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REVIEW ARTICLE

Opportunities for biomaterials to address the challenges of COVID-19

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic has revealed major shortcomings in our ability to mitigate transmission of infectious viral disease and provide treatment to patients, resulting in a public health crisis. Within months of the first reported case in China, the virus has spread worldwide at an unprecedented rate. COVID-19 illustrates that the biomaterials community was engaged in significant research efforts against bacteria and fungi with relatively little effort devoted to viruses. Accordingly, biomaterials scientists and engineers will have to participate in multidisciplinary antiviral research over the coming years. Although tissue engineering and regenerative medicine have historically dominated the field of biomaterials, current research holds promise for providing transformative solutions to viral outbreaks. To facilitate collaboration, it is imperative to establish a mutual language and adequate understanding between clinicians, industry partners, and research scientists. In this article, clinical perspectives are shared to clearly define emerging healthcare needs that can be met by biomaterials solutions. Strategies and opportunities for novel biomaterials intervention spanning diagnostics, treatment strategies, vaccines, and virus-deactivating surface coatings are discussed. Ultimately this review serves as a call for the biomaterials community to become a leading contributor to the prevention and management of the current and future viral outbreaks.

KEYWORDS

antivirals, biomaterials, COVID-19, diagnostics, filtration

1 | INTRODUCTION

Due to increased public hygiene, vaccination and antibacterial advancements, humanity is less likely than ever to succumb to infectious diseases of any kind. Despite this, in the past several months coronavirus disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has escalated to a global pandemic at an unprecedented rate. Identified as a novel beta-coronavirus and closely related to other zoonotic SARS-coronaviruses, it is believed that SARS-CoV-2 originally existed in a bat host and entered human populations via a wet-market in Wuhan City, China.[1] To put this most recent outbreak into perspective, the waves of novel zoonotic viruses began largely with severe acute respiratory syndrome (SARS) in 2002, and include Middle East respiratory syndrome (MERS), various animal influenza strains, and now COVID-19. Regardless of this growing trend, much of the biomaterial

community has focused their research on antibacterial work; a cursory search on Pubmed, as of May 2020, shows 90 articles including the keywords "biomaterial and antiviral" in the last 5 years, but over 3,500 results for the same search with "biomaterial and antibacterial." To facilitate rapid problem solving and scientific advancement during this viral pandemic, it is our goal to review the current clinical practices against COVID-19 and how current and future biomaterials work can contribute.

1.1 | Etiology, epidemiology, and morphology

The SARS-CoV-2 virus was first identified in December 2019 in Wuhan Province, China as a cluster of pneumonias.[2] Since then, the virus has spread globally at an astonishing rate and is expected to cause millions of infections and hundreds of thousands of deaths in the next 2 years.[3] A brief comparison of SARS-CoV-2 to the related viruses SARS coronavirus (SARS-CoV) and MERS coronavirus (MERS-CoV) provides some interesting insights.

The first SARS outbreak began in November 2002 in Guangdong Province, China and by July fifth, 2003 the World Health Organization (WHO) declared the SARS outbreak contained. Approximately 8,000 SARS cases and 774 deaths (9.2% mortality) were reported in total across 29 countries. The majority of these cases were people in close contact with animals and healthcare workers who were associated with aerosol generating procedures while the overall human-to-human transmission was limited.[4] The MERS outbreak began in September 2012 in Saudi Arabia and by June 2019, ~2,500 cases and 845 deaths (34.5% mortality) were reported in total across 27 countries. A similar transmission pattern to SARS is documented, with overall limited human-to-human transmission.[5]

Although all three are zoonotically transmitted novel coronaviruses, COVID-19 differentiates itself significantly in how widely and quickly it has spread, and how low the mortality rate is compared to the other two viruses.[4,5] To illustrate this point, consider that SARS and MERS were found to have a basic reproduction number (R_0), a measure of how contagious an infectious disease is, between 2.5 and 3.5, whereas the most recent estimates for COVID-19 are around 4–9 making it at least twice as contagious.[6] Not only is this number important to project rate of spread, but R_0 is directly related to the concept of herd immunity – that in a given population, a threshold of immunized individuals confers protection from pathogen transmission to the unimmunized individuals. The basic relationship between R_0 and herd immunity is the "herd immunity threshold" and is calculated as $1\text{-}1/R_0$.[7] Given this equation, diseases with an R_0 of 3 would require 67% of the population be immunized to achieve the herd immunity threshold, whereas an R_0 of 5.5, such as COVID-19, would require 82% to be immunized.[8]

Taxonomically, SARS-CoV-2 is an enveloped positive sense RNA virus and part of the beta-coronavirus family (Figure 1). The viral genome is around 30 kb and is divided into several open reading frames which encode both structural and nonstructural proteins.[9] Following successful entry into cells, viral RNA is released into the cell cytoplasm, where positive-sense RNA is translated by host cells into proteins. The structural proteins include spike (S) glycoprotein, envelope (E) glycoprotein, membrane (M) glycoprotein, and nucleocapsid (N) protein.[10] Briefly, the S protein interfaces with angiotensin-converting enzyme 2 (ACE2) to fuse with host cells and is of great interest for ongoing research. The E protein assists with assembly and budding of new virions in the endoplasmic reticulum. The M protein is the main structural protein. The N protein binds to viral RNA and is involved in processing and stabilizing the RNA.[10,11] Nonstructural proteins (NSPs) include enzymes that assemble to form replication-transcription complexes involved in viral replication.[12,13] Replication is believed to take place within a network of modified endoplasmic reticulum membranes. Following assembly, virions are released via exocytosis into the surrounding extracellular space, where they go on to infect other host cells or are expelled or excreted from the body.

