococktail: simultaneous inhibition of drug-resistant tumor growth and metastasis via a cancer cells and tumor vasculature dual-targeting strategy. Theranostics. 2018;8(10):2683–2695.

115. Lin Y, Zhong Y, Chen Y, et al. Ligand-modified erythrocyte membrane-cloaked metal-organic framework nanoparticles for targeted antitumor therapy. Mol Pharm. 2020;17(9):3328–3341.

116. Zhou H, Fan Z, Lemons PK, et al. A facile approach to functionalize cell membrane-coated nanoparticles. Theranostics. 2016;6 (7):1012–1022.

117. Han Y, Gao C, Wang H, et al. Macrophage membrane-coated nanocarriers Co-Modified by RVG29 and TPP improve brain neuronal mitochondria-targeting and therapeutic efficacy in Alzheimer's disease mice. Bioact Mater. 2021;6(2):529–542.

118. Wang T, Luo Y, Lv H, et al. Aptamer-based erythrocyte-derived mimic vesicles loaded with siRNA and doxorubicin for the targeted treatment of multidrug-resistant tumors. ACS Appl Mater Interfaces. 2019;11(49):45455–45466.

119. Chen HY, Deng J, Wang Y, et al. Hybrid cell membrane-coated nanoparticles: a multifunctional biomimetic platform for cancer diagnosis and therapy. Acta Biomater. 2020;112:1–13.

120. Molinaro R, Corbo C, Martinez JO, et al. Biomimetic proteolipid vesicles for targeting inflamed tissues. Nat Mater. 2016;15 (9):1037–1046.

121. Zinger A, Soriano S, Baudo G, et al. Biomimetic nanoparticles as a theranostic tool for traumatic brain injury. Adv Funct Mater. 2021; n/a(n/a):2100722.

122. Jiang L, Zhu Y, Luan P, et al. Bacteria -anchoring hybrid liposome capable of absorbing multiple toxins for antivirulence therapy of escherichia coli infection. ACS Nano. 2021;15(3):4173–4185.

123. Sato YT, Umezaki K, Sawada S, et al. Engineering hybrid exosomes by membrane fusion with liposomes. Sci Rep. 2016;6(1):21933.

124. Angsantikul P, Fang RH, Zhang L. Toxoid vaccination against bacterial infection using cell membrane-coated nanoparticles. Bioconjug Chem. 2018;29(3):604–612.

125. Fang RH, Luk BT, Hu C-MJ, et al. Engineered nanoparticles mimicking cell membranes for toxin neutralization. Adv Drug Deliv Rev. 2015;90:69–80.

126. Hu CM, Fang RH, Copp J, et al. A biomimetic nanosponge that absorbs pore-forming toxins. Nat Nanotechnol. 2013;8(5):336–340.

127. Zhang Y, Chen Y, Lo C, et al. Inhibition of pathogen adhesion by bacterial outer membrane-coated nanoparticles. Angew Chem Int Ed Engl. 2019;58(33):11404–11408.

128. Wang F, Fang RH, Luk BT, et al. Nanoparticle-based antivirulence vaccine for the management of methicillin-resistant staphylococcus aureus skin infection. Adv Funct Mater. 2016;26(10):1628–1635.

129. Wei X, Gao J, Wang F, et al. In situ capture of bacterial toxins for antivirulence vaccination. Adv Mater. 2017;29(33).

130. Hu CM, Fang RH, Luk BT, et al. Nanoparticle-detained toxins for safe and effective vaccination. Nat Nanotechnol. 2013;8(12):933–938.

131. Li M, Zhou H, Yang C, et al. Bacterial outer membrane vesicles as a platform for biomedical applications: an update. J Control Release. 2020;323:253–268.

132. Gao F, Xu L, Yang B, et al. Kill the real with the fake: eliminate intracellular staphylococcus aureus using nanoparticle coated with its extracellular vesicle membrane as active-targeting drug carrier. ACS Infect Dis. 2019;5(2):218–227.

133. Li Y, Liu Y, Ren Y, et al. Coating of a novel antimicrobial nanoparticle with a macrophage membrane for the selective entry into infected macrophages and killing of intracellular staphylococci. Adv Funct Mater. 2020;30(48):2004942.

134. Wei X, Ran D, Campeau A, et al. Multiantigenic nanotoxoids for antivirulence vaccination against antibiotic-resistant gram-negative bacteria. Nano Lett. 2019;19(7):4760–4769.

135. Shi M, Shen K, Yang B, et al. An electroporation strategy to synthesize the membrane-coated nanoparticles for enhanced anti-inflammation therapy in bone infection. Theranostics. 2021;11(5):2349–2363.

136. Thamphiwatana S, Angsantikul P, Escajadillo T, et al. Macrophage-like nanoparticles concurrently absorbing endotoxins and proinflammatory cytokines for sepsis management. Proc Natl Acad Sci U S A. 2017;114(43):11488–11493.

137. Wei X, Zhang G, Ran D, et al. T-cell-mimicking nanoparticles can neutralize HIV infectivity. Adv Mater. 2018;30(45):e1802233.

138. Liu X, Yuan L, Zhang L, et al. Bioinspired Artificial nanodecoys for hepatitis B virus. Angew Chem Int Ed Engl. 2018;57 (38):12499–12503.

