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REVIEW ARTICLE

Polymer-based nano-therapies to combat COVID-19 related respiratory injury: progress, prospects, and challenges

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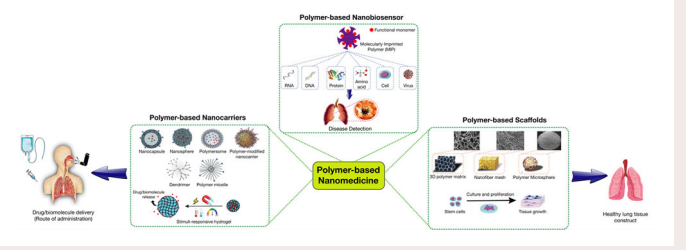
ABSTRACT

The recent coronavirus disease-2019 (COVID-19) outbreak has increased at an alarming rate, representing a substantial cause of mortality worldwide. Respiratory injuries are major COVID-19 related complications, leading to poor lung circulation, tissue scarring, and airway obstruction. Despite an in-depth investigation of respiratory injury's molecular pathogenesis, effective treatments have yet to be developed. Moreover, early detection of viral infection is required to halt the disease-related long-term complications, including respiratory injuries. The currently employed detection technique (quantitative real-time polymerase chain reaction or qRT-PCR) failed to meet this need at some point because it is costly, time-consuming, and requires higher expertise and technical skills. Polymer-based nanobiosensing techniques can be employed to overcome these limitations. Polymeric nanomaterials have the potential for clinical applications due to their versatile features like low cytotoxicity, biodegradability, bioavailability, biocompatibility, and specific delivery at the targeted site of action. In recent years, innovative polymeric nanomedicine approaches have been developed to deliver therapeutic agents and support tissue growth for the inflamed organs, including the lung. This review highlights the most recent advances of polymer-based nanomedicine approaches in infectious disease diagnosis and treatments. This paper also focuses on the potential of novel nanomedicine techniques that may prove to be therapeutically efficient in fighting against COVID-19 related respiratory injuries.

GRAPHICAL ABSTRACT



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Schematic illustration of potential polymer-based nanomedicine strategies for the diagnosis and treatment of COVID-19 related respiratory injury.

Abbreviations: SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; COVID-19: Coronavirus disease 2019; WHO: World health organization; ALI: Acute lung injury; ARDS: Acute respiratory distress syndrome; DNA: Deoxyribonucleic acid; RNA: Ribonucleic acid; ACE2: Angiotensin-converting enzyme 2; AECII: Alveolar epithelial type II cells; TMPRSS2: Transmembrane serine protease 2; VILI: Ventilator-induced lung injury; VV-ECMO: veno-venous-Extracorporeal membrane oxygenation; IL: Interleukin; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; PMMA: Poly(methyl methacrylate); PAA: Poly(amino acid); QCM: quartz crystal microbalance; COPD: Chronic obstructive pulmonary disease; POEGMA: Poly(Oligo(ethylene glycol) monomethyl ether methacrylate); DOTA: 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrakisacetic acid); GMA: Glycidyl methacrylate; DPA: 2-(Diisopropylamino)ethyl methacrylate; TPE-4SH: Tetrakis[4-(2-mercaptoethoxy)phenyl]ethylene; pHLIP: pH-low insertion peptide; PVAS: Poly(vinyl alcohol) sulfate; AMPS: 2-acrylamido-2-methylpropane sodium sulfonate; PPCM: Polyphenylene carboxymethylene; PLGA: Poly(lactic-co-glycolic acid); PNIPAm: Poly(N-isopropylacrylamide); PLA: Polylactic acid; PICA: Poly(isobutyl cyanoacrylate); pHEMA: Poly(2-hydroxyethyl methacrylate); DDS: Drug delivery system; PCL: Poly(ε-caprolactone); PEG: Poly(ethylene glycol); VEGFR: Vascular endothelial growth factor receptor; SAHA: Suberoylanilide hydroxamic acid; DOX: Doxorubicin; HCC: Hepatocellular carcinoma; COPD: Chronic obstructive pulmonary disease; PAA: Poly(acrylic acid); AZT-TP: Azidothymidine-triphosphate; CDDP: Cis-platinum or cis-diamminedichloroplatinum(II); HIV: Human immunodeficiency virus; PAMAM: Polyamidoamine; HSV: Herpes simplex virus; PVP: Polyvinylpyrrolidone; VZV: Varicella zoster virus; PVL-co-PAVL: Poly(valerolactone)-co-poly(-allyl-δ-valerolactone); PVA: Poly(vinyl alcohol); PLL: Poly-L-lysine; PPI: Polypropylene polybenzyl isocyanate; gp120: Envelope glycoprotein GP120; CD4: Cluster of differentiation 4; PCD: Polyanionic carbosilane dendrimer; MPN-HANP: Metal-phenolic network-coated hyaluronic acid nanoparticles; PDEAAm: Poly(N,N-diethylacrylamide); PEO: Poly(ethylene oxide); PPO: Poly(phenylene oxide); PVCL: Poly(N-vinyl caprolactam); PDLLA: Poly(D, L-lactic acid); HAG: Hyaluronic acid hydrogel; ESCs: Embryonic stem cells; iPSCs: Induced pluripotent stem cells; MSC: Messenchymal stem cells; siRNA: Small interfering RNA; APCs: Antigen-presenting cells; MHC: Major histocompatibility complex; VANs: Vaccine adjuvant nanoparticles; CSPG: Chondroitin sulphate proteoglycan; ASCs: Adipose-derived stem cells;

Background

The outbreak of the novel β-coronavirus (severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); family: *Coronaviridae*) responsible for Corona Virus Infectious Disease-2019 or COVID-19 is considered the worst crisis since World War II.[1] This pandemic's impact is frightening as the human race faces a critical situation with mandatory lockdowns with a long-lasting dent in the world economy. Critically

ill patients can develop acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) (about 30–40%), which is associated with high mortality.[2] ARDS is a catastrophic disease condition characterized by noncardiogenic pulmonary edema, decrease pulmonary compliance and acute onset of hypoxic respiratory failure.[3,4] All of these complications can subsequently trigger a cascade of other severe injuries, including multiple organ failure. Unfortunately, to date, contemporary therapeutic strategies to treat ALI/ARDS have not been rewarding.[5,6] Due to the complex pathogenesis and nature of the infection, some therapeutic targets for the blockade of specific cytokines and chemokines have failed to show an optimistic outcome.[7–9] Currently, only protective lung ventilation strategies are the accepted gold standard for ARDS treatment.[10] However, targeted delivery of anti-viral drugs, proteins, peptides, and silencing RNAs is some potential therapies for ARDS treatments.[11] Despite these potential candidates' prospects, their delivery to the lung is a significant challenge for potential use in preventing viral infection and treating the respiratory injury.[12,13] A major hurdle in lung tissue engineering is developing lung-appropriate scaffold materials for soft tissue regeneration.[14]

Nano-therapies have become an attractive approach to overcome these limitations and the targeted delivery of potential therapeutic candidates to the lung.[15] Nanocarriers are mainly designed to increase the biodistribution of therapeutic agents to target organs, which results in improved efficacy with minimizing drug toxicity.[16] Nanomaterials can also be designed to support the production of bioengineered lung tissue in lung damage repair.[17] Polymer chemistry offers the capability to develop a wide range of nanocarriers with broad classes of functional groups to provide unique possibilities to bypass the conventional limitations of viral infection prevention and respiratory injury treatments. Among different drug delivery systems proposed for pulmonary or respiratory applications, biodegradable polymeric nanocarriers' use represents more potentiality.[18] Moreover, biocompatible polymeric hydrogel materials are considered one of the most suitable options to use as scaffolds because of its capability to provide lung-appropriate three-dimensional (3D) architecture with mechanical properties required to help the breathing and gas exchange processes.[19]

This review article will first focus on lung pathophysiology during the development of ARDS in COVID-19 infected patients. In the next section, a short synopsis of polymer-based nanobiosensing approaches for SARS-CoV-2 virus detection will be given. Later on, conventional treatments of respiratory injury and their shortfalls will be explored. In the later part of this review, advances in polymer-based nanotherapies will be emphasized to control respiratory complications and the treatment of ARDS in COVID-19 infected patients.