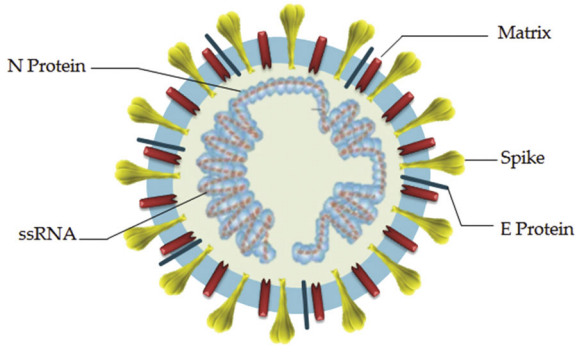

FIGURE 1 Structure of SARS-CoV-2 virus particle. Nucleocapsid (N), envelope (E), and spike (S) proteins along with matrix form a shell surrounding single-stranded (ss) RNA. Reproduced with permission from Astuti et al.[10]

1.2 | Mechanism of transmission and infection

While originally a zoonotic virus, the primary method of transmission has transitioned to human-to-human via close contact, fomites, and droplet.[14] Of great concern is the "asymptomatic carrier" – a patient who sheds the virus for days to weeks before symptoms occur, if at all.[15] Additionally, there is growing evidence that SARS-CoV-2 is highly contagious partly due to its ability to travel in aerosols, which are widely defined as small respirable droplets <5 to 10 μm in diameter. Unlike large (>20 μm) droplets, these small aerosols do not immediately settle due to gravity but are instead capable of long-range airborne transport.[16,17] Once the particles are inhaled, pathogenesis begins in the lungs due to direct invasion of host epithelial cells. This creates a localized inflammatory response driven by several cytokine-mediated pathways. It has been shown that S protein interaction with ACE2 activates a signaling pathway which significantly upregulates chemokine (C-C motif) ligand 2 production (CCL2), a cytokine which attracts T cells, monocytes and basophils.[18] Another important pathway involves intracellular antigenic peptide presentation via major histocompatibility complex (MHC) to cytotoxic T lymphocytes. These immune triggers are also responsible for a systemic inflammatory

response which can range from a normal immune response to a cytokine storm—an uncontrolled production and circulation of pro-inflammatory cytokines which can damage other organ systems and lead to superinfection, acute respiratory disease syndrome (ARDS), cardiac injury, stroke, and multi-organ dysfunction.[18-20]

The largest clinical report on COVID-19 (72,314 cases) was published by the Chinese Center for Disease Control (CDC) and was summarized in the Journal of the American Medical Association in February 2020. It categorized patients by clinical manifestation into mild (81%), severe (14%), and critical infection (5%) groups.[21] Symptoms ranged from headache, gastroenteritis, and cough for mild infection, to ventilator-dependent respiratory failure, sepsis and multi-organ dysfunction (MOD) for those critically infected.[2,19] No fatalities were reported for mild and severe cases, but in critical infections the case fatality rate approached 50%. These numbers are similar to smaller studies in the United States.[22,23] Treatment of these patients revolves largely around supportive respiratory care and targeted intervention of secondary injuries. Successively more severe stages of acute respiratory failure require successively more invasive treatments. In practice respiratory status is monitored by using a pulse oximeter to assess blood oxygen saturation (SpO_2), a measure of the percentage of hemoglobin which is oxygenated, with a target saturation of >90%. The most basic oxygen treatment includes the use of low flow nasal cannula. The next step up includes high flow nasal oxygen (HFNO) and noninvasive ventilation (NIV) treatments. These are newer therapies that show promise in decreasing intubation rates and intensive care unit (ICU) mortality and length of stay. HFNO utilizes a specialized nasal cannula to deliver high volumes of oxygen and due to such high flow also improves the physiology of breathing. NIV uses an oro-nasal mask to deliver mechanical ventilation and oxygenation without the need for intubation.[24,25] However, if a patient continues to be hypoxic on these therapies then intubation with invasive mechanical ventilation becomes necessary. The details of ventilator management is outside the scope of this paper, but if a patient continues to be hypoxic despite maximum ventilatory support, then extracorporeal membrane blood oxygenation (ECMO) is a final rescue therapy. Such critically ill patients almost uniformly suffer from ARDS which severely inhibits oxygen diffusion across their lung alveolar membranes. ECMO bypasses the lungs and affords the patient time to recover by using a device to drain, perform gas exchange on, and then recirculate oxygenated blood back to the patient.[26] Despite their necessity, all these oxygen treatments carry risk to healthcare workers with viral particle aerosolization from the intubation procedure carrying the highest risk.

2 | OPPORTUNITIES FOR BIOMATERIALS RESEARCH

Following the outbreak of the COVID-19 pandemic, SARS-CoV-2 rapidly became one of the most important subjects in biomedical research. In the following sections, we outline a series of focus areas for biomaterials researchers by first providing a brief description of current clinical standards and then opportunities for biomaterials intervention. In many cases, multidisciplinary approaches involving biomaterials are expected to play a major role in disease detection and management.