139. Zhang G, Campbell G, Zhang Q, et al. CD4(+) T cell-mimicking nanoparticles broadly neutralize HIV-1 and suppress viral replication through autophagy. mBio. 2020;11(5):e00903-20.

140. Zhang C, Zhang P-Q, Guo S, et al. Application of biomimetic cell-derived nanoparticles with mannose modification as a novel vaccine delivery platform against teleost fish viral disease. ACS Biomater Sci Eng. 2020;6(12):6770–6777.

141. Yan H, Shao D, Lao Y-H, et al. Engineering cell membrane-based nanotherapeutics to target inflammation. Adv Sci. 2019;6 (15):1900605.

142. Harris JC, Scully MA, Day ES. Cancer cell membrane-coated nanoparticles for cancer management. Cancers (Basel). 2019;11(12)

143. Pereira-Silva M, Santos AC, Conde J, et al. Biomimetic cancer cell membrane-coated nanosystems as next-generation cancer therapies. Expert Opin Drug Deliv. 2020;17(11):1515–1518.

144. Cao H, Dan Z, He X, et al. Liposomes coated with isolated macrophage membrane can target lung metastasis of breast cancer. ACS Nano. 2016;10(8):7738–7748.

145. Pitchaimani A, Nguyen TDT, Aryal S. Natural killer cell membrane infused biomimetic liposomes for targeted tumor therapy. Biomaterials. 2018;160:124–137.

146. Ma W, Zhu D, Li J, et al. Coating biomimetic nanoparticles with chimeric antigen receptor T cell-membrane provides high specificity for hepatocellular carcinoma photothermal therapy treatment. Theranostics. 2020;10(3):1281–1295.

147. Oroojalian F, Beygi M, Baradaran B, et al. Immune cell membrane-coated biomimetic nanoparticles for targeted cancer therapy. Small. 2021;17(12):e2006484.

148. Corbo C, Parodi A, Evangelopoulos M, et al. Proteomic profiling of a biomimetic drug delivery platform. Curr Drug Targets. 2015;16 (13):1540–1547.

149. Molinaro R, Pastò A, Corbo C, et al. Macrophage-derived nanovesicles exert intrinsic anti-inflammatory properties and prolong survival in sepsis through a direct interaction with macrophages. Nanoscale. 2019;11(28):13576–13586.

150. Wang K, Lei Y, Xia D, et al. Neutrophil membranes coated, antibiotic agent loaded nanoparticles targeting to the lung inflammation. Colloids Surf B Biointerfaces. 2020;188:110755.

151. Xia Q, Zhang Y, Li Z, et al. Red blood cell membrane-camouflaged nanoparticles: a novel drug delivery system for antitumor application. Acta Pharm Sin B. 2019;9(4):675–689.

152. Xiao P, Wang J, Zhao Z, et al. Engineering nanoscale artificial antigen-presenting cells by metabolic dendritic cell labeling to potentiate cancer immunotherapy. Nano Lett. 2021;21(5):2094–2103.

153. Kunde SS, Wairkar S. Platelet membrane camouflaged nanoparticles: biomimetic architecture for targeted therapy. Int J Pharm. 2021;598:120395.

154. Bahmani B, Gong H, Luk BT, et al. Intratumoral immunotherapy using platelet-cloaked nanoparticles enhances antitumor immunity in solid tumors. Nat Commun. 2021;12(1):1999.

155. Molinaro R, Pasto A, Taraballi F, et al. Biomimetic nanoparticles potentiate the anti-inflammatory properties of dexamethasone and reduce the cytokine storm syndrome: an additional weapon against COVID-19?. Nanomaterials (Basel). 2020;10(11):2301.

156. Wang C, Wang S, Chen Y, et al. Membrane nanoparticles derived from ACE2-rich cells block SARS-CoV-2 infection. ACS Nano. 2021. doi:10.1021/acsnano.0c06836.

157. Wang C, Wang S, Chen Y, et al. Membrane nanoparticles derived from ACE2-rich cells block SARS-CoV-2 infection. bioRxiv. 2020;247338

158. Lei C, Qian K, Li T, et al. Neutralization of SARS-CoV-2 spike pseudo-typed virus by recombinant ACE2-Ig. Nat Commun. 2020;11(1):2070.

159. Richtering W, Alberg I, Zentel R. Nanoparticles in the biological context: surface morphology and protein corona formation. Small. 2020;16(39):e2002162.

160. Mosselhy DA, Virtanen J, Kant R, et al. COVID-19 pandemic: what about the safety of anti-coronavirus nanoparticles? Nanomaterials. 2021;11(3):796.

161. Yang X, Yu T, Zeng Y, et al. pH-Responsive biomimetic polymeric micelles as lymph node-targeting vaccines for enhanced antitumor immune responses. Biomacromolecules. 2020;21(7):2818–2828.

162. Wang R, Yan H, Yu A, et al. Cancer targeted biomimetic drug delivery system. J Drug Delivery Sci Technol. 2021;102530. doi:10.1016/j.jddst.2021.102530

163. Nel AE, Miller JF. Nano-enabled COVID-19 vaccines: meeting the challenges of durable antibody plus cellular immunity and immune escape. ACS Nano. 2021. doi:10.1021/acsnano.1c01845