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Nanosponges: An overlooked promising strategy to combat SARS-CoV-2

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Among explored nanomaterials, nanosponge-based systems have exhibited inhibitory effects for the biological neutralization of, and antiviral delivery against, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). More studies could pave the path for clarification of their biological neutralization mechanisms as well as the assessment of their long-term biocompatibility and biosafety issues before clinical translational studies. In this review, we discuss recent advances pertaining to antiviral delivery and inhibitory effects of nanosponges against SARS-CoV-2, focusing on important challenges and opportunities. Finally, as promising approaches for recapitulating the complex structure of different organs/tissues of the body, we discuss the use of 3D *in vitro* models to investigate the mechanism of SARS-CoV-2 infection and to find therapeutic targets to better manage and eradicate coronavirus 2019 (COVID-19).

Keywords: SARS-CoV-2; COVID-19; Nanosponges; Biological neutralization; Antiviral delivery; Viral inactivation

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Introduction

Various antivirals and immune modulatory agents as well as potential inhibitors, either organic or inorganic materials, have been proposed against SARS-CoV-2.[1–3] Recent advances in nanoscience and nanotechnology have revolutionized various fields of research, particularly medicine.[4–8] The application of nanotechnology in medicine has led to the emergence of a new realm of research, known as nanomedicine, opening new horizons and applications.[9] For instance, nanomedicine has shown significant achievements in, and potential for, the management of SARS-CoV-2, which causes COVID-19, including, but not limited to, the design of innovative drug and delivery systems with high efficiency and efficacy, the design of smart nanobiosensors for early detection of the virus, production of high-efficiency personal protective equipment, and so on.[10,11] However, comprehensive clinical trials and clinical translational studies are needed to evaluate the efficacy of these approaches. Innovative pharmacological formulations are under development, and elaborative works have focused on the preparation of drugs and inhibitory agents for combating viral infections and modulating efficient antiviral immunity[12,13]; pharmacological agents have been studied for homing in on the different stages of the life cycle of SARS-CoV-2. One of the main challenges to developing drugs and potential inhibitory agents with completed preclinical/clinical assessments is the time required for exhaustive clinical trials.[14] In addition, the impact of viral mutations can have a significant effect on both the resistance and susceptibility of the virus to inhibitory agents as well as their pathogenicity; the ensuing complications ought to be considered when designing advanced nanoscale materials against SARS-CoV-2.[15,16] Thus, there is an urgent need to fast-track efficient inhibitory agents, such as nanodevices and nanoformulations, with high safety to control and eliminate this virus.[10,17–20] Some of the targets comprise the RNA-dependent polymerases, hemagglutinin esterase, spike (S) and envelop (E) proteins, and viral proteases (e.g., 3-chymotrypsin-like protease), which have been explored as inhibitory agents, whereas other candidates are aimed at targeting the angiotensin-converting enzyme 2 (ACE2) receptor to treat COVID-19.[21–23] In addition, various nanovaccines, including mRNA–lipid nanoparticle-based vaccines, have been developed and are in clinical trials for further evaluations against a variety of viruses, including Zika, influenza, and rabies.[24] However, the higher costs associated with maintaining, manufacturing, and transporting thermolabile molecules (such as RNA, or lipids) might be prohibitive to massive vaccination of the developing world.[25]

Limitations to the efficacy and delivery of drugs, and their associated adverse effects, have led researchers to move toward nanocarriers with unique properties, optimal effectiveness, specificity, and fewer adverse effects; an effective solution is to deploy nanostructures to effectively transport antiviral drugs or other formulations.[26,27] In this context, nanosponges have shown several advantages, such as biocompatibility, porosity, biomimetic features, sustained release behavior, and therapeutic activity (e.g., antimicrobial action against pathogenic bacteria), which make them suitable candidates for improving the bioavailability, stability, and solubility of therapeutic agents or drugs to provide the desired pharmacokinetics (PK) effects[28–30]; nanosponges can generate a variety of complexes with hydrophilic or lipophilic molecules, improving their transferring and protecting them from degradability.[31–33] For instance, β-cyclodextrin nanosponge-based delivery systems[34] were designed to formulate lipophilic drugs (e.g., dexibuprofen), offering an alternative strategy for enhancing the solubility of these drugs and improving their oral administration.[35] Versatile applications of nanosponges in different fields of biomedical, pharmaceuticals, environmental, catalysis, and sensors, along with their advantages in each field, are discussed in detail elsewhere [36–39]; in this review, we focus mainly on the delivery of drugs and antiviral agents using nanosponges.

Fig. 1 shows a schematic of the structure of cyclodextrin-based nanosponges. Nanosponges with high drug-loading or release behavior could improve the solubility of docetaxel in aqueous media, offering a promising strategy for the efficient and specific delivery of drugs, proteins/peptides, genetic materials, antineoplastic agents, and so on.[40–42] Lapatinib nanosponges were formulated to enhance solubility and bioavailability parameters and reduce the oral dose required for the anticancer drug lapa-