ARDS in COVID-19 patients: Pathological changes of lungs

The primary target organ of SARS-CoV-2 is the respiratory tract, particularly the upper airways and lungs.[20] The virus initially reaches alveoli, and the spike protein of the virus binds to angiotensin-converting enzyme 2 (ACE2) and enters alveolar epithelial type-II (AECII) cells *via* transmembrane protease serine 2 (TMPRSS2) catalysis.[21] These cells act as a reservoir of the virus. Pulmonary dendritic cells and

macrophages sense the presence of viral antigens, thereby initiate an innate immune response to discharge immense amounts of proinflammatory cytokines, including Tumor Necrosis Factor-α (TNF-α), interleukin-1 (IL-1) and IL-6, and interferon (IFN-γ), resulting in a 'cytokine storm'.[22] Elevated levels of secreted cytokines induce the disruption of the alveolar-capillary membrane. Moreover, these cytokines also induce endothelial contraction, resulting in vasodilation and increased vascular permeability.[23] The disrupted alveolar-capillary membrane integrity allows the plasma leakage into the alveoli and the lungs interstitial spaces. Osmotic pressure gradient loss leads to a leaky barrier, and enhanced sensitivity to hydrostatic forces is considered key in diffuse edema formation.[24] The formation of protein-rich edema (also known as exudate) in the alveolar spaces and interstitium leads to alveolar flooding; such events make it difficult to breathe and triggers hypoxemia, one of the common symptoms of COVID-19 related respiratory injury.[23,25] The flooded interstitium provokes alveoli contraction. Moreover, alveoli collapsing is also induced by the decreased surfactant level due to the damaged AECII cells. Pulmonary macrophages also release more TNF-α and interleukins that move towards Polymorpho-nuclear Neutrophils (PMNs) *via* chemotactic phenomena.[26] Interleukins and TNF-α trigger PMNs of the inflamed tissue to invade the alveoli and release reactive oxygen species (ROS), neutrophil extracellular traps (NETs), and proteases that damage different cells existing in the lung inflammatory microenvironment, including endothelial cells and alveolar epithelial cells.[23] These disease outcomes expedite inflammatory clusters containing fibrinoid materials and multinucleated giant cells, carbon dioxide diffusion and gas exchange disorders, and vascular congestion.[27,28] All these pathological changes lead to intractable hypoxemia and a consolidation process that enhances and worsens the alveolar collapsing. In normal physiological conditions, the inhaled oxygen reaches the alveoli to oxygenate the blood which then returns to the heart and then to the body's different cells.[23] Hence, the alveolar-capillary membrane in a healthy human is very thin to help exchange of gases. In ALI/ARDS patients, the inflammatory process is widespread in both alveoli and interstitium, making the lungs stiff, and it becomes more difficult to inflate due to fluid and inflammation; thus, pulmonary failure occurs in infected patients.

Polymer-based nanomedicine strategies for SARS-CoV-2 detection

Generally, methods for detecting viral infections rely on the detection of genetic materials or unique markers of the pathogen itself. In the case of COVID-19, the currently employed detection technique is quantitative real-time polymerase chain reaction (qRT-PCR), where the detection mainly relies on the presence of RNA of the SARS-CoV-2 virus.[29] Besides, some combined approaches including RT-PCR, chest X-ray, CT-scans, identification of some biomarkers and their level (e.g. procalcitonin: low level, IL-6 and 10: high concentrations, C-reactive protein: elevated level, and lymphocyte counts: low level) in blood have also been practiced for the diagnosis of COVID-19 infected patients.[30] These techniques are labor-intensive, time-consuming, and cannot be available in resource-limited settings. Moreover, some false positive/negative responses are also reported in many cases.[31] Contrarily, nanomaterial-based sensing strategies are suitable for viral detection with better sensitivity and

selectivity, authenticity, scalability, specificity, and minimal false positive/negative responses.[32] Among different nano- and biosensing approaches, molecularly imprinted polymers (MIPs) provide potential applicability and physicochemical robustness for detecting viral pathogens.[33] Fabrication of MIPs is done by molecular imprinting of novel functional polymers with pre-designed molecular target selectivity. MIP-based sensors with unique selectivity and sensitivity can be employed for the detection of the SARS-CoV-2 virus. Previously, the detection of the Influenza virus, HIV, Zika virus, Ebola virus, and Dengue virus have been performed successfully by selecting virus-specific biomarkers as the recognition element.[34–38] For example, Wangchareansak et al. developed a MIP sensing tool in combination with the quartz crystal microbalance (QCM) method for proof-of-concept of Influenza A virus subtypes (H5N1, H5N3, H1N1, H1N3, and H6N1) screening.[37] They used acrylamide, methacrylic acid, methylmethacrylate, and N-vinylpyrrolidone as the polymer system for imprinting. Influenza A virus surface antigens are composed of two glycoproteins, i.e. hemagglutinin (HA) and neuraminidase (NA), that play a vital role in the subtype classification.[33] In that study, MIP was made for each Influenza virus subtype whereby each MIP possessed a better recognition property towards its original viral template. Findings of that study suggest that both the H and N domains play crucial roles in the molecular recognition of MIP. This report has opened a new option to screen Influenza A virus subtypes in unknown samples with detection limits of up to 105 particles/mL. Similarly, Tai et al. fabricated MIP-based film in the presence of a pentadecapeptide (15-mer peptide: linear epitope of the non-structural (NS1) protein of Dengue virus) onto a QCM chip.[38] Such epitope-mediated imprinting resulted in an enhanced polymer affinity toward the virus protein. They enhanced the binding effect using a monoclonal antibody to form a sandwich with the MIP-NS1 protein complex on the chip. These studies indicated that the detection of SARS-CoV-2 could be done by selecting a polymer belonging to the acrylic group (e.g. acrylamide, acrylic acid, methyl acrylate, ethyl acrylate, and methyl methacrylate) and applying the CoV-specific biomarker as the recognition element.[39] Only polymer-based biosensing approaches have been summarized here with their potential application to detect the SARS-CoV-2 virus. A more detailed discussion of other nanomaterial-based biosensors for CoV detection can be found elsewhere.[40]

Current therapeutic options to treat ARDS: Limitations and challenges

Despite the improved molecular understanding of the infection, there is still no specific treatment for ARDS. Some common therapeutic strategies include protective mechanical ventilation, prone-positioning ventilation, fluid-conservative strategy, and other supportive care.[41] These strategies have some limitations like the development of ventilation-induced lung injury (VILI), exacerbation of lung injury, and stimulating inflammatory reactions.[42] Veno-venous extracorporeal membrane oxygenation or VV-ECMO is an effective life-saving intervention to treat ARDS. However, the routine application of ECMO as salvage therapy in severe ARDS patients is a matter of debate.[43,44] Broad-spectrum antiviral therapy could be an option to treat COVID-19 related ARDS patients. However, a low success rate due to ongoing inflammatory

response, the emergence of rapid mutation of SARS-CoV-2 strains, and antibiotic administration's timing make such pharmacologic treatments completely ineffective.[45]

Short-term use of a neuromuscular blockade in the early stage of moderate to severe ARDS improved survival rates by reducing epithelial and endothelial injury markers and systemic inflammations.[46] However, such pharmacological therapies have failed to show long-term benefit.[46] Moreover, a wide range of conventional anti-inflammatory drugs have been proposed to treat ARDS because these drugs work by regulating inflammatory signalling targets (Losartan: Angiotensin II receptor blocker, Tocilizumab, Siltuximab: Interleukin-6 or IL-6 inhibitor, Baricitinib: Janus kinase or JAK-1/2 inhibitor, Anakinra: IL-1 inhibitor, Polyphenolic compounds: Kinase inhibitors, and so on) within the inflammatory systems in the body.[8,47–49] Despite the potentiality of these proposed treatments, developing these therapeutics is lagging behind the need for them due to extensive research and clinical trials to prove their efficacy and safety.[50] Recently, Russel et al. investigated the efficacy of corticosteroid treatment for COVID-19 related lung injury.[51] This study suggested that dexamethasone is not effective enough to treat lung injury. Hence, to circumvent life-threatening complications due to ARDS or other infection-related respiratory injuries, alternative therapeutic strategies are required on urgent basis to eradicate respiratory injuries and induce damaged lung tissue repair. In this regard, polymer-based nano-therapies have drawn the attention recently to overcome all the shortfalls of conventional treatments.