2.1 | Diagnostics

2.1.1 | Nucleic acid testing

Nucleic acid testing via reverse transcription polymerase chain reaction (RT-PCR) has emerged as the most common means of screening patient samples for current SARS-CoV-2 infection globally.[19,27] Polymerase chain reaction (PCR)-based assays are useful clinical tools as they offer exceptional detection limits and excellent pathogen specificity. Following the COVID-19 outbreak, international collaboration facilitated the rapid development of these RT-PCR-based SARS-CoV-2 detection kits, a major accomplishment for global medicine. Most of these tests employ the same three steps: first, biological samples undergo chemical treatment to extract and purify RNA. This is typically achieved by lysing viral membranes to release nucleic acids, which are then chemically precipitated and collected via centrifugation. Next, reverse transcriptase enzymes are used to transcribe RNA to complimentary DNA (cDNA), which is subsequently completed by the same reverse transcriptase enzyme to form highly stable double-stranded cDNA. Through iterative cycles of heating and cooling (thermocycling), target sequences of cDNA corresponding to custom-designed primers can be specifically amplified. Thermocycling consists of sequential denaturation, annealing, and extension phases. During denaturation, cDNA is heated to induce separation of double-stranded cDNA into single strands. During annealing, the reaction mixture is cooled to induce the formation of double-stranded primer/cDNA structures. During extension, the reaction mixture is again heated to an intermediate temperature at which the polymerase enzyme binds to primer-containing regions of DNA and replicates the target DNA strand. When fluorescent reporter probes are included in the reaction mixture, accumulation of target cDNA sequences can be monitored in real-time. Notably, current probes are designed to increase fluorescence in direct proportion to target nucleic acid sequence accumulation. In this way, low detection limits are achieved by amplifying target cDNA prior to detection.

POC nucleic acid tests

Current SARS-CoV-2 RT-PCR testing has several limitations at sample collection and processing stages, introducing bottlenecks in testing workflows and severely limited access to testing in regions that lack PCR instrumentation infrastructure. Given these limitations, point-of-care (POC) strategies are an attractive alternative and accordingly are a subject of current research. As the name implies, POC tests can rapidly provide diagnoses without requiring off-site laboratory processing of samples. Ideally, POC solutions eliminate the need for specialized equipment, allowing tests to be conducted in the field or even self-administered at home. This dramatically reduces the risk of disease spread during centralized testing and processing, increases testing throughput and capacity, and expands testing access for less

developed or lower income areas. Biomaterials research can provide key solutions to the challenges and limitations faced by current diagnostic approaches. At the most rudimentary level, biomaterials laboratories can help manufacture key disposables, including test swabs used to collect specimens. For example, the company Formlabs has developed and validated 3D printed nasal swabs for collection of respiratory samples.[28] Beyond offsetting disposables shortages, biomaterials can also play a supporting role in the development of POC tests. Emerging POC nucleic acid tests combine state-of-the-art molecular and synthetic biology discoveries with biomaterials advances to facilitate low technology disease detection.[27] To bypass instrumentation needs, multidisciplinary research is now underway to develop novel methods of purifying genetic material from complex biological samples, amplifying genetic material of interest, detecting target sequences, and conveying those results in simple and intuitive ways.[29-32]

Isothermal RT-PCR tests

In conjunction with emerging biology-based advances, biomaterials scientists can contribute important technologies to facilitate next-generation diagnostic test development. To aid in nucleic acid purification for example, Ali et al. developed a magnetic nanoparticle-based scheme that allowed for rapid isolation of RNA and DNA from biological samples via application of a magnetic field.[33] In the same study, the authors also developed a magnetic nanoparticle-based chemiluminescent reporter system that allowed for detection of target sequences with relatively simple instrumentation. Biomaterials also form the basis of colorimetric readout options that allow for interpretation of assay results without the use of any specialized optics, making them ideal tests for POC detection. Biomaterials-based surface plasmon resonance biosensors such as gold nanoparticles or quantum dots have been demonstrated to change color according to size, shape, surface chemistry, and aggregation state thus making them excellent optical probes.[34,35] This can be exploited to produce simple colorimetric readouts from complex molecular reactions.[10] For example, Kellner et al. leveraged CRISPR/Cas (clustered regularly interspaced short palindromic repeats/CRISPR-associated) technology to develop a novel nucleic acid test called SHERLOCK (specific high-sensitivity enzymatic reporter unlocking), with a colorimetric readout option.[36] This strategy capitalizes on nonspecific nuclease activity exhibited by some Cas proteins—upon exposure to target RNA, the Cas proteins become activated and cleave reporter molecules in the immediate vicinity (Figure 2a). By incorporating antigen-RNA-biotin reporter molecules, detection was made possible with commercially available lateral flow dipsticks containing antibody-conjugated gold nanoparticles. For the end user, making a diagnosis from a complex assay is incredibly simple: positive and negative tests can be determined by the location of a dark purple line on a paper strip. Efforts to apply this technology (and other similar ones) to develop COVID-19 tests are underway.[2,22] One SHERLOCK test has received US Food and Drug Administration Emergency Use Authorization (FDA EUA) for COVID-19 detection in clinical samples.