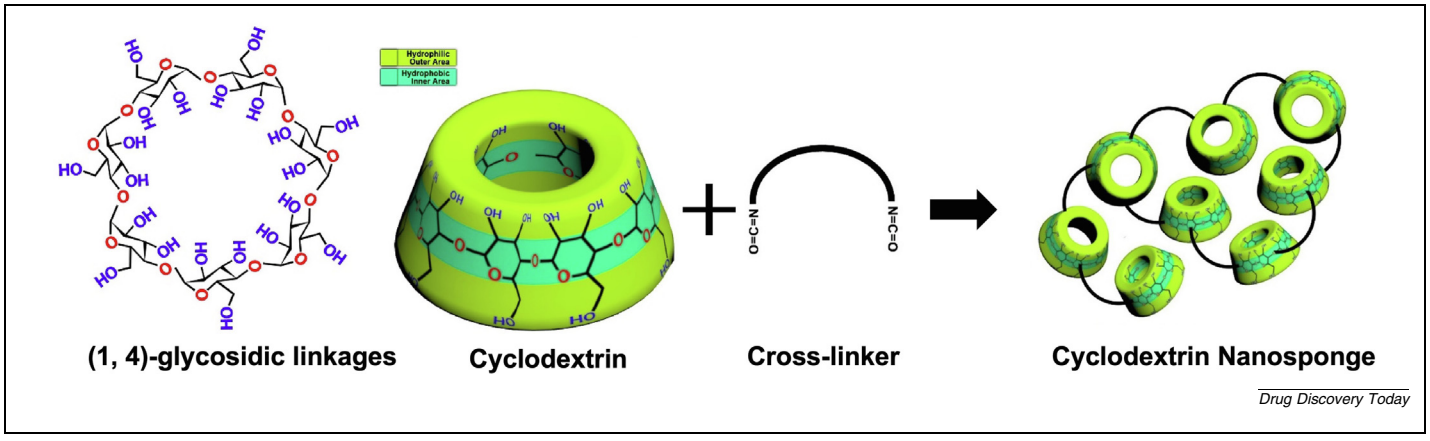


FIGURE 1
Schematic of the structure of cyclodextrin-based nanosponges. Adapted, with permission, from [31].

tinib.[43] Extensive research has been conducted to improve the selectivity, solubility, and targeting properties of anticancer drugs/agents. Palminteri *et al.*[44] reported an innovatively designed smart drug delivery system based on cyclodextrin nanosponges for glutathione-mediated delivery of resveratrol to the targeted cancer cells. In addition, the oral bioavailability of avanafil and dapoxetine could be improved by cyclodextrin nanosponges.[45] By contrast, recent advances in the preparation of bioinspired self-catabolic DNAzyme nanosponges for programmable and controllable drug delivery and efficient gene-silencing activity provide promising opportunities for the development of smart gene therapeutic- and personalized nanomedicine-based strategies.[46,47].

One of the efficient ways to target viruses is via biological neutralization using biofunctionalized nanostructures to attach to harmful molecules/agents or pathogenic viruses to block their activities, thus preventing their replication. By developing efficient nano-scaled therapeutics with attractive advantages, such as low toxicity, targeted/sustained release behavior, good biosafety, and improved long-term biocompatibility, nanosponges can be suitable options for improving immunizations (cellular ad humoral immune responses) besides the specific/controlled delivery properties providing personalized therapeutics potentials.[48–50] Herein, recent advancements pertaining to the delivery of antiviral agents as well as the inhibitory effects of nanosponge-based systems as an overlooked but promising nano-based strategy against SARS-CoV-2 are deliberated, focusing on important challenges and future perspectives.

Nanosponges against SARS-CoV-2

Nanosponges exist in both crystalline and paracrystalline forms, which are determined based mainly on the reaction/synthesis and processing conditions; crystallization of nanosponges can help in controlling and determining their drug-loading capacity.[38] Different approaches have been explored for synthesizing nanosponge-based systems, including interfacial phenomena, hot melting processes, hyper-crosslinked cyclodextrin, ultrasound-assisted synthesis, solvent condensation, microwave-assisted synthesis, interfacial condensation, mechanochemical synthesis, chain-growth polycondensation, and emulsion solvent evaporation [33]. A full description of each method can be found elsewhere.[36,37] In contrast to extensive research on the biological neutralization potential of cellular nanosponges, there are only limited investigations pertaining to their applicability as nanoplatforms for antiviral delivery (Fig. 2).[26,51] Cyclodextrin-based nanosponges (~400 nm) bearing carboxylic groups within their structures have been evaluated for the delivery of acyclovir and demonstrated high loading capacity