Polymer-based nano-therapies for respiratory injury treatment

Polymeric nanocarriers and drug delivery systems (DDS)

Polymers are soft materials that have been proposed and used in the preparation of nanomedicine. Natural and synthetic polymers with both hydrophilicity and hydrophobicity are used for such purpose. Proteins like albumin, gelatin, lectin, and polysaccharides such as cellulose, dextran, chitosan, and alginates are natural hydrophilic polymers that have been used as nanomedicine.[52] Polymethacrylate (PMMA), poly(-lactic-co-glycolic acid) (PLGA), polystyrene, poly(N-isopropylacrylamide) (PNIPAm), polylactic acid (PLA), poly(isobutyl cyanoacrylate) (PICA), poly(hexyl cyanoacrylate) are some synthetic polymers with hydrophobic property for nanomedicine formulation.[53,54] Various polymeric nanocarriers using these materials have been designed for the controlled release of drugs.[55,56] To reduce the nonspecific interaction with healthy cells and serum proteins and avoid uptake by phagocytosis, surface modification with several functional groups onto polymeric nanocarriers has been designed over the past decades.[57] On the other hand, some polymeric materials are sensitive to environmental stimuli like temperature (e.g. PNIPAm) and pH (e.g. pHEMA).[58–60] Thereby, nanomedicine strategy from these stimuli-responsive materials can help prevent the drug or biomolecules degradation before reaching the target site of action which subsequently helps decrease the toxic effects of nonspecific sites and increase the bioavailability of the delivered therapeutic components.[58] The availability of stimuli-responsive polymer materials and flexibility of nanocarrier fabrication techniques with the application of target ligands on the nanocarrier surface

enables the design of biomolecule loaded nanocarriers to boost antiviral effects. There are nearly 90 antiviral drug candidates have been approved for the treatment of emerging viruses.[61] The administration of these drugs is often accompanied by side effects due to their accumulation in the body's off-target site. Some drugs require high concentrations in the body to become effective against the virus, causing toxic effects to host cells with other side effects. For example, ribavirin is associated with hemolytic anemia.[62] Most of the approved antiviral drugs are poorly water-soluble as well, which hinders their successful use.[52] Hence, the polymeric nanomedicine strategies can be a potential solution for delivering a broad range of active moieties like antiviral biologics and nucleic acids to the target site for the COVID-19 related respiratory injury treatments.

Polymeric nanoparticles

Polymeric nanoparticles are the primary type of nanocarriers that can change the pharmacokinetic parameters of the encapsulated drug compound, and controlled drug release helps to reduce required drug concentration for biological activity. Polymeric nanoparticles can be fabricated by a broad range of fabrication techniques like solvent evaporation, ionic gelation, spray-drying, living- or free-radical polymerization, nanoprecipitation, and polymer dispersion technique.[52] Nanoparticles as nanocarriers have some advantages over other drug delivery systems (DDS) like low toxicity, site-specific delivery and degradation, better cellular uptake, controlled release of incorporated drug molecules. They can be used as theranostics in antiviral therapy.[63] Nanoparticles with 100–500 nm in size, which can incorporate the drug molecules inside its core, are known as nanocapsules. In nanocapsule system, the targeted drug is infused in the inner core, surrounded by the polymeric shell. High drug loading, controlled release profile, and target specific delivery are vital features of nanocapsules.[64] For example, nanocapsule consisting of poly(isobutyl cyanoacrylate) core and polyethyleneimine shell has been designed to deliver azidothymidine-triphosphate (AZT-TP) into the cytoplasm directly.[65] Contrarily, nanoparticles with 10–200 nm in size are known as nanospheres and the drug molecules can be adsorbed onto its surface or embedded in the matrix of the particles.[66] This type of nanocarrier can resist the drug molecules from unwanted degradation, and rapid drug clearance is observed because of its smaller size. In a study, chitosan nanospheres were developed with an average size of 200 nm for HSV-1 and HSV-2 treatment.[67] This polymeric nanosphere loaded with acyclovir showed better permeation and higher potency against the viral treatment compared to free acyclovir itself. This kind of smaller nanocarrier also offers site-specific drug delivery and controlled drug release profile.

Nanoparticles developed by polymeric materials such as PLGA, PLA, poly(ethylene glycol)-poly(ε-caprolactone) (PEG-PCL), PLA-PEG, and some others have been studied exclusively as nanocarriers for the systematic delivery of drug molecules and biomolecules for the antiviral and other disease treatment (Figure 1).[68–72] Previously, Li et al. developed a unique cocktail therapeutic strategy containing biodegradable polymeric nanoparticles for antiviral treatment.[73] They developed this PEG-PLA-based cocktail nanoparticles to encapsulate HIV-1 entry inhibitor and conjugate with reverse transcriptase inhibitor, resulting in strong virucidal effects against HIV-1.

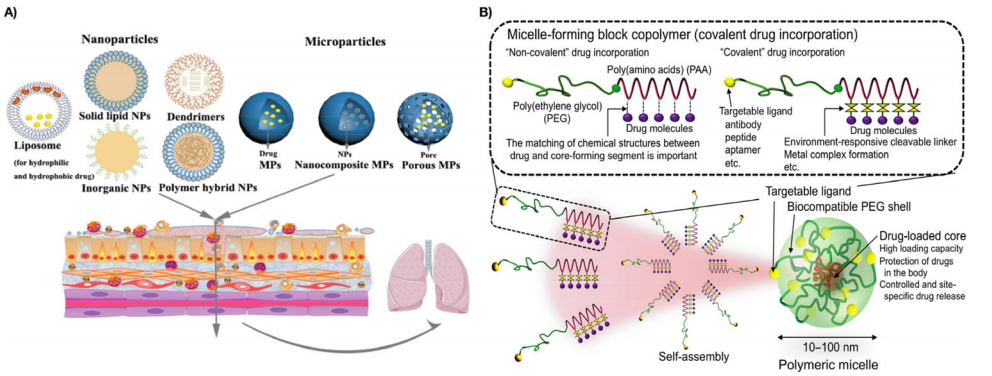

Figure 1. Different types of polymeric nanocarrier systems. (A) Different nanoparticles used to deliver antioxidants in chronic obstructive pulmonary disease (COPD) treatment. Reprinted from Xu et al.[68] Owing to some advantages of nanocarrier systems like small size, high stability, targeted deposition, sustained release, biodegradation, and reduced dosing frequency, they can be used to integrate and deliver hydrophobic and hydrophilic drugs in COPD treatment. Some of the promising novel DDS for COPD treatment include polymeric nanoparticles, micelles, dendrimers, microspheres and microparticles, nanoemulsion, lipid nanoparticles, and liposomes. Copyright 2020 BioMed Central. (B) PEG-PAA block copolymer endowed micelles with on-demand functionalities and specific targetability. Reprinted from Nishiyama et al.[69] Polymeric micelles can be engineered through block copolymers' self-assembly with a controllable size range of 10–100 nm. These micelles have a core-shell structure where biocompatible PEG shell surrounds the drug-loaded core. Copyright 2016 John Wiley & Sons Australia.

Polymeric nanoparticles can be administered in a systemic route (e.g. dermal, oral, intravenous, and so on) or directly into the lung *via* inhalation or intranasal route.[74] Nanoparticles containing antiviral drugs or small interfering RNA (siRNA) could be very effective if deliver through nasal epithelia and lungs in order to attack viruses that infect the respiratory tract, like Influenza viruses, Respiratory syncytial virus, and Rhinoviruses. Earlier, Jamali et al. developed a siRNA-chitosan nanoparticulate therapy that effectively target viral nucleoprotein to reduce virus infections.[75] They reported that the intranasal administration of this nanoparticles enhanced therapeutic effect on mice attacked with a lethal dose of Influenza virus, revealing *in vivo* antiviral activity of such nanoparticles. It is important to note that majority of the studies performed so far to assess the efficiency of polymer nanoparticles as DDS and recommendation are mostly based on preclinical data performed on lab animals, and these are not ready yet to administer in humans.[76]

Nevertheless, these investigations provide some promising hope to develop efficient polymeric nanoparticle-based nano-therapies to deliver antiviral drug molecules and immunomodulate cytokine storms in COVID-19 infected patients with respiratory complications.