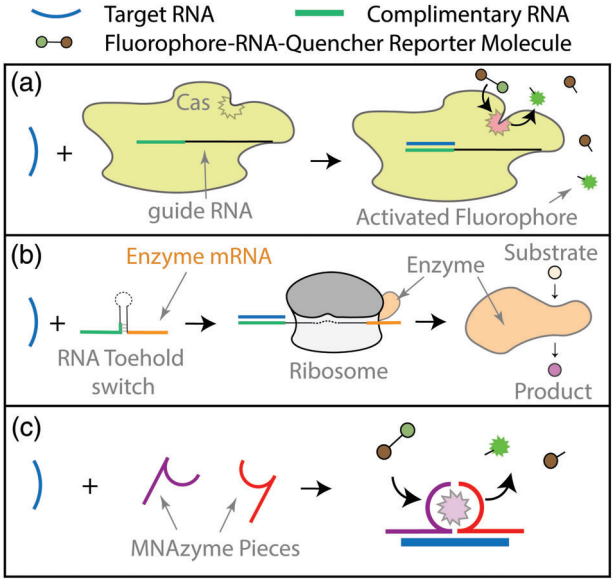

FIGURE 2 Diagnostic strategies for SARS-CoV-2 nucleic acid detection. (a) CRISPR/Cas-based detection; in the presence of target RNA sequences (blue), Cas proteins become activated and cleave fluorophore-RNA-quencher reporter molecules, resulting in an increase in fluorescence. (b) RNA toehold sensors; in the presence of target RNA, toehold sensors unfold, allowing ribosomes to bind and synthesize enzymes encoded by a messenger RNA (mRNA) sequence located downstream from the loop region. Newly synthesized enzymes then convert substrate into colored product. (c) MNAzymes; multi-part nucleic acid (MNA)-based enzymes assemble in the presence of target RNA and subsequently cleave reporter molecules to generate signal

An alternative colorimetric method involves the use of RNA toehold switches coupled with paper-based, cell-free protein expression platforms. Although traditionally RNA has not been considered a biomaterial, a recent definition expands the field to include any material "designed to take a form that can direct, through interaction with biological systems, the course of any therapeutic or diagnostic procedure."[37] This includes materials built from biomolecules, such as RNA, using synthetic biology principles, as reflected by the increasing number of synthetic biology-focused sessions that are now held at major biomaterials conferences. RNA toehold switches are rationally designed, synthetic RNA molecules comprised of toehold and coding regions separated by a hairpin structure that blocks translation by sequestering the ribosome-binding site and start codon. Upon exposure to a specific trigger RNA, the target sequence binds to the toehold region to induce a conformational shift, unfolding the hairpin and allowing for ribosome binding and subsequent gene expression (Figure 2b). Pardee et al. designed toehold switches that, in combination with ribosomes, generated LacZ enzyme upon exposure to Zika-derived trigger RNA.[38] When substrate was added to the mix, colored product was generated by the enzyme, resulting in easy detection by the naked eye. To improve detection limits, an isothermal amplification step was added, allowing viral RNA to be converted into cDNA, amplified, and then converted back into RNA to trigger toehold

switches. With amplification, target sequences could be detected in clinically relevant low femtomolar concentrations. In addition, inclusion of CRISPR/Cas9 editing technology allowed differentiation between viral RNA sequences differing in just a single nucleotide. Most importantly, all test reagents (including buffers, enzymes, ribosomes, and substrates) could be lyophilized onto a single paper disk, allowing for one-step testing of clinical samples. In addition to requiring minimal instrumentation this platform was shown to be highly economical, expanding access to testing. Work is currently underway to extend this technology to develop tests for COVID-19.[39] Both the CRISPR and RNA-toehold based detection strategies make use of enzymatic reporter systems that not only transduce but also amplify signal. Conventional nucleic acid probes allow for signal growth in direct proportion to target sequence accumulation, but enzymatic reporters allow for exponential relationships between target sequence concentration and signal intensity. When combined with excellent specificity, this can theoretically allow for detection of much lower concentrations of target nucleic acids. From a COVID-19 perspective, lower detection limits could allow for detection of exceptionally low viral loads associated with asymptomatic but infectious patients.

Nucleic acid biosensors

Emerging biosensors with ultra-low limits of detection may one day allow for complete elimination of reverse transcription and/or cDNA amplification steps, providing faster and simpler one-step detection. Biomaterials can play key roles in the development of such sensors. An enormous range of nucleic acid biosensors and transducers have been reported, including surface-functionalized nanostructures and programmable DNA-responsive smart materials.[40,41] Qiu et al. for example, built a gold nanoisland-based plasmonic biosensors to aid in the detection of SARS-CoV-2 RNA.[42] Nanoislands were functionalized with complimentary DNA, allowing for selective capture of target RNA. Changes in localized surface plasmon resonance could be detected in response to RNA binding. In addition, biomaterials strategies can be utilized to enhance existing sensor technology. For example, synthetic multi-component nucleic acid enzymes, or MNAzymes, can be designed to self-assemble in the presence of defined target sequences (Figure 2c). Upon assembly, MNAzymes become catalytically active and process substrates to yield fluorescent or otherwise detectable products. To enhance this signal amplification and reduce the need for cDNA amplification, Gao et al. developed a cationic copolymer that assisted in the assembly of MNAzymes, dramatically increasing the catalytic ability of the enzyme to yield a 200 times faster rate of substrate conversion to detectable product.[43] In the presence of copolymer, nanomolar concentrations of MNAzymes could detect picomolar amounts of target sequence at physiological temperature.