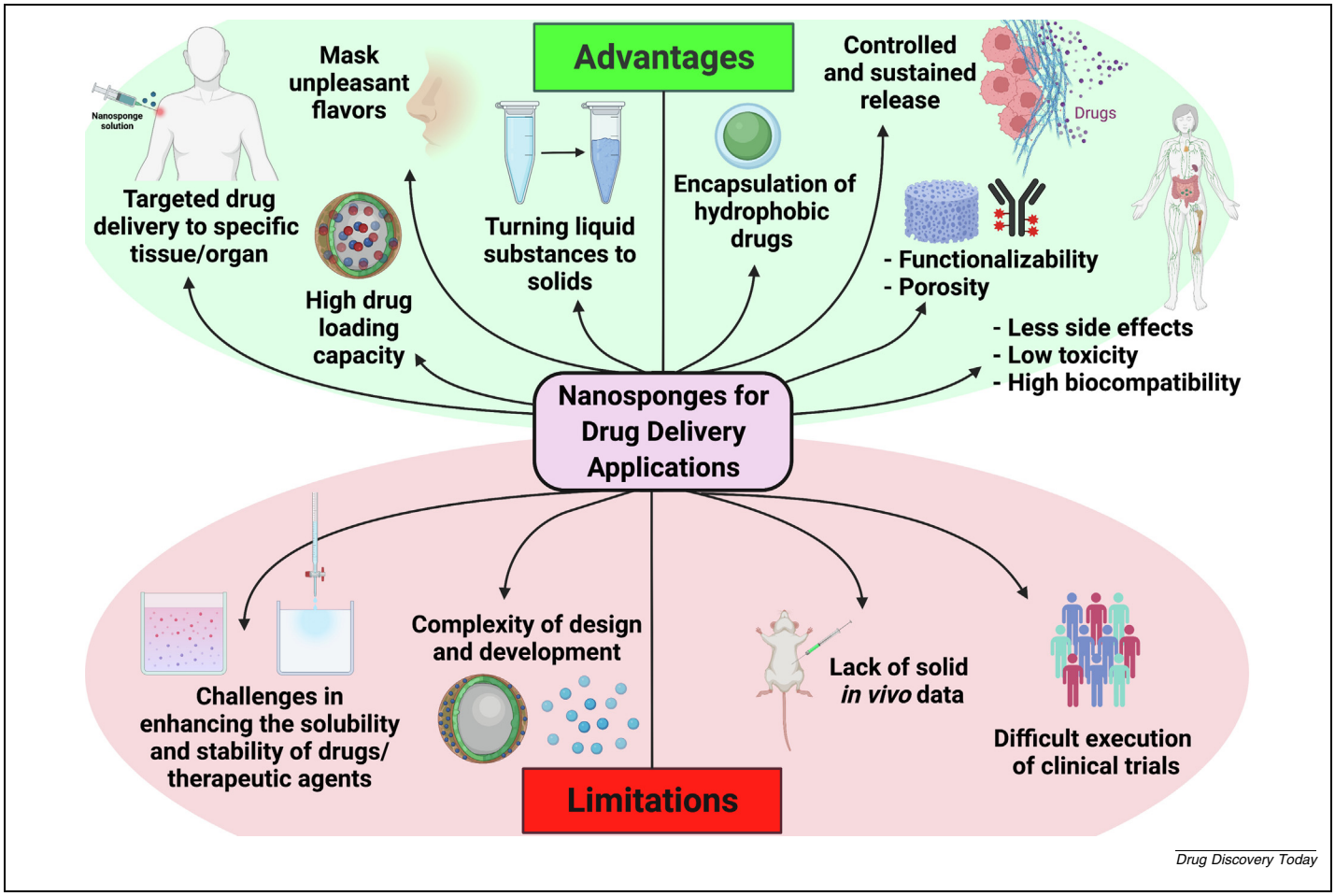


FIGURE 2
Advantages and disadvantages of nanosponges in drug delivery applications.

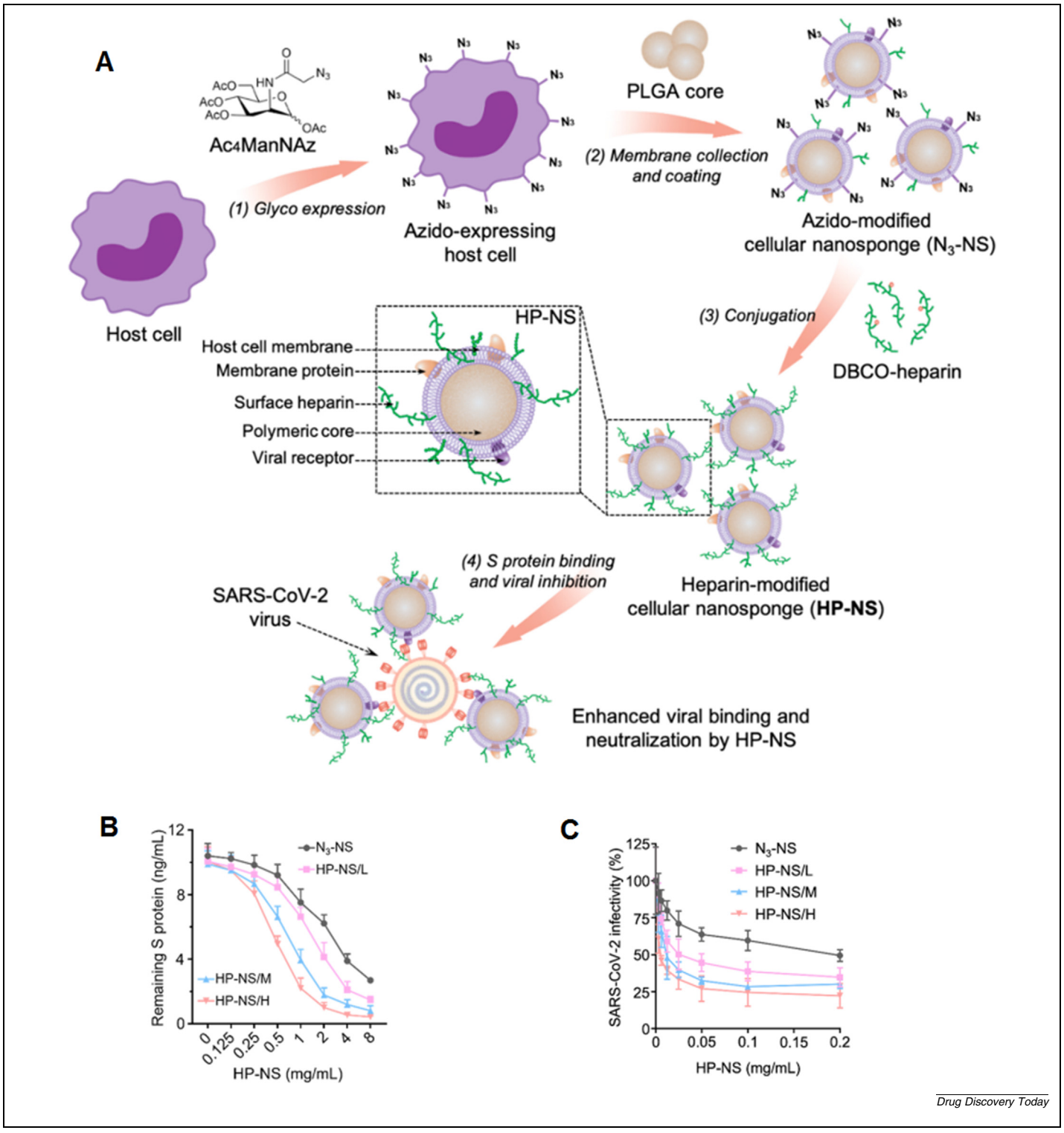


FIGURE 3

(a) Cellular nanosponges engineered for inhibitory effects against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). To express azido groups, the host cells were incubated with *N*-azidoacetylmannosamine-tetra-acylated (Ac4ManNAz). Then, the collected membranes were used to coat poly(lactic-co-glycolic acid) (PLGA) polymers to produce cellular nanosponges expressing azido groups (N_3-NS). Functionalization with heparin was performed by applying dibenzocyclooctyne groups (DBCO-heparin), which conjugated to azido-NS via copper-free click chemistry. The resulting heparin-modified cellular nanosponges (HP-NS) were examined for SARS-CoV-2 viral infectivity applications. **(b)** Dose-dependent binding of different HP-NS preparations with SARS-CoV-2 S proteins. **(c)** Dose-dependent viral infectivity inhibition by N_3-NS and various HP-NS formulations with low (L), medium (M), and high (H) heparin densities. Reproduced, with permission, from [55].