Polymeric micelles

Polymeric micelles are amphiphilic block copolymers consisting of a hydrophobic core incorporate water-insoluble drugs and a hydrophilic shell that acts as a barrier to protect the drug. This type of nanocarrier structure allows higher drug loading and

minimizes the premature drug release in the off-target site.[77] Polymeric micelles can be used as a targeted drug delivery vehicle by surface modification with specific ligands. In a recent study, ε-caprolactone has been used as a hydrophobic core to encapsulate silibinin and further grafted with methoxy PEG (mPEG) to form amphiphilic block copolymeric micelles.[78] Such micelles are bioengineered auto-assembly copolymers formed in a liquid medium. Due to the micelle's hydrophilic outer layer, the whole micelle remains stable and biocompatible with tissues and blood. A recent study reported the development of polymeric micelles of isoniazid and rifampicin using the di-block polymer, PEG and PLA.[79] This formulated drug-loaded polymeric miceller delivery was reported to enhance the efficacy by reducing minimum inhibitory concentration (MIC) against *Mycobacterium tuberculosis* up to 8-fold. In a different study, polymeric micelles of isoniazid and rifampicin using ethylene oxide-propylene oxide tri-block copolymers, Pluronic® was developed.[80] A multifunctional PLA-b-PEG copolymer modified methyl-b-neuraminic acid (mNA) has been prepared as drug delivery micelles to treat Influenza virus infection.[81] It has been found that amantadine loaded in these micelles inhibit hemagglutination by binding to the hemagglutinin of Influenza viruses and efficiently alleviating viral infection.

The limited intracellular intake of antiviral drugs due to limited aqueous solubility is one of the major drawbacks to the successful treatment of respiratory illness in COVID-19 infected patients. Hence, due to the amphiphilic auto-assembly nature of polymeric micelles, these nanocarrier systems can be served as vehicles for delivering insoluble hydrophobic antiviral and anti-inflammatory therapeutics for the COVID-19 related ARDS treatments.

Polymeric conjugates

Conjugation of polymer with the targeted drug can be obtained by covalent bonding between a polymer and the therapeutic drug molecules. Polymeric conjugates are another potential delivery vehicle candidate for the treatment of COVID-19 because of several advantages like lower dosages of the required drugs that cause fewer side effects, decreasing the likelihood of drug resistance, and useful for the delivery of multiple drugs with different physicochemical properties.[82] A wide variety of negatively charged polymers and glycosaminoglycans like heparin, chondroitin sulphate, keratan sulphate, dermatan sulphate, and heparan sulphate have the potentiality to bind to the HIV envelope and resist the entry of viral particles inside the host cells.[83] Conjugation of azidothymidine (AZT) and ribavirin with synthetic polymers like methacrylates have been investigated broadly.[84] Results from these studies have shown greater antiviral potency with decreased toxicity. Conjugation of AZT with some natural polymers such as chitosan and dextrin *via* succinic ester linkage has shown longer plasma half-life and high drug loading capacity. In another study, conjugation of antiviral drug compound stavudine with chitosan by phosphoramide linkage has shown beneficial results in viral infection treatments.[84] Despite the benefits of polymer-drug conjugates for a wide range of treatments, optimizing the drug conjugation rate with polymers is still an uphill task. Some optimization challenges include controlling the interaction between two or more drugs and the release profile

of individual drug from the conjugated cargo system.[85] Hence, it is recommended that high-throughput screening profiles are needed to understand the biological interactions and find out if there is any synergism present or not (Table 1).

Other polymeric carriers to treat respiratory injury

Dendrimers are radially symmetric, highly branched, monodisperse, and homogeneous, nanoparticles with greater ability to attach multiple functional groups on their surface. Like polymeric micelles, dendrimers are made up of a central core, an inner shell composed of repeating units of building blocks, and an outer shell with many functional groups attached. Such configuration of dendrimers enables them to encapsulate non-water soluble, hydrophobic therapeutic agents in their core and specific surface functional groups to allow them to interact with the target biological site to deliver encapsulated agents. Such nanocarriers can be used as theranostics due to their outstanding ability to uptake by cells, longer circulation times, and improved stability and solubility in targeted drug delivery. Some of the commercially available dendrimers are poly(propyleneimine) (PPI), polyamidoamine (PAMAM), and poly-L-lysine (PLL).[112] Dendrimers' strong ability to interact with the viral cell surface and enhance antiviral activities can be used to treat viral infection in the host, such as HIV and Influenza virus infections.[113] PLL-based dendrimers with anionic naphthalene disulphonate surface have been designed to block the entry of HIV viruses by binding to the gp120 protein (viral envelope protein), thereby preventing the formation of CD4-gp120 complex.[114] Poly(phosphor-hydrazone) is a biodegradable dendrimer with end phosphoric acid functionalities, which have been proposed for anti-HIV activity.[115] Polyanionic carbosilane dendrimers (PCDs) have been designed, and combination therapy of PCDs with tenofovir and maraviroc has shown enhanced efficacy against HIV and minimizes the emergence of multidrug-resistant HIV mutants.[116] It has also been reported that some nanocarriers' surface properties have shown promising result in binding ACE2 receptor.[117] The cationic PAMAM nanoparticles have the property to bind to the ACE2 receptor, blocking angiotensin's cleavage, causing ARDS.[118]

A variety of sulfated polymers, including sulfated derivatives of PVA, polystyrene, poly(vinylsulfonic acid), poly(anethole sulfonate), and poly(2-acrylamido-2-methyl-1-propanesulfonic acid), have been reported earlier to inhibit HIV replication.[119] Sulfated polymers like poly(vinyl alcohol) sulfate (PVAS) have also proved their efficacy to inhibit HSV, Cytomegalovirus, Respiratory syncytial virus, Vesicular stomatitis virus, and Retroviruses.[120] Previously, Danial et al. investigated combining the antiviral lamivudine with a terpolymer synthesized from sulfonated side chains (2-acrylamido-2-methylpropane sodium sulfonate (AMPS)).[121] They found that at higher concentrations, the homopolymer poly(AMPS) combined with lamivudine exhibited nearly full inhibition against HIV infection. Polyphenylene carboxymethylene (PPCM) is a broad-spectrum antiviral polymer that binds to the viral envelope glycoproteins V3 loop and interferes with the interaction between gp120 and $CD4^{+}$T cells.[122]

Table 1. Polymeric nanocarrier systems in anti-microbial drug delivery applications.

Nanocarrier system	Carrier material	Drug target	Diseases	Major findings	Ref.
Nanoparticle	PLGA + transferrin	Nevirapine	HIV	Increased uptake in brain microvascular endothelial cells	[86]
	PLGA	Lamivudine	Herpes	High targeting ability	[87]
	PLGA	Combination therapy (lopinavir + ritonavir + efavirenz)	HIV	Efficient drug entrapment (>79%) Inhibition of HIV infection Efficient uptake in nonimmune cells High nuclear and membrane drug levels in infected cells	[88]
	Chitosan	Lamivudine	HIV	Brain targeting	[89]
	Alginate	Pyrazinamide, ethambutol, isoniazid, Rifampicin	Tuberculosis	Higher drug payload, Enhanced therapeutic efficacy, Improved pharmacokinetic profile	[90]
	PLGA	Rifampicin, Pyrazinamide	Tuberculosis	Higher drug payload Higher efficacy	[91]
	PLGA	Efavirenz, Nevirapine	HIV	Increased permeability, Enhanced blood brain barrier (BBB) interacting ability	[92]
	PLGA	Elvitegravir	HIV	Improved intracellular uptake	[93]
	CAB	Nevirapine	HIV	Enhanced efficacy	[94]
Nanosphere	PLA	Arjunglucoside	Leishmaniasis	Reduced toxicity	[95]
	PCL	Amphotericin B	Candidiasis	Reduced accumulation into the kidney Decreased toxicity	[96]
	PEG-PLA	Acyclovir	Ocular HSV	Sustained release, no eye inflammation	[97]
	PEG-PECA	Acyclovir	Ocular HSV	Significant drug level increase in aqueous humor	[98]
Nanocapsule	PEG-PLA	Halofantrine	Malaria	Prolonged circulation time	[99]
	PCL	Indomethacin	Arthritis (anti-inflammatory)	Increased corneal penetration	[100]
Micelle	Stearic acid + chitosan	Lamivudine	Hepatitis B	Higher cellular uptake in infected hepatoblastoma cells, High drug loading	[101]
	PEG + PAA	Pyrazinamide	Tuberculosis	Significant therapeutic efficacy than original drug	[102]
	PCL + PEG	Acyclovir	HSV	Efficient drug uptake and delivery, Nontoxic in nature	[103]
	PAMAM	Acyclovir	HSV, Shingles	Enhanced mucoadhesion	[104]
Dendrimer	PAMAM	Sulfamethoxazole	Influenza	Increased antimicrobial activity, Sustained drug release	[105]
	PEGylated lysine	Chloroquine phosphate	Malaria	Increased drug stability, Enhanced drug circulation time	[106]

(*continued*)

Table 1. Continued.