2.1.2 | Protein testing

Protein tests are employed to detect viral antigens or antibodies raised against them. While the presence of viral antigens indicates active infection, antibodies can take several days to appear in the blood.[2,44] Thus, antibody tests are more routinely used to demonstrate evidence of previous infection. Although it is currently unclear if blood antibodies raised against SARS-CoV-2 confer immunity, antibody tests are still expected to prove useful for disease tracking and surveillance as well as for monitoring vaccine efficacy. In addition, as the relationship between antibodies and immunity is further revealed, individuals testing positive for antibodies may be able to resume normal daily activities on a shorter timeline or even donate plasma to aid in the treatment of sick patients. To date, enzyme-linked immunosorbent assays (ELISAs) and other immunoassays have been used to screen for the presence of antibodies raised against SARS-CoV-2N or S protein antigens. Significantly more FDA EUAs have been granted to immunoglobulin (Ig) G tests over IgM, most likely because IgM responses generally precede IgG responses and fade quickly, while serum levels of IgG antibodies are sustained and believed to be more closely related to conferred immunity.[45]

Lateral flow immunoassays and ELISA

Biomaterials make the basis for emerging immunoassays for antibody detection. In many cases, colloidal gold-antigen conjugates can be used as optical probes.[46] For example, Cellex™ offers a gold nanoparticle-based lateral flow assay for detection of IgG and IgM antibodies. When sample is added to the test strip, antibodies in the sample bind to antigen immobilized onto the particle surface. In the event of a positive test, two strips of anti-human IgG or IgM secondary antibody located further along the strip capture gold complexes, resulting in the development of a dark red line. Magnetic nanoparticles have also found use in antibody detection applications—the biotechnology company Abbott has been granted an EUA for an IgG test that utilizes viral antigen-coated magnetic nanoparticles. Nanoparticles can be immobilized after capturing antibodies, washed extensively, and tagged with anti-human IgG conjugates capable of producing chemiluminescent signals.

In the US, several ELISA-based tests have also been granted EUA status. ELISAs typically exhibit lower limits of detection than colloidal gold lateral flow assays because they include a signal amplification step—when antibodies of interest are present, captured enzymes generate detectable product. In addition, ELISAs typically use 96-well plate formats or similar, allowing many samples to be tested at once. Despite these advantages, processing of samples can be labor-intensive and involves many wash steps that can introduce error. In addition, samples must be processed at centralized facilities, resulting in increased turnaround times. Microfluidics allow for the design of POC ELISA tests that require very little user input.[47-49] Microfluidic lab-on-a-chip devices consist of micron-scale channels and chambers and allow multi-step diagnostic assays to be conducted rapidly and efficiently.[50] For broad surveillance of population antibody titers, these microfluidic ELISA tests are appealing—they can be conducted in the field, reduce user error, dramatically reduce required sample volume, and minimize reagent use. Tan et al. are currently developing a microfluidic ELISA for quantitative detection of IgG antibodies raised against SARS-CoV-2 S proteins.[51] The test requires only 10 μl of sample and returns results in 15–20 min.

Viral antigen testing

Although nucleic acid testing is the predominant means of diagnosing current COVID-19 patients, biomaterials strategies can also be designed to detect viral antigens presented at the surface of intact virus. Such diagnostics would prove immensely beneficial, as they require little to no sample preprocessing and can directly sense the presence of virus in complex biological fluids. Because no amplification is involved, extremely low detection limits are required to confer clinical relevance. In addition, as detection limits decrease, excellent pathogen selectivity is paramount to maintaining good specificity. The development of such biosensors has been an active area of biomaterials research for years—promising technologies include piezoelectric, electrochemical, or optical biosensors that can detect incredibly minute changes in mass, electrical activity, or optical characteristics.[52-56] To replace current standards, emerging biomaterials sensors must demonstrate an ability approach or surpass the sensitivity and specificity of conventional nucleic acid tests. Applications of biosensors to SARS-CoV-2 detection should screen for S protein antigens, as these are presented on the outside of viral particles and readily accessible. For example, Seo et al. developed a field-effect transistor biosensor that could detect SARS-CoV-2 in unprocessed clinical samples.[57] To build the device, graphene sheets of a field-effect transistor were modified with antibody raised against the SARS-CoV-2 S protein. When samples were added, viral particles were sequestered by the antibody, resulting in measurable changes in the electrical behavior of the transistor. Notably, the biosensor platform had a far lower limit of detection in clinical samples than ELISA. Antigen tests can also probe for other viral antigens, but disruption of viral particle structure is required. For example, Quidel® received EUA for a fluorescent immunoassay-based antigen test that detects viral N proteins. The approach requires virus to first be denatured and uses a cassette-based lateral flow sandwich immunoassay that generates fluorescent outputs that must be read with an instrument also sold by the firm.

2.2 | Therapeutics and vaccines

In addition to diagnostics development, biomaterials technologies can be employed to develop novel treatment strategies for effective management of COVID-19 infection. In the following section, opportunities for biomaterials-based strategies are discussed.