for this antiviral drug (~70 % w/w) with prolonged-release performance[52]; further *in vivo* analysis is required in terms of comprehensive efficacy and biodistribution assessments of these nanosponges. Notably, the cytotoxicity and biosafety parameters are vital for future clinical and biomedical uses of nanosponge-based systems. Rao *et al.*[53] evaluated the cytotoxicity of β-cyclodextrin nanosponges constructed for encapsulation of a phytotherapeutic agent (Babchi oil) against HaCaT cell lines. The prepared nanosponge-based delivery system exhibited high biosafety, stability, and therapeutic effects with targeting properties, reducing the required dose/consumption of the drug/therapeutic agents and minimizing systemic adverse effects, with improved drug localization at the targeted sites. Babchi oil has been explored for its antibacterial, antifungal, antioxidant, anti-inflammatory, immunomodulatory, and antitumor effects; however, its antiviral effects should be further explored.[53].

Various innovatively designed nanomaterials have been widely explored as antivirals because of their potential to mimic the cellular attachment of pathogenic viruses. Given that these viruses bind to molecules on host cells using glycoproteins on their surfaces, nanosponges could be designed based on this premise after eliminating the cellular contents while retaining only the membranes. Subsequently, these membranes can be broken into thousands of tiny vesicles ~100-nm wide. Biocompatible and biodegradable nanostructures built from polymers, such as poly(lactic-co-glycolic acid), could be coated with cellular membranes to form core–shell structures with high stability, functioning as a decoy of a human cell. The designed nanosponges with their binding points on the membranes can surround viruses, preventing them from entering host cells.[54,55] Rao *et al.*[56] reported a powerful two-step neutralization approach based on a decoy nanoparticle against COVID-19, including SARS-CoV-2 neutralization, followed by cytokine neutralization. These nanosponges can effectively protect host cells from infection by SARS-CoV-2 by competing with them for virus binding. By introducing these nanosponges, interactions between the complex of the SARS-CoV-2 S protein and human ACE2 decreased and, instead, viral receptors of the nanosponges showed high affinity for binding to ACE2.

Overall, cellular binding and the entry of SARS-CoV-2 can be mediated by its S protein via attachment to the ACE2 receptor and glycosaminoglycans (e.g., heparin).[55] Accordingly, cellular nanosponges mimic host cells for attracting and neutralizing SARS-CoV-2 through natural cellular receptors, thus providing a broad-spectrum antiviral approach. Increasing the heparin density on the cellular nanosponge surface also improved the inhibitory effects of heparin against the virus. Consequently, azido was expressed on host cell membranes to prepare cellular nanos-

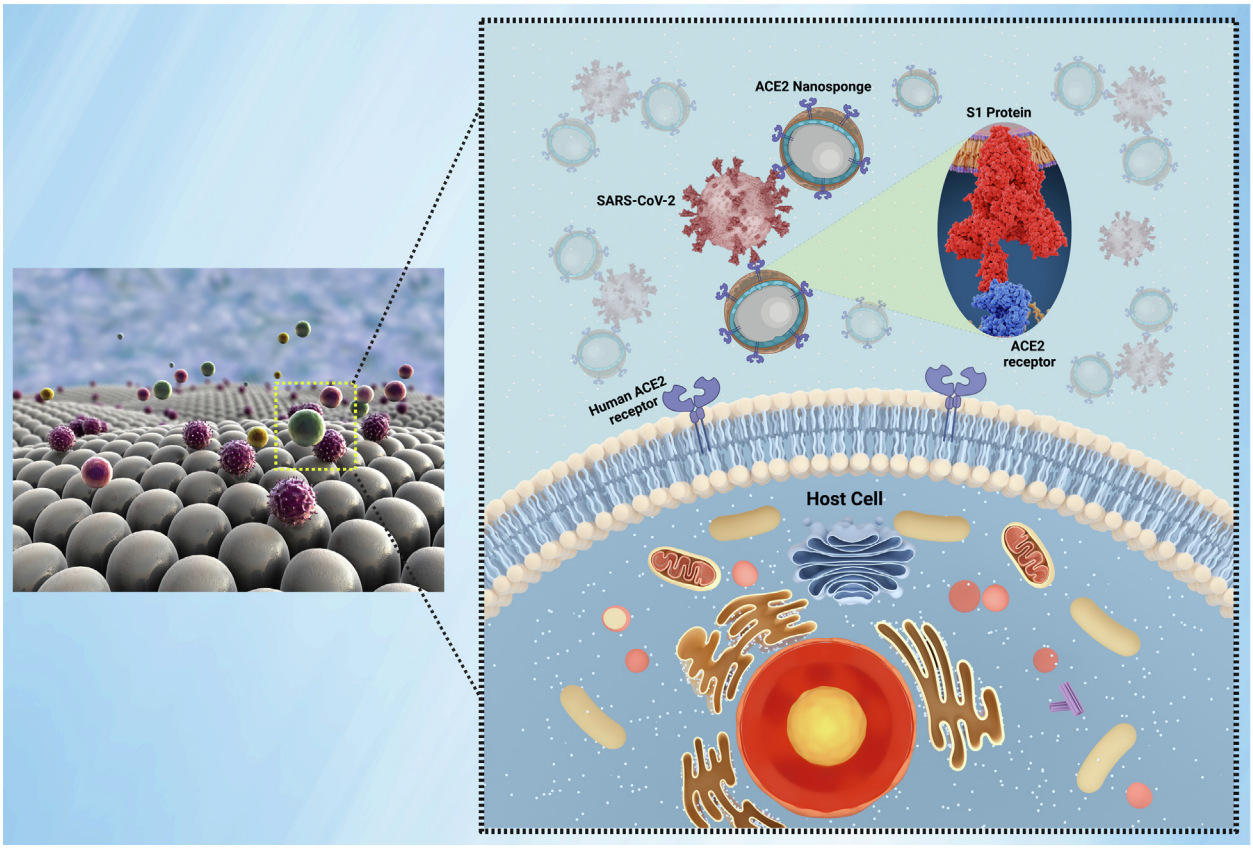


FIGURE 4
Membrane nanoparticles constructed from angiotensin-converting enzyme 2 (ACE2)-rich cells with inhibitory effects against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