Nanocarrier system	Carrier material	Drug target	Diseases	Major findings	Ref.
	PAMAM	Nadifloxacin, Prulifloxacin	Anti-bacterial	Improved water solubility	[107]
Nano-emulsion	PVP, methyl cellulose	Darunavir, Nelfinavir, Atazanavir	HIV, HSV, VZV, Shingles	Improved therapeutic efficacy	[108]
Nano-sponge	PVA, ethyl cellulose, PVL-co-PAVL	Acyclovir	HSV	Increased stability and solubility, formulation flexibility	[109]
Nano-dispersion	PVP, PEG, PVA	Efavirenz	HIV	Extended availability of drug, Increased solubility	[110]
Nanocrystal	PVA, PVP, cellulose derivative	Nevirapine	HIV	Improved bioavailability, Facilitates phagocytosis and targets the spleen	[111]

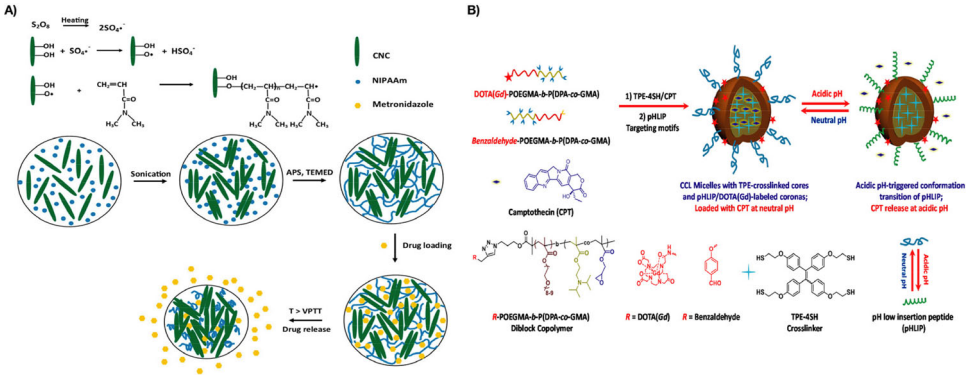

Figure 2. Stimuli-responsive polymer-based nanocarrier systems. (A) Thermo-responsive PNIPAm-cellulose nanocrystals (CNC) hydrogels for wound dressing application. The thermal stability of this hybrid hydrogel decreased while the rheological property increased with increasing CNC content. This smart hydrogel showed good drug-loading ability at room temperature and sustained drug-release at 37 °C. Reprinted from Zubik et al.[124] Copyright 2017 MDPI. (B) Core cross-linked micelles (CCL) fabricated with fluorescence and magnetic resonance (MR) dual imaging modalities from tetrakis[4-(2-mercaptoethoxy)phenyl]ethylene (TPE-4SH) fluorophores, and DOTA(Gd)-POEGMA—P(DPA-co-GMA) and benzaldehyde-POEGMA-b-P(DPA-co-GMA) deblock copolymers *via* co-assembly and click chemistry. Further, pH-responsive CCL micelles were fabricated with pH-low insertion peptide (pHLIP) through Schiff base linkage formation. Under a neutral pH state, pHLIP of the micelles formed coil state while turned to α-helical conformation under acidic pH conditions. Such transition helps to enhance cellular internationalization and allows for imaging in live cells. Reprinted from Tian et al.[125] Copyright 2016 MDPI.

Polymer hydrogels are 3D crosslinked networks of hydrophilic polymer chains that can swell and hold a bulk amount of water while maintaining the polymers' structure. The crosslinking structure provides the physical integrity of the hydrogels and required mechanical strength as well. Hydrogels can be synthesized using both natural and synthetic biodegradable polymers. The hydrogels' high-water content can possess similarity (e.g. the higher degree of flexibility, biocompatibility) to that of normal tissue.[123] These advanced properties of hydrogels make them potential candidates for nanomedicine applications. Stimuli-responsive hydrogels are another potential nanocarrier system for the specific delivery of therapeutic agents (Figure 2).[124,126–128]

One example of such hydrogel-based delivery systems is thermoresponsive injectable hydrogels. Hydrogels of this group can show phase-transition behavior below and above the physiological temperature.[129] Thermoresponsive hydrogels including PNIPAm, poly(N,N-diethylacrylamide) (PDEAAm), poly(ethylene oxide)/poly(propylene oxide) (PEO/PPO), poly(N-isopropylmethacrylamide) (PNIPAm), poly(N-vinyl caprolactam) (PVCL), PEG-based biodegradable polyester copolymers have been designed and developed as drug delivery systems.[129,130]

Polymer-based cellular nanosponges are another novel nanomedicine strategy to combat COVID-19 related infections. Zhang et al. recently prepared two cellular nanosponges (i.e. Epithelial-nanosponge (NS) and Macrophage-nanosponge or MΦ-NS) by coating cell membranes of human lung epithelial cells and macrophages onto polymeric nanoparticle cores made from biodegradable PLGA.[131] These nanosponges carry the same identified and unidentified protein receptors required by

SARS-CoV-2 for cellular entry. The results obtained after incubation of these nanosponges indicate that both have the comparable ability to inhibit the viral infectivity of SARS-CoV-2. Moreover, MΦ-NS can neutralize the viral activity early to reduce the viral load in the host and the later stage of the infection. It is well established that macrophages play a significant role in the pathogenesis of respiratory virus infection.[131] Hence, MΦ-NS may play significant roles in treating inflammatory viral infections such as SARS-CoV-2 and related complications.

It is important to note that advances in polymer chemistry along with pathophysiological changes in human due to COVID-19 infection can enable us to develop smart biodegradable polymeric delivery systems with the great potential for controlled delivery of immunomodulatory therapeutic agents to treat respiratory injuries in critically ill patients.

Polymer-based nanomedicine strategies for COVID-19 vaccine delivery

From the history of vaccine development, it is well established that vaccination is one of the most effective strategies to prevent and control the spread of infectious diseases, where naturally developed immunity induces protective long-term immune memory in patients.[132] In general, vaccines introduce specific viral antigens on the cell surface of antigen-presenting cells (APCs), particularly dendritic cells, embodied in the major histocompatibility complex (MHC) I and II.[133] Such an event triggers the adaptive immune system by recognizing these antigens as invaders and induces antibodies production or T cells to eliminate these unwanted invaders. Consequently, memory B cells in the body develop virus-specific antibodies on its cell surface, which triggers a fast immune response to clear the similar viral infection in the future. There are three different generations of vaccine formulations currently used to trigger immune responses against infection, including live attenuated (whole inactivated pathogen) vaccines or first-generation vaccines, recombinant subunit vaccines (second-generation), and RNA/DNA vaccines or third-generation vaccines.[134,135] Since the outbreak of COVID-19, several different vaccine candidates have been developed and reached clinical phases due to a high urgency to halt the pandemic.[136]