2.2.1 | Antiviral therapies

Traditional antiviral therapies can be classified into non-specific antiviral agents (e.g., ribavirin, remdesivir, chloroquine) and targeted inhibitors of a specific viral element (e.g., HIV protease inhibitors, RNAi).[58-61] In addition, immunomodulatory agents (e.g., interferons and corticosteroids) have been used to decrease the inflammatory state associated with viral infection. These therapies are compelling but also have major shortcomings. Nonspecific antivirals are generally more prophylactic, not effective against all viruses, and can have significant side effect profiles.[59,61,62] At the same time, targeted inhibitors are definitionally limited by their specificity to one target and offer no guarantee of efficacy in future viral outbreaks. Finally, immunomodulation to control cytokine storm carries risk of suppressing beneficial parts of the immune response to the point of harm. In the case of SARS-CoV-2, it is fortunate that there is a large degree of similarity to previous viral outbreaks, otherwise a considerable amount of time would be required to find new targets and develop therapies against them. Instead, the acute and pressing need for treatment options has resulted in attempts to repurpose existing drugs.[63,64]

Several drugs have come to the forefront of the medical and research community, including hydroxychloroquine, remdesivir, and dexamethasone. Hydroxychloroquine is a drug with multiple mechanisms of action, illustrated by its use as an antimalarial and anti-inflammatory in several rheumatological diseases. Three main proposed mechanisms in COVID-19 include blocking viral entry into host cells, decreased viral replication, and anti-inflammatory properties.[65] Despite initial promise, hydroxychloroquine serves as a reminder to the medical community that even during a pandemic robust clinical data are required to make informed recommendations for treatments with known, severe side effects. Another consideration is the sudden shortage of hydroxychloroquine and the effect it has had on rheumatological patients who rely on it for chronic treatment.[66,67] Remdesivir is a broad spectrum antiviral prodrug which is converted to a nucleoside analog in cells and has been shown to be effective against Ebola, SARS-CoV and MERS in vitro.[68] It is currently being studied in randomized studies with preliminary data supporting use in hospitalized COVID-19 patients requiring oxygen therapy, though once again further data are pending.[69] Dexamethasone is a strong synthetic corticosteroid with anti-inflammatory and immunosuppressive mechanisms of action.[70] Based on the current data from the RECOVERY trial, dexamethasone is the most promising repurposed drug with significant data showing decreased mortality in patients requiring either invasive or noninvasive oxygen therapy.[71] Despite these heroic efforts, relatively little progress has been made toward the development of COVID-19 therapeutics that directly target SARS-CoV-2. Instead, hospitalized patients are provided with symptomatic relief, repurposed compassionate-use drugs and life-supporting interventions while they fight off the viral infection, as previously described. Biomaterials offers several opportunities to address the limitations of existing therapeutic strategies (Figure 3).

Drug delivery

Drug candidates may directly inhibit viral processes including infection or replication, modulate pro-inflammatory cytokine signaling, or stimulate regenerative healing processes. Unfortunately, many of these drug candidates are not ideally suited for systemic administration using standard oral or intravenous routes. Antibodies, anti-inflammatory cytokines, and other protein-based drugs often exhibit short half-lives, while sufficiently hydrophobic drugs suffer from low accumulation in target tissue. In addition, many existing antiviral medications demonstrate significant off-target effects that hinder clinical use.[72] For example, some drug candidates that were found to robustly inhibit SARS-CoV-2 infection and replication in vitro did not yield clinical

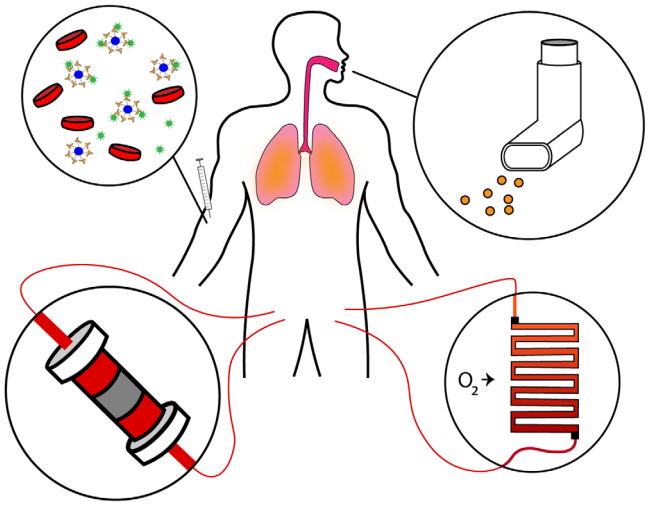

FIGURE 3 Biomaterials-based therapeutic strategies for treatment of COVID-19. Nanodecoys designed to trap and sequester virus can be directly injected into the blood (top left), while nanoparticles loaded with drugs can be formulated as inhalants to provide local delivery to lung tissue (top right). Extracorporeal blood treatments can replenish O_2 (bottom right), modulate immune signaling via proinflammatory cytokine removal or anti-inflammatory cytokine supplementation, or directly remove viral particles from the bloodstream (bottom left)

success in vivo due to adverse off-target effects.[63,73-75] When therapeutic concentrations of a potential drug cannot be safely achieved in target tissue, use becomes infeasible, as lower doses confer no therapeutic benefit while higher doses cause safety concerns.