ponges with heparin adhered to their surfaces. These cellular nanosponges demonstrated significant binding potential with viral S glycoproteins, providing effectual inhibition against SARS-CoV-2 infectivity. Thus, the surface engineering of host-mimicking cellular nanosponges with glycosaminoglycans is a promising technique for enhancing inhibition of SARS-CoV-2, and could extended to other glycan-dependent viruses (Fig. 3).[55] In addition, plasma membrane-derived nanosponges have been evaluated for *in vitro* neutralization of SARS-CoV-2; these plasma membranes originated from human lung epithelial type II cells or human macrophage-coated poly(lactic-co-glycolic acid) nanoparticles.[54] The designed nanosponges contained protein receptors essential for the cellular entry of SARS-CoV-2. Consequently, SARS-CoV-2 was neutralized, and its infectivity was reduced in a concentration-dependent manner; virus was unable to infect cells after the incubation with these engineered nanosponges. Such nanosponge-based platforms with promising inhibitory effects should be further evaluated against SARS-CoV-2 mutants and other viral species. Notably, nanosponges shrouded with the cell membranes of macrophages offer the extra advantage of soaking up circulating inflammatory cytokine proteins generated as a result of the immune system response to viral infection.[54]

Hybrid membrane-coated biomimetic nanomaterials with attractive and unique biological properties have attracted increasing research attention for biological and biomedical applications, especially for drug delivery,[57] with an emphasis on immune therapy, tumor vaccines, phototherapy, and detoxification.[58] For example, membrane nanoparticles derived from ACE2-rich cells displayed efficient blocking effects against SARS-CoV-2 infectivity (Fig. 4) because they efficiently suppressed the entrance of SARS-CoV-2 S pseudo-virions into host cells by obstructing viral infectivity both *in vitro* and *in vivo*.[59] Biomimetic nanocarriers have been constructed for antiviral drug

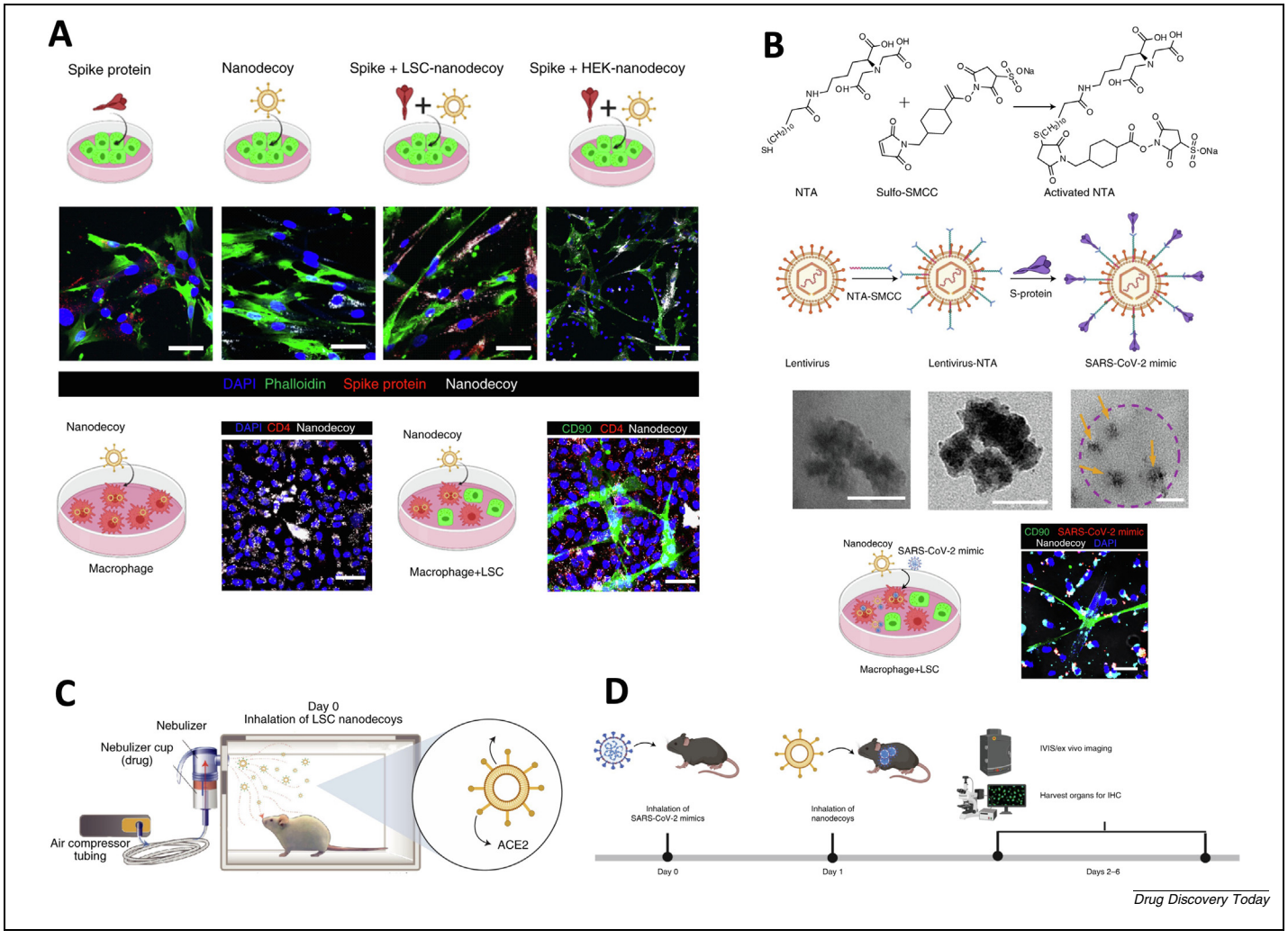


FIGURE 5

(a) Nanodecoys designed for neutralizing the S1 spike protein. S1 (red) and nanodecoys (white) interacted after their co-culture with lung cells (green). These nanodecoys were internalized by macrophages (confocal image; CD4, red). In addition, the nanodecoys were internalized by macrophages after co-culturing with lung cells (confocal image; CD90, green). Scale bars: 50 μm. **(b)** SARS-CoV-2-mimicking viruses were neutralized using the designed nanodecoys. Scale bars: 100 nm. **(c)** Inhalation of nanodecoys in a mouse model: these nanodecoys directly accumulated in the lung, which is one of the main targets of SARS-CoV-2 replication/infection. **(d)** The inhalation of nanodecoys enhanced clearance of the SARS-CoV-2 mimic in a mouse model. Reproduced, with permission, from [66].