In the novel vaccine development for COVID-19, some studies have indicated that the viral S protein or receptor-binding domain (RBD) and N-terminal domain of S protein can be an excellent target for vaccine preparation in order to enhance the immunological response.[137] Different mRNA, DNA, and non-replicating adenovirus vector-based vaccines are under clinical trial to check their efficacy in COVID-19 treatment. The University of Oxford, in collaboration with AstraZeneca, developed a vaccine (AZD1222; formerly known as ChAdOX1) composed of a non-replicating adenovirus vector and able to replicate the S protein of SARS-CoV-2.[138] Some recently developed mRNA vaccine candidates are Moderna's mRNA-1273 (NCT04405076), Arcturus Therapeutics' LUNAR-COV19, BioNTech and Pfizer's BNT162a1, b1, b2, and c2, Globe Biotech's BANCOVID, and an CVnCoV developed by CureVac.[139–143] These mRNA vaccine candidates target the S protein (or a specific region of S protein) of the SARS-CoV-2 cell surface. On the other hand, vaccine

candidates developed by Inovio Pharmaceuticals (INO-4800), Genexine's GX-19, and Zydus Cadila's ZyCoV-D are some DNA vaccines targeting viral S protein.[144,145] Epivax is a cocktail vaccine made up of antigens (i.e. non-structural proteins and nucleoproteins) other than S protein to provide partial protection against the virus.[146] Gamaleya Research institute developed Gam-COVID-Vac, and CanSino Biologics developed Ad5-nCoV to fight against SARS-CoV-2.[147] Johnson & Johnson also developed a vaccine candidate (Ad26.COV2.S), a recombinant, replication-incompetent adenovirus serotype 26 (Ad26) vector encoding a stabilized full-length SARS-CoV-2 S protein.[148] Previously, this Ad26 vector was approved by the European Medicines Agency for the Respiratory syncytial virus, Zika virus, and Ebola virus.[148,149] Vaccine made of Ad26 vector is considered safe and highly immunogenic.[149] A couple of vaccine candidates developed by Sinopharm in collaboration with the Beijing Institute of Biological Products are currently in phase III clinical trial[146]. Some other protein-based vaccines, including COVAX-19 by Vaxine PTY Ltd. and NVX-CoV2373 by Novavax, are under clinical trials to evaluate their efficacy against COVID-19.[150] So far, vaccine candidates developed by Pfizer-BioNTech, Moderna, Oxford-AstraZeneca, Johnson & Johnson, CanSino, Sinopharm, Gamaleya, and Sinovac have been approved by health regulatory agencies throughout the world for early and emergency use.[151]

In COVID-19 vaccine research, some significant challenges are finding practical approaches to stimulate both the T cell and B cell immunity against the virus and developing precise next-generation vaccine for patients with compromised immunity.[152] Besides, poor immunogenicity and premature degradation of the antigens in harsh *in vivo* conditions and failing to reach the target sites of DNA and RNA vaccines are some other limitations that result in the weak immune response.[153] Therefore, it is crucial to develop smart strategies to deliver the COVID-19 vaccine more protectively, providing enduring protection with enhanced patients' immunity. Nanocarrier-based vaccine delivery program can be an option to deliver vaccines to induce complimenting immunomodulatory effects. Polymeric nanocarriers can be used to deliver antigens without premature degradation and potential side-effects, which allow directed targeting of the vaccine towards APCs.[117] Additionally, with the growing interest in RNA and DNA vaccines to fight against coronavirus, combining them with nanoscale cargo devices will be an effective approach to overcome all the limitations mentioned above. It has been already reported that the nanocarrier-based strategy can be an effective approach to deliver small interfering RNA (siRNA) for the treatment of malignancies, infections, and autoimmune diseases.[154]

The vaccine delivery using nanocarrier systems can be done either by encapsulating the antigen or DNA/RNA within the nanocarrier or by attaching antigens on the nanocarrier surface.[155] The antigen encapsulated nanocarrier-based vaccine delivery strategy shows the potential efficacy that prolongs the antigen exposure towards the immune cells.[117] Antigens with amphoteric nature are suitable candidates to be adsorbed on polymeric nanocarrier surfaces like chitosan and dextran sulphate-based nanoparticles.[156] In such cases, nanocarriers are predesigned with stimuli-responsive properties like pH, temperature, and ionic strength to release antigens from the carrier surface inside patients' bodies. PLGA nanoparticles are suitable candidates for

encapsulating the antigens within the nanocarrier to provide extended and controlled biological release.[157] Previously, these PLGA nanoparticles have shown efficacy preclinically in carrying antigen vaccines like HBsAg, Malaria antigens, *Bacillus anthracis* spores to generate extended cellular and humoral immune response.[158,159] For example, Galloway et al. developed a PLGA nanoparticle-based Particle Replication in Non-wetting Templates (PRINT®) technology to deliver influenza vaccine antigens.[160] This vaccine delivery approach requires low amount of vaccine antigens to induce immune responses. Naked mRNAs are prone to degradation by extracellular RNases; therefore, it is essential to deliver them in a protective way to prolong their efficacy.[161] Some of the polymeric nanocarriers are under investigation to use for the delivery of mRNA-based vaccines. These mRNA nanocarriers include PEG-lipid functionalized dendrimers (200 nm), polyethyleneimine (PEI) nanoparticles ($100-300$ nm), chitosan (cationic) nanoparticles ($300-600$ nm), and protamine (cationic peptide) nanoliposomes ($\sim$100 nm).[156] Like mRNAs, naked DNAs also experience premature degradation by nucleases and require protective delivery to boost immune response.[156] Polymeric nanocarriers with DNA encapsulation helps to prevent premature inactivation of DNA and provide controlled release.[156] Composite PLGA nanocarriers with cationic glycol-chitosan or PEIs are under investigation to improve DNA loading efficiency, systemic protection, and controlled release.[157] Surface electroporation of DNA coated-PLGA nanoparticles has been developed recently to improve DNA/RNA delivery across the cells and nuclear membrane.[162] This electroporation strategy has shown efficient delivery of DNA to elicit T cell and B cell response in pigs.[162] This kind of portable electroporation approach is, therefore, become an attractive option in COVID-19 vaccine research. Vaccine adjuvant nanoparticles (VANs) are designed to tackle the shortfalls of conventional molecular adjuvant delivery and improve the efficacy and safety of the generated immune response.[163] Vaccines and vaccine adjuvants which induce T helper type 1 or Th1-biased immune responses are highly preferrable to fight against COVID-19 or related viral infections.[164] It has been reported that five protein subunit vaccine candidates using a combination of antigen and adjuvant are in the pipeline of preclinical COVID-19 vaccine candidates.[165] Recently, a SARS-CoV-2 recombinant full-length S protein nanoparticle vaccine combined with the saponin-based Matrix-M™ adjuvant has been developed by Novavax.[150] This vaccine candidate is currently in phase I/II clinical trial (NCT04368988), and it has been demonstrated that the adjuvant triggers the entry of APCs into the injection site and induces the antigen presentation in local lymph nodes, resulting in enhanced immunological response.[166] Some *in vivo* studies of PLGA and calcium phosphate nanoparticles co-encapsulating both adjuvants and antigens have shown improved efficacy by inducing antigen uptake, APC activation, and higher antibody titers.[167] VANs like PLGA are also used to co-deliver immunoregulatory drugs or self-antigens as adjuvants to trigger antigen-specific peripheral tolerance of autoreactive T cells and obstruct any possible autoimmune response as well.[156]