Drug delivery systems can be designed to administer less drug overall while selectively targeting affected tissue, dramatically reducing systemic exposure and expanding the candidate pool of potential drugs. In addition, delivery of drugs with poor stability or low bioavailability to targets of interest can be more readily achieved. In our lab, this concept has already been applied to challenging hydrophobic cancer therapeutics by using novel self-assembling tyrosine-derived polymeric nanospheres (Tyrospheres) to minimize toxic side effects and maintain bioactivity.[76-79] Tyrospheres and other polymeric particle systems built from commonly used polyesters have been shown to locally deliver immunosuppressants and antibacterial therapeutics.[80-82] Other methods of creating polymeric drug delivery devices include electrospun fibermats and drug eluting stents.[83-85] These techniques can be used to overcome the challenges of implementing current therapeutics for COVID-19 that have failed due to unacceptably severe side effects. Because SARS-CoV-2 has been shown to target the lung epithelial tissue, formulation of drug delivery systems such as polymeric particles as inhalants may hold promise and have previously been demonstrated for treatment of other diseases like lung cancers.[86,87] Concerns have been raised regarding the potential for exhaled particles to aerosolize viruses and facilitate disease spread, but careful design of particle size may be able to ameliorate this risk.[88] Notably, inhalants could be administered at home, or even as a prophylactic measure. For intubated patients, drug-eluting coatings of endotracheal tubes placed into the airway could similarly target affected tissue while sparing the rest of the body; such coatings have been previously reported.[89]

Nanodecoys

In an alternate nanomaterials-centered strategy, nanostructures can be designed to mimic living cells. These particles, called nanodecoys, are built from, or incorporate cell membrane-derived materials to trap and sequester viruses. Rao et al. captured Zika virus with nanodecoys comprised of gelatin nanoparticles cloaked in mosquito-derived cell membrane, attenuating infection and preventing passage of the virus into the fetal mouse brain.[75] Current knowledge of routes of entry used by SARS-CoV-2 could be exploited to create nanoscale cell-mimicking decoys for viral trapping. In particular, SARS-CoV-2 fusion with host cell membranes is now known to proceed through interactions between viral S proteins, ACE2 and proteases such as the transmembrane protein TMPRSS2.[9,51,90] Administration of soluble ACE2 has been proposed for blocking S proteins from interacting with membrane-bound ACE2, and efforts to identify short peptide fragments of the full length protein with equivalent or enhanced S protein-binding capabilities have been reported.[51,91] Moreover, decorating cell-mimetic nanoparticles with the ACE2 protein or related peptide fragments could provide an even more biomimetic presentation of the protein. At the same time, nanodecoys could present cocktails of surface proteins in defined spatial arrangements to more closely mimic host cells. Such strategies could actively engage S protein fusion machinery rather than simply block S protein receptor-binding domains, resulting in deactivation of the virus.

Extracorporeal blood treatment

Another therapeutic strategy involves the use of extracorporeal blood treatments to mitigate the most damaging aspects of COVID-19. ECMO devices are used clinically for the most critically ill patients, but these machines are typically in even shorter supply than ventilators, are costly to operate, and are typically only found at specialized centers.[92,93] Alternatively, emerging nanoparticle and microparticle oxygen carriers could lead to the development of more accessible extracorporeal blood oxygenation strategies.[94] For severely ill patients however, oxygenation alone may not be sufficient to reduce mortality rates. A recent retrospective analysis of Chinese patient data revealed that almost half of the COVID-19 patients treated with ECMO still died from septic shock or multi-organ failure.[63] To improve survival, mitigation of inflammatory signaling is crucial. Pro-inflammatory cytokine removal can be achieved by flowing blood through polymeric sorbent cartridges, while administration of mesenchymal stem cell (MSC)-derived factors can exert potent anti-inflammatory immunomodulatory effects.[95,96] For example, CytoSorbents™ developed an extracorporeal blood purification device called CytoSorb®. The device, which looks like a large cylindrical cartridge, utilizes proprietary polymer beads to sequester pro-inflammatory mediators from blood, is designed for use with standard dialysis equipment, and recently received EUA for the treatment of COVID-19 patients. Alternatively, Sentien Biotech has developed a combination product called

SBI-101 that houses allogeneic MSCs in a hollow-fiber hemofilter device. By flowing blood through the device, anti-inflammatory MSC-derived molecules can perfuse patient blood without necessitating cell transplantation, eliminating risks of immune rejection while improving cell survival and overcoming pharmacokinetic barriers associated with transplantation. This strategy has shown promise for treatment of kidney and liver failure in animal model, and a Phase I/II clinical trial evaluating use in human acute kidney injury patients is underway (NCT03015623).[97-99] In late June 2020, another Phase I/II trial was also announced to investigate the use of SBI-101 for treatment of COVID-19 patients suffering from acute kidney injury and already receiving renal replacement therapy (NCT04445220). Finally, a more direct approach to hemofiltration has been taken by ExThera Medical with the Seraph® 100 filter, a heparin-functionalized ultra-high molecular weight polyethylene bead-based filter. This technology has been shown to sequester a variety of pathogens from methicillin-resistant *Staphylococcus aureus* to cytomegalovirus, without filtering out anti-infectious drugs, and has been granted an EUA for treatment of COVID-19 patients.[100-103]