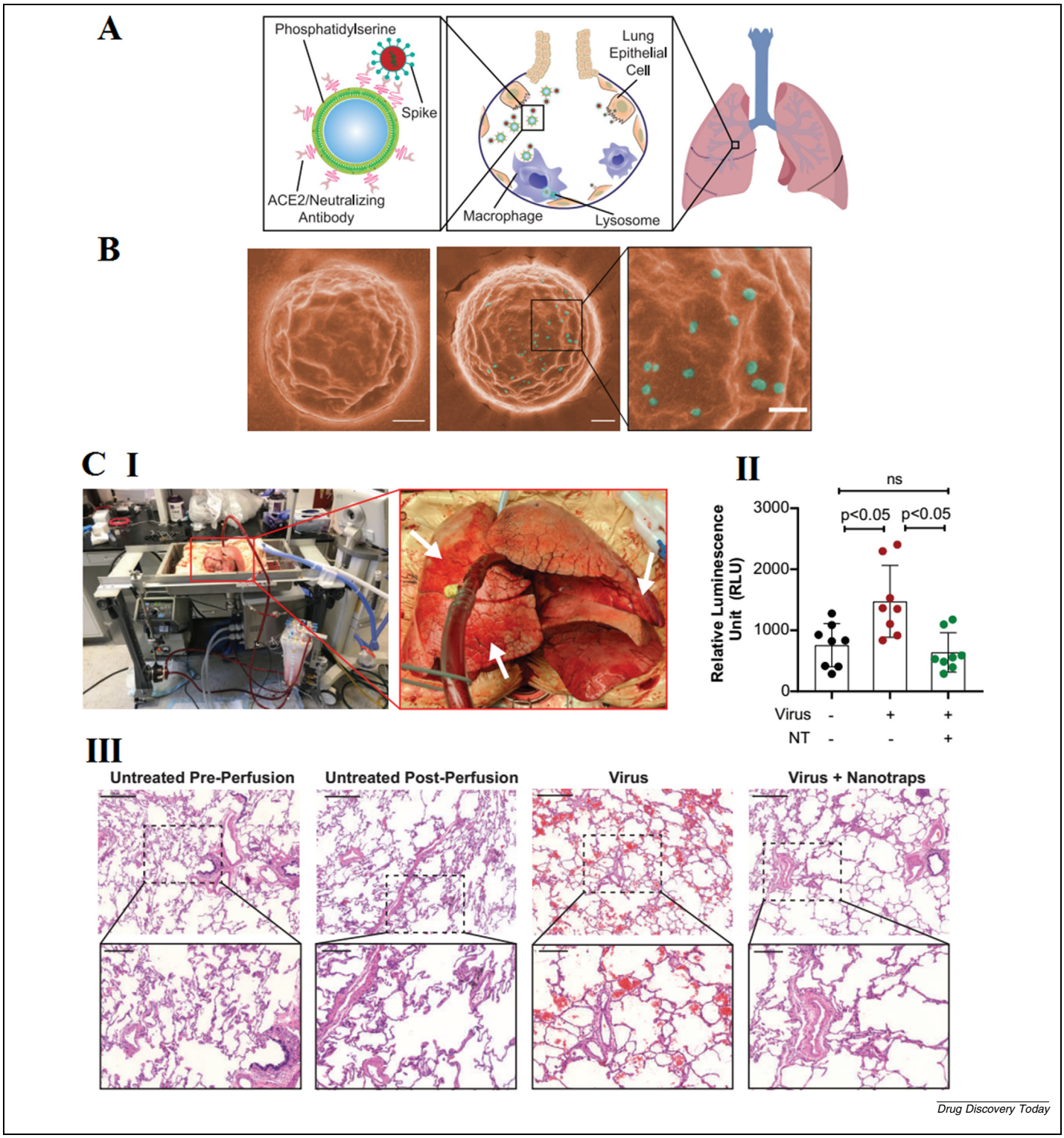
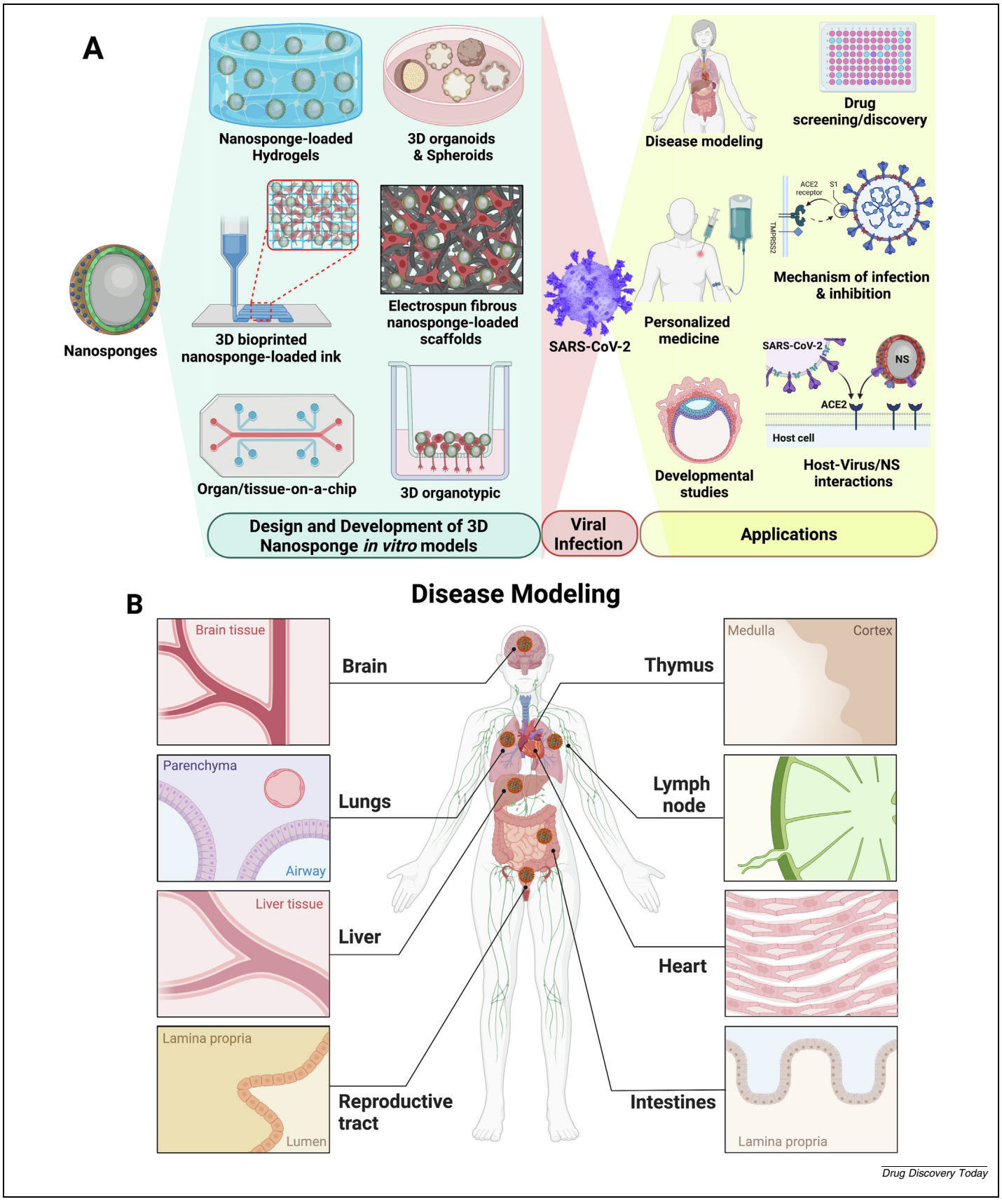


