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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 2.8 million deaths worldwide. Several health-related strategies have been successfully developed to contain the rapidly-spreading virus across the globe, towards 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, which mobilized huge efforts to block disease progression and overcome the shortage of effective measures available at this point.

Areas covered: This perspective covers the breakthrough of multifunctional and 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, towards 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.

Keywords: nanoparticles; biomimetic; COVID-19; SARS-CoV-2; cell membrane-coated; infection; bacteria; virus.

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 are able to reproduce 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.

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 130 million cases are reported as of April 3, 2021, with above 2.8 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 2020 and beyond is to develop and come up with 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 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 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 bioderived or bioinspired components can be leveraged by unleashing the potential of cell membranes as complex, fully-replicable and multivalent biological components for coating nanoparticle cores, by assembling cutting-edge cell membrane-coated nanoparticles, or by functioning as cell-derived nanovesicles devoid of nanoparticle core. 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. These cell membrane-based nanotechnologies 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 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 on cell membrane bioengineering and surface functionalization towards 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 **(Fig. 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 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 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 turn, 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 is mainly employing 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 targeting, and weakening the resistance development mechanisms [56, 57]. Nanocarrier platforms are able to deliver a range of small molecules, biologicals (RNA interference, antibodies, proteins, peptides, among others), 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 antiviral molecules can also prevent the viral rebound and improve the overall therapeutic management. In addition 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 towards virus immobilization and cytokine neutralization [58] **(Fig. 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 challenge associated with the development of COVID-19 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 to 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 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 bioinspired nanosystems possess a great potential both for therapeutic delivery and as a vaccine carrier [66-70]. Furthermore, the therapeutic or vaccine efficacy may also be benefited by their nature-inspired design and an intrinsic activity possessed by 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 towards 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 pose as safe and fully-biocompatible nanovesicles towards 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 immune cells and enabling recognition and immune response from the immune system [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 (Fig. 3-A) [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 (Fig. 3-B, C). The nanovaccine was able to induce significative 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 (Fig. 3-D, E, F, G), thus promoting humoral activation and enhanced secretion of neutralizing antibodies, as well as B cell activation in the spleen (Fig. 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 (Fig.3-J, K, L, 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 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 nanocarriers, of which nanoparticles have been explored the most, and the multivalent interactions performed by cells in a biological environment, cell membrane-coated nanocarriers 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 wrapped around nanocarrier cores by multiple possible combinations, resulting in cell membrane-coated nanoparticles, or 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 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 biofunction 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 (**Fig. 5**) [106].

So far, several classes of ligands from sugars (Fig. 5-1), aptamers (Fig. 5-2), peptides (Fig. 5-3), cell-penetrating moieties (Fig. 5-4), proteins (including enzymes and antibodies) (Fig. 5-5) and small molecular weight molecules (Fig. 5-6) have been actively explored for surface functionalization of cell membrane-based nanoparticles, including cell membrane-coated ones [107-114] **(Table 1)**.

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	Cancer	[116]

			the NPs		
Magnetic nanoclusters	Leukocyte	apolipoprotein A-I mimetic 4F 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.

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 (Fig. 5-7); by (2) producing liposomes enriched with membrane-extracted constituents (Fig. 5-8); or by (3) fusing liposome lipid bilayer with cell membrane nanovesicles (Fig. 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 now find 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.

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, such nanocarriers 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 membrane binding sites 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* (Fig. 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 – , adhesins –

allowing binding to target cells – and 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 nanocarriers 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 (Fig. 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 was able to improve 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 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 (Fig. 6-D) [134]. These nanotoxoids were able to 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] (Fig. 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 (Fig. 7-A) [137], Zika virus (Fig. 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 (Fig. 7-C) with prophylactic effects (Fig. 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 towards 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 biointerfacing properties. For 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 (Fig. 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] (Fig. 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 (Fig. 8-C) ; (4) platelets, owing to their mechanical flexibility and innate tropism to inflamed endothelium, injured tissue and vasculature (Fig. 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 *ghosts.* 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 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, 293T genetically-engineered human embryonic kidney 293T 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 (Fig. 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 (Fig. 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-293T 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 (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 immunological function [19] **(Fig. 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 intratracheal 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-239T cells overexpressing human ACE2 (HEK-293T-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 (Fig. 11-A). However, other strategies could be possible undertaken towards 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 (Fig. 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 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 Fig. 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 **Fig. 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).

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-239T cells and	100 nm	*In vitro:* THP-1 cells, Vero-E6 cells *In vivo*:	Inhalation of HBSS containing 100, 200, and 400 μg of	-	[20]

	human macrophage (THP-1) cells		adult ICR mice treated with LPS *via* nebulization	nanodecoys		
Cell membrane nanovesicles	ACE-2-rich kidney-293T cells	100 nm	*In vitro*: HK-2 cells, HEK-293T-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 (3h); • Distribution lungs and liver; • No pathological changes.	[156]
Liposomes enriched in cell membrane content (*Leukoso*	Mouse macrophage J774 cells	120 nm	*In vitro:* Balb/c mouse pulmonary vein endothelial cells	Intravenous injection (5 mg/Kg of dexamethasone)	-	[149]

mes)			*In vivo:* LPS-induced endotoxemia murine model			
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/6 NHsd 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.

While the biomimetic facet of cell membrane-based nanosystems are known to improve their biocompatibility towards 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 towards their relatively safe profile [19, 156], however the *in vitro* and *in vivo* models as wels as the experience settings are distinct, which can difficult comparability of results. Undoubtedly, more data specifically concerning

to 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-coated nanoparticles a potentially real frontrunner in the development of new therapeutic and vaccination/prophylaxis approaches towards 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 towards 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 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. 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, of which cell 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, and 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.

Multivalence benefits of nanotechnology-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.

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 nanocarrier-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 (Fig- 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 coating 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 towards potential viral mutations, as reported to other vaccines [163].

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Declaration of interests

NF Steinmetz is a co-founder of Mosaic ImmunoEngineering Inc. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Figure captions

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

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.

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.

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.

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).

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.

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.

Figure 8. Distinct cell types as cell membrane sources towards 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 with bearing the same cell attributes.

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 293T/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.

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).

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.