Emulsion-based adjuvants like Freund's adjuvant and montanide ISA51 are easy to develop at comparatively very low cost among different adjuvants available for vaccination. These adjuvants can be made as water-in-oil (W/O) emulsion with dispersed

antigenic media and continuous oily phases.[168] These adjuvants based on emulsion have the advantages of improving the vaccine's nontoxicity and securing long-term protective immunity. Nevertheless, these adjuvants' preparation time, difficulties during injection by syringe, and localized toxicities at the injection sites are some common problems with these emulsions.[169] Synthetic low molecular weight block polymer has been proposed as a better replacement to reduce the toxicity of surfactants used during the manufacturing of such adjuvants. TiterMax is an ideal example of this kind of modified adjuvant for vaccination. TiterMax is a squalene-based W/O emulsion containing polyoxyethylene-polyoxypropylene-polyoxyethylene (POE-POP-POE) polymer.[170] To overcome the mild toxicity and poor degradability of TiterMax, recently, Huang et al. have reported multiphase emulsion based on the hydrophilic polymeric emulsifiers PEG-*b*-PLA, PEG-*b*-PCL, and PEG-*b*-PLACL in the antigen phase of oily ISA51-adjuvant-based vaccines.[171] This hydrophilic polymer-stabilized ISA51 emulsion increase fluidity and conceptually diminish local reactions. The excellent biodegradability and biocompatibility of these modified adjuvants make them promising candidates for SARS-CoV-2 vaccine delivery applications. Huan et al. recently studied the effect of CoVaccine HT^{TM} (W/O emulsion type adjuvant) against the SARS-CoV-2 spike S1 protein in mice.[172] The CoVaccine HT^{TM} has already proven its efficacy in Malaria, Zika, Ebola, and other antiviral vaccine formulations.[173] This adjuvant is composed of negatively charged sucrose fatty acid sulfate ester and plant-derived squalene.[174] In that study, they compared the potency and efficacy of CoVaccine HT^{TM} against two gold standard adjuvants (i.e. alum and Th2 adjuvant). They found that the CoVaccine HT^{TM} induced cell-mediated immune responses, antigen-specific antibody titers and virus-neutralizing antibody titers significantly compared to alum adjuvant. High potency, efficacy, biodegradability, and biocompatibility are key features in these modified adjuvants that make them attractive for SARS-CoV-2 vaccine delivery applications.[164]

Polymers in lung tissue engineering applications

Tissue engineering is a process to reconstruct a tissue for clinical use or repair damaged ones by seeding stem cells (e.g. ESCs, iPSCs, and MSCs) on a biological scaffold with extracellular matrix (ECM) proteins. The seeded cells are expected to proliferate and differentiate into the proper cell populations, followed by reconstructing targeted organs or tissue for clinical applications. In ARDS injury, one way to alleviate lung injury is to regenerate physiologically functional lung tissues to replace the damaged tissue.[175] In tissue engineering approaches, a scaffold is used as a 3D substrate that maintains the specific biological environment for tissue regeneration, keeps the mechanical structure of the regenerated tissue or organ, and provokes a minimal toxicity level, low or no inflammation.[176] Scaffolds can be synthesized using polymeric materials either from natural or from synthetic sources (Figure 3).[177–179] The first 3D scaffold has been made of Gelfoam (vacuolar sponge based on gelatin) and used to culture rat fetal lung cells.[180] In that study, it has been reported that fetal lung cells survived both in and around the collagen matrix and proliferated into new epithelial and endothelial cells. In another study, chondroitin sulphate proteoglycans (CSPGs)

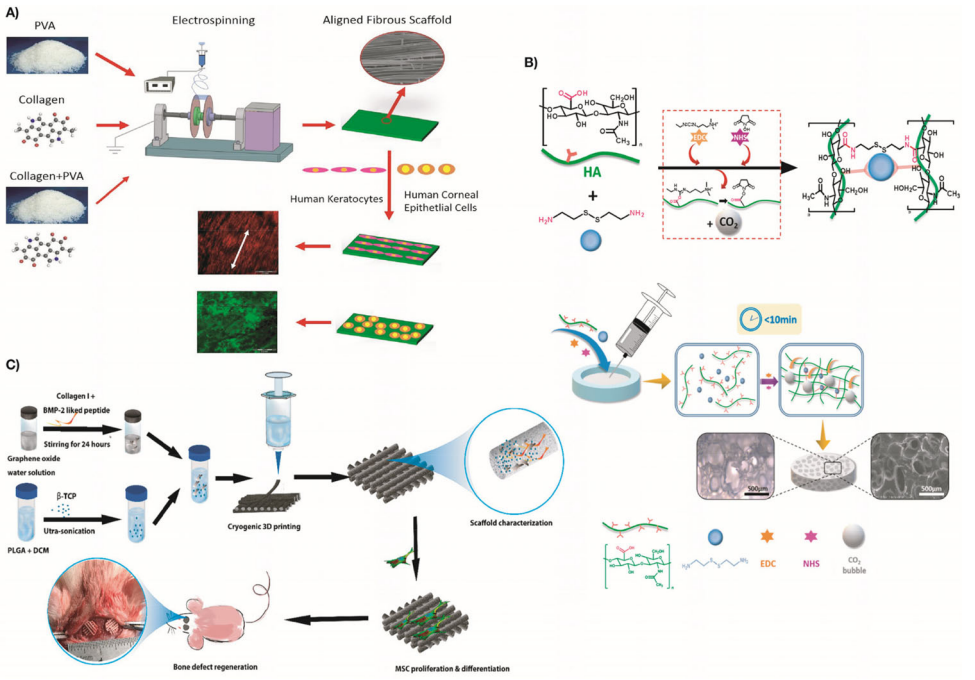

Figure 3. Polymer-based scaffolds in tissue engineering applications. (A) PVA/Collagen composite nanofibrous electrospun scaffold for application in tissue-engineered cornea. Reprinted from Wu et al.[177] Copyright 2018 MDPI. (B) Peptide/GO/β-TCP/PLGA scaffold from cryogenic 3D printing for critical-sized bone defect repair. Reprinted from Zhang et al.[178] Copyright 2019 MDPI. (C) Fabrication of an injectable, porous hyaluronic acid-based hydrogel by in-situ and bubble-forming hydrogel entrapment process. Reprinted from Wang et al.[179] Copyright 2020 MDPI.

scaffold has been developed for pulmonary tissue regeneration, and further studies indicated its potentiality to construct biomimetic matrices for inducing lung epithelial morphogenesis.[181]

On the other hand, synthetic materials are another potential candidate for use as scaffolds in tissue engineering applications, although these materials' low biocompatibility hinders their broad applications. Synthetic materials are combined with natural biomaterials to overcome this limitation and enhance scaffold properties. Elasticity and biodegradability are two key features for materials to be used as a scaffold for lung tissue engineering. Synthetic materials containing biodegradable polymers like PLGA are vigorously explored to develop porous scaffolds for tissue engineering.[182] Due to the lack of biocompatibility, synthetic polymers often fail to drive the differentiation of cultured cells.[183] Even sometimes, synthetic polymers coated with natural ECM proteins failed to guide seeded cells into required destiny despite the cells' initial attachment onto the scaffold. Therefore, it is necessary to employ some surface modification approaches (e.g. coating with instructive peptide domains) to enhance scaffolds' biocompatibility.[184] Besides, elastomeric polymers with more organotypic mechanical properties essential for cell growth and differentiation can also be useful for better cyclic respiration strain.[185] A widely used biodegradable polymer is poly(-glycolic acid) (PGA), which has been used previously as a patch grafted to the rat's

incised lung.[186] It is reported that the adipose-derived stem cells (ASCs) seeded onto PGA graft succeeded to regenerate alveolar and vascular tissues.[187] Another popular biodegradable hydrophobic polymer is poly(D,L-lactic acid) (PDLLA) that is suggested to be used as a scaffold for lung tissue due to its elasticity feature that resembles the lung environment.[188] Few polymeric hydrogels have been designed to meet certain requirements (i.e. mechanical strength, elasticity, stiffness, and controlled degradation kinetics) needed for lung tissue regeneration. A novel porous hydrogel scaffold has been developed recently from a blend of hyaluronic acid hydrogels (HAG) gel.[189] This hydrogel scaffold provided a lower inflammatory response, high elasticity with rapid hydration ability due to the interconnected porous network. This novel HAG gel fulfilled the characteristics compatible with lung engineering. Polymer-based porous matrices are considered ideal scaffolds because of their appropriate 3D structure, biocompatibility and biodegradability. Hence, they operate as appropriate substrate to induce stem cells' differentiation by regeneration of physiologically functional lung tissues.

Scope of polymer-based nano-therapies to combat respiratory injury: Progress, prospects, and challenges

For the detection of respiratory viruses, various polymeric nanobiosensors, including MIP-based sensors, have been developed in recent years.[40] Modification and surface functionalization of MIPs are unique nanobiosensing strategies for faster and more specific detection of viral infection. In recent years, these low-cost, affordable, and highly selective detection systems have drawn the research community and biomedical industry's attention to replacing costly, time-consuming, and labor-intensive traditional detection techniques. It is well established that patients with severe COVID-19 infection experience long-term respiratory complications of the infection.[190] Therefore, detection of early-stage infection is vital to mitigate long-term complications. The low-level detection of a specific SARS-CoV-2 biomarker can be an option for early evaluation, management, and infection treatment. Nanobiosensors with multi-functionalities could also have the potential for immediate detection of the SARS-CoV-2 virus. Despite their potential application in virus detection, there are still some significant limitations like reliability, reproducibility, and diagnosis performance and accuracy. Therefore, more elaborative analyses and research should be conducted in the near future to solve these drawbacks.