FIGURE 6

(a) Functionalized liposomal-based nanotrappers utilizing anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-neutralizing antibodies, phagocytosis-specific phosphatidylserines, or recombinant angiotensin-converting enzyme 2 (ACE2). The accumulation and trapping of SARS-CoV-2 virions was achieved by these nanotrappers in the lung, producing virus–nanotrap complexes. **(b)** Pseudo-colored scanning electron microscopy (SEM) images of nanotrap complexes with SARS-CoV-2 pseudovirus. **(c)** (i) Untreated (right upper lobe), virus alone (right middle lobe), and virus–nanotrap complexes (lingula) regions in a human *ex vivo* lung perfusion system. (ii) Luciferase expression quantification analyses, 8 h after infection. (iii) *Ex vivo* lung perfusion after hemoxylin and eosin (H&E) staining, including untreated, virus alone, and virus–nanotrap complex samples. Reproduced, with permission, from [69].


A
Nanosponge-loaded Hydrogels
3D organoids & Spheroids
Disease modeling
Drug screening/discovery
Nanosponges
3D bioprinted nanosponge-loaded ink
Electrospun fibrous nanosponge-loaded scaffolds
SARS-CoV-2
Personalized medicine
ACE2 receptor
S1
TMPRSS2
Mechanism of infection & inhibition
Organ/tissue-on-a-chip
3D organotypic
Developmental studies
SARS-CoV-2
NS
ACE2
Host cell
Host-Virus/NS interactions
Design and Development of 3D Nanosponge in vitro models
Viral Infection
Applications
B
Disease Modeling
Brain tissue
Brain
Thymus
Medulla
Cortex
Parenchyma
Airway
Lungs
Lymph node
Liver tissue
Liver
Heart
Lamina propria
Lumen
Reproductive tract
Intestines
Lamina propria
Drug Discovery Today

delivery applications against COVID-19 and concurrently exhibit anti-inflammatory effects.[60] Lopinavir-loaded polymeric nanoparticles were coated with macrophage membranes, neutralizing proinflammatory cytokines and suppressing macrophage/neutrophil activation. The increased potential to target inflammation as well as enhanced therapeutic effects resulting in the reduction of viral loads are the important advantages of these nanosystems.[60]

Zhou *et al.*[61] illustrated an innovative tool with prophylactic and therapeutic uses. Plasma membrane-ACE2-extracellular vesicles were deployed for neutralizing SARS-CoV-2 (pseudo-type and authentic) in human ACE2 transgenic mice, with efficient blocking effects reported against viral loads of authentic SARS-CoV-2, thus protecting the host from lung inflammation induced by SARS-CoV-2 infection.[61] Typically, antiviral agents target a singular viral site, thus suffer limitations of infectiveness against viruses because of their various mutations and escape strategies.[62–64] For instance, biomimetic proteolipid bilayer decoy receptor nanosponges constructed molecularly (~100-nm nanospheres) were explored against SARS-CoV-2, and demonstrated promising inhibitory effects. This nanosystem neutralized SARS-CoV-2 infections in animal/human cells and also trapped the viral particles. Intravenous (I)-injected nanosponge-based platforms can be suitable for multivalent capturing of SARS-CoV-2 in the body; however, preclinical and clinical evaluations are required to understand the underlying mechanisms and its efficacy against several mutated variants of SARS-CoV-2.[62] In particular, the emergence of new variants of concern (VOCs) of SARS-CoV-2 (such as Omicron and its different variants) caused health experts to re-evaluate the effectiveness of available strategies and think about more comprehensive and critical studies to better manage the ongoing pandemic as well as possible future outbreaks [64,65]. Li *et al.*[66] designed human lung spheroid cell-derived ACE2 nanodecoys for binding and neutralizing SARS-CoV-2, as well as protecting host lung cells from infection (Fig. 5); these nanodecoys with no noticeable toxicity could be transported through inhalation therapy and remained in the lungs for over 72 h after delivery, accelerating viral clearance and reducing lung injury. Such nanodecoys with unique properties and efficiency can be considered as potential inhibitory and therapeutic agents against COVID-19.[66] These nanosponge-like nanodecoys can be deployed to unravel crucial issues regarding drug development and nanotherapy, including the reduction of off-target effects (the improvement of targeting features) and unwanted biodistribution. Notably, complexes of nanosystems encompassing viruses can be used for the development of vaccine production technologies; cell membrane-mimicking nanodecoys with their ability to trap and detain pathogenic viruses should be further evaluated for the systemic protection against, and prevention of, infectious diseases.[67,68].

Various nanotrappers have been designed to neutralize and capture SARS-CoV-2 and inhibit viral infections, as exemplified by functionalized nanosponges that perform as nanotrappers against SARS-CoV-2. Chen *et al.*[69] functionalized liposomal-based nanotrappers using anti-SARS-CoV-2-neutralizing antibodies, phagocytosis-specific phosphatidylserines, or recombinant ACE2 proteins to capture SARS-CoV-2 with complete blockage of viral infection; these nanotrappers illustrated high *in vitro* and *in vivo* biosafety and biocompatibility, representing an innovative nano-based strategy for inhibiting SARS-CoV-2 infection (Fig. 6).[69] It appears that these innovatively designed nanosponges- and other nanotrap-based nanoformulations have excellent potential for application as nasal sprays or inhalers[70] for simple and direct delivery/accumulation in the respiratory system. Moreover, additional formulations for specific targeting of these nanosystems to different sites of SARS-CoV-2 exposure show promise.

Engineered in vitro 3D-nanosponge models to combat SARS-CoV-2

The severity of COVID-19 and its exponential rate of spread (particularly newly emerged variants, such as Omicron) are clear. Therefore, the development of techniques and strategies, therapeutics targets, vaccines, and all other types of platform that can improve our understanding of the virus and its mechanism of infection in the body will help manage the spread of infection and eradicate the virus. However, because of a lack of appropriate and reliable *in vitro* models to recapitulate the complex structure of different organs of the body (from the early stages of development to a mature state), our understanding of the mechanism of SARS-CoV-2 infection in different tissues/organs is limited. Therefore, there is an unmet need for further well-developed models to be able to accurately investigate the ultrastructural, functional, molecular analysis, histochemical, and gene expression characteristics of different organs in the presence of SARS-CoV-2. Among various *in vitro* models, 3D *in vitro* models have been extensively used in viral and antiviral studies, with promising results,[71] given that such bioengineered 3D models provide a more realistic platform compared with simple 2D monolayer cell cultures. They can also properly and adequately recapitulate the physiological microenvironment of the tissue/organs of the body and, therefore, are able to successfully model SARS-CoV-2 virus infection and replication for the development of new drugs or vaccines to eventually manage COVID-19 (Fig. 7A). The most frequently used 3D *in vitro* models include hydrogels,[72] orga-

FIGURE 7

Development of nanosponge-laden 3D *in vitro* models to manage severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and replication. **(a)** Once produced, nanosponges active against SARS-CoV-2 infection can be loaded into various 3D *in vitro* models, including hydrogels, organoids, spheroids, 3D bioprinted constructs, nanofibrous scaffolds, microfluidic-on-chips, and so on. The developed 3D model can be then used against SARS-CoV-2 infection for different applications, such as: discovery of novel and effective drugs to treat COVID-19; to study the development of different diseases in the presence of SARS-CoV-2, and the inhibitory roles of nanosponges in these developmental stages; to study the mechanism of infection and inhibition in the presence of nanosponges; to investigate host–virus complex interactions; and for disease modeling of **(b)** different tissues/organs that can be severely affected by SARS-CoV-2.

noids,[71,73–75] spheroids,[76] 3D bioprinted constructs,[77,78] nanofibrous scaffolds,[79] microfluidics-on-chips,[73] among others. For instance, microfluidics-on-a-chip or organoid models loaded with multiple cell lineages together with nanosponges are potential platforms for the early diagnosis of symptoms related to multiorgan infection. This is particularly relevant given that SARS-CoV-2 is capable of rapid spread to, and infection of, different organs of the body, including lung,[80] heart,[81,82] liver,[74] brain,[75,83,84] intestine,[85] reproductive system,[86] thymus,[87] and lymph nodes[88] (Fig. 7B).

Concluding remarks, challenges, and prospects

Nanosponges have been deployed against SARS-CoV-2 with promising inhibitory effects for biological neutralization and antiviral drug delivery applications. However, more research is needed to clarify the precise mechanisms of action and their efficacy in animal disease models as well as their long-term biocompatibility and biosafety issues. Furthermore, some important challenging questions need to be addressed before clinical assessments, including the identification of suitable delivery pathways for these engineered nanosponges, given that they can be directly delivered to the lungs by an inhaler or intravenously transported for the treatment of cytokine storm-related complications. Future studies need to harness the additional beneficial attributes of these membrane-cloaked nanosponges for vaccine and antiviral delivery as well as their use as broad-spectrum antiviral therapy. Additionally, such cellular nanosponges could be appropriate for the biological neutralization of chemical toxic agents, inflammatory cytokines, bacterial toxins, viral particles, and pathological antibodies. Remarkably, high-compatibility cell membrane-originating nanomaterials have opened the door to effective pharmacotherapy by circumventing the limitations of currently deployed methods, especially for immune modulation. 3D *in vitro* models can be used in viral and antiviral studies as platforms that can help understand better the SARS-CoV-2 and its mechanism of infection in the body and, thus, to manage the spread of infection, support the drug-screening process and discovery of therapeutic agents, eventually eradicating the virus.

Conflict of Interest

The authors declare no competing interest.

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