It is well established that COVID-19 infected patients often experience hyperinflammation correlated with acute respiratory injury, e.g. ARDS. Such respiratory injury might cause severe, long-lasting damage to the lungs, resulting in a substantial reduction of the patient's life quality. Therefore, it is crucial to develop a unique treatment strategy to treat the consequences of COVID-19 infection, including attenuation of the inflammatory response leading to respiratory injury. In respiratory injuries, microvascular leakiness is the outcome of inflammatory vasoactive factors that induce permeability.[191] Hence, drugs can be administered systemically and will localize to the lungs by passive targeting.[192] A controlled drug delivery system is an innovative, passively targeted therapeutic strategy that maximizes efficacy and

increases inflammation resolution, resulting in reducing collateral damage to healthy organs in patients. Polymeric nanoparticles as nanocarriers have already proved their ability in anti-viral treatment.[193] Such nanocarrier systems have shown improved and efficient drug delivery against HIV, Influenza virus, HSV, Respiratory syncytial virus, Zika virus, and Monkeypox virus.[194] Therefore, the nanoencapsulation of anti-viral drug candidates for COVID-19 may be an attractive and safer treatment strategy.[195] Theranostic nanoparticles as nanocarriers have already been investigated against various viral infections like SARS or MERS.[196] Theranostic nanocarriers can improve the drug delivery, ensure selective delivery of siRNA, block viral entry inside the cells, and trigger host cells' immune systems.[196] Therefore, biocompatible theranostic nanocarriers can be another promising strategy to deliver therapeutic agents *via* the intranasal route to combat against CoV-related respiratory injuries.

Despite the potentiality of polymeric nanocarrier systems, some bottlenecks must be addressed to facilitate its broader implementation. Since most recent studies have used *in vitro* approaches to evaluate the biocompatibility, it is crucial to ensure the safe use of nanomaterials inside the biological systems. Developing polymeric nanocarrier to deliver drugs, vaccines, genes, and other biologics in a controlled manner that can precisely cure the respiratory injury and other COVID-19 related complications is the ultimate goal of nanotechnology experts. The development of such smart polymeric nanocarrier with high efficacy and target specific functionality in the human body is very challenging to achieve. Additionally, the nanocarrier-based delivery system's efficacy is also related to the size, shape, and the surface charge of the nanoparticles.[16] It has been reported that spherical nanoparticles compared to rod-shaped particles are more prone to phagocytosis by macrophages and APCs (e.g. dendritic cells).[197] Positively charged nanomaterials are taken up more easily by the epithelial cell membranes due to its anionic nature. Due to the multifaceted interactions between nanomaterials and biological systems, nanomaterials' fate and behavior can be changed under physiological conditions. A high dose of these agents may cause severe side effects inside human body due to the off-targeting feature can be worse than SARS-CoV-2 infection. However, it is challenging to foresee the response of the nanomaterials under harsh biological conditions particularly in SARS-CoV-2 virus infection. Once the nanocarriers reach the blood circulation inside the body, they can interact with proteins to form protein corona.[198] Other complications may appear when nanoparticles enter blood circulation due to the complex matrix containing ions, small molecules, proteins, and cells in the circulation.[199] Thus, the characterization of protein corona is a vital step to be investigated during polymeric nanomedicine development to treat COVID-19 related complications including respiratory injury. Moreover, reliable *in vivo* models are required to explore the toxicokinetic behavior of the nanoparticulate carriers in the body. In the case of aerosol therapy of nanoparticles, although the incidence of adverse events is minimized, however, some observational studies have indicated that there is potential to cause local or systemic toxicity in the form of coughing, airway irritation, bronchospasms, and in some cases pulmonary injury.[191] Therefore, a more detailed investigation to assess the safety profile of polymeric and other organic/inorganic nanoparticles that are considered for delivery *via* aerosol therapy is necessary. Off-targeting limitation of the

nanocarrier can be overcome by introducing stimuli-responsive nanocarrier that can deliver therapeutic agents to the infected respiratory system in a controlled and target specific manner to combat CoV-associated symptoms. Polymeric hydrogels (e.g. PEG) are widely used for the controlled release of biomolecules. Control of gelation is crucial in delivering therapeutic agents because appropriate dosing and release kinetics rely on the understanding of fundamental gelation kinetics of hydrogel-based nanocarrier systems.[200] Thermoresponsive injectable hydrogels (e.g. PNIPAm) is a type of hydrogel-based delivery system developed in recent years as a drug delivery system and cell encapsulation system.[129] These hydrogels are free-flowing solutions below physiological temperature, and after *in vivo* injection, they convert into non-flowing gels at body temperature. A key feature of living systems is the ability to sense and react to external environmental stimuli. Therefore, cells and tissues' physiological responses with advances in polymer chemistry can enable the development of stimuli-responsive biohybrid hydrogels that can functionally interconnect with the living systems. These hybrid hydrogel-based delivery systems can be a promising nanomedicine strategy for drug or other biomolecule delivery applications to treat CoV-related respiratory injury.

The addition of cells to the scaffold to produce tissue construct under the controlled addition of specific growth factors to support tissue growth *in vitro* is the classical tissue engineering approach. Interestingly, lung tissue reconstructs using this classic approach are not suitable because the reconstructed tissues lack appropriate vascularization and the intricate organizational patterns found in normal lung tissue.[201] Bioprinting offers the advantages of placing various cell types in layer-by-layer constructs into a soft scaffold using a computer-controlled design template to resolve this issue.[201] Concurrent printing of hydrogel scaffold containing biomolecules will allow for precise placement of cells and proteins within 3D structures of complex tissues like lung. This hydrogel-based organ printing approach will also provide the advantage for spatial control of the scaffold structure, the type and arrangement of cells, the thickness of the tissue, and the formation of capillaries and vessels to make physiologically functional lung tissue. Despite these technological advantages in polymer-based lung tissue engineering, precise control of hydrogel properties like porosity remains a major hurdle in scaffold design.[202] The porosity, pore architecture, and interconnectivity between pores are some significant features that play a vital role in cell survival, proliferation, and migration during tissue regeneration.[202] Control of these features can influence the scaffold's cell movement and movement of oxygen and nutrients and regulate cell attachment to the scaffold. Therefore, it is now crucial to develop hybrid stimuli-responsive hydrogel scaffolds with ECM components similar to natural tissue to provide cells and developing lung tissue with the environment required to function like natural tissue in a native *in vivo* environment.

Concluding remarks

Amid the COVID-19 pandemic, primary diagnostic tools for SARS-CoV-2 detection are mainly based on RT-PCR-based assays. Although PCR-based tools are broadly applied in recent times, such tools are only limited to detect viral nucleic acids.

Moreover, the testing capacity, cost, detection time, and availability are some issues of this technique. Contrarily, polymeric nanobiosensing devices are more versatile and can be used for antigen, antibody, and nucleic acid detection. These novel sensing tools can also provide rapid, reliable, broadly accessible, and low-cost diagnosis in this pandemic. A wide range of treatment strategies using polymer-based nanotechnologies has been developed and commercialized so far for different viral infections like HIV and HSV-1 and 2. Advancements in these nano-therapeutics developments can help to invent novel treatments and vaccines to tackle COVID-19 related complications to the next level. Although polymer-based nano-therapies offer a broad range of antiviral therapeutics opportunities, it is still in the infantile stage. Some of the major barriers in nanomedicine development are long-term toxicity, fabrication and characterization complexities, and large-scale production difficulties. Moreover, tissue engineering approaches in respiratory injury treatment is still limited and far from clinical use. Therefore, future perspective should focus on addressing and solving current drawbacks of polymeric nano-therapies to develop a revolutionary solution for the treatment of COVID-19 and other viral infection related respiratory injuries.

Disclosure statement

No conflict of interest is reported.

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