2.2.2 | Vaccines

While therapeutics are designed to treat actively infected patients, vaccines effectively reduce population susceptibility to infection. The development of a SARS-CoV-2 vaccine holds the most potential for attenuating COVID-19 spread, motivating a flurry of research in vaccine development as recently reviewed by Liu et al.[2,104] Previous work on SARS vaccine development focused on live attenuated whole virus vaccines and S protein subunit vaccines; an inactivated virus MERS vaccine was also developed. During in vivo studies however, these vaccines were derailed by evidence of an immune hypersensitive-type lung pathology on exposure of vaccinated subjects to a live virus challenge.[33,105] Another problem with the S protein subunit vaccines was antibody-dependent enhancement—post-immunization antibodies which actually enhance viral cell entry upon live virus challenge. A commentary by Hotez et al. attempts to address both these issues and suggests that for COVID-19 a subunit vaccine of just the receptor binding domain of the S protein may confer immunity without inducing immunopathologies.[105]

With that in mind, the ideal vaccine elicits a robust immune response characterized by sustained antibody production and conferred immunity across a large and diverse patient population. Biomaterials strategies to augment conventional vaccine design and development have been extensively reviewed.[47,106] The key advantage to biomaterials-based approaches is enhanced control over the vaccination process. Conventional vaccine strategies are essentially comprised of one to several bolus injections of antigenic material, while engineered systems allow for fine manipulation of antigen delivery rate and presentation as well as host immune cell response. As our understanding of acquired immunity continues to evolve, biomaterials can provide the tools for precise immune modulation.

Multiple biomaterials-based solutions such as nanoparticles, liposomes, scaffolds, and microneedles have been proposed. Nanoscale structures can be designed to protect antigen cargo, present antigens in biomimetic formats, and allow for specific immune cell targeting.[47] This can be achieved by leveraging modifications in nanoparticle size, shape, surface chemistry (particle charge, hydrophobicity), and material composition.[107] Microneedles are applied topically and slowly dissolve allowing for pain-free sustained antigen delivery into the skin, a highly immune-reactive organ.[108,109] Dr. Mark Prausnitz and colleagues have conducted extensive work to develop microneedle-based polio, influenza, and hepatitis B vaccines.[110-112] Kim et al. developed a polymeric microneedle array-based MERS vaccine using a MERS-CoV S protein subunit trimer as an antigen, and demonstrated robust and sustained antigen-specific antibody responses in mice.[113] Ongoing efforts to develop the MERS vaccine were then applied to rapidly design and produce a similar microneedle vaccine based on SARS-CoV-2 S protein subunit trimers that similarly showed promise in mice. Plans are underway to coordinate a first-in-man Phase I clinical trial.[45] In some cases, polymeric materials may also act as adjuvants. Adjuvants are broadly defined as a substance that enhances the antigenicity of an antigen. Babensee et al. have shown that certain biomaterials have the ability to selectively upregulate the differentiation and maturation of dendritic cells, which play an important role in antigen presentation, and therefore act as adjuvants.[114] Another example of this is when mice mounted robust antibody responses to bovine serum albumin when antigen was delivered from subcutaneously implanted biodegradable tyrosine-derived polymer devices.[115] This was due to adjuvant activity of one of the polymer degradation byproducts. In addition, anti-bovine serum albumin (BSA) antibody titers were significantly higher when BSA was delivered from tyrosine-derived polymer devices as compared to poly(bisphenol A-iminocarbonate) controls.

2.3 | Ex vivo antiviral strategies

2.3.1 | Surface inactivation

As previously discussed, the main method of virus spread is through aerosolized particles. Large droplets (>20 μm) land on surfaces close to the point of emission while small droplets (<5–10 μm) begin to evaporate and become small enough to be transported by air several meters from the point of emission.[116] A major problem with viruses is their ability to remain active on surfaces. In this way, contaminated surfaces such as doorknobs, toilet handles, tables, and utensils used in restaurants, and touch screens can facilitate viral transfer from sick to healthy individuals. While surfaces can be sanitized with a variety of household cleaners, sterilizing after each individual use is difficult to maintain. This is especially problematic for areas with a high concentration of infected patients or a particularly susceptible population such as hospitals or senior living facilities. Surface stability varies by virus, but according to a recent study, SARS-CoV-2 can remain active on plastic, stainless steel, and cardboard for ~3.8, ~5.8, and ~ 6.5 hr, respectively at a temperature of 21–23°C with 40% humidity.[117] Strategies aimed at mitigating viral spread generally look to deactivate viruses upon landing on surfaces.[118,119] Existing antiviral surfaces see

limited use in clinical practice even though ongoing research supporting different biomaterials coatings has been around for decades.[120,121] Biomaterials have been used for virus inactivation and have great potential to help combat the spread of SARS-CoV-2 and future viral outbreaks.[122-124] Indeed, reformulating antiviral materials as virucidal surface coatings can attenuate contamination of surfaces and minimize disease propagation.[125,126] In addition, antiviral biomaterials coatings can be applied to conventional personal protective equipment (PPE) to allow for multiple uses.[127]

Metals

Biomaterials coatings with known antiviral properties can be made from metals, surfactants, and natural products. Metals, especially silver, gold, and copper have been used for decades as antiviral agents.[128-130] It is important to acknowledge the NIH and FDA's guidance on silver particles and that colloidal silver can cause serious side effects and are not meant for internal ingestion.[131,132] Silver nanoparticles have shown to inactivate HIV-1, herpes simplex virus type 1, and influenza among other viruses.[133-136] The nanoparticle size plays a key role in HIV-1 deactivation, where only particles within the range of 1–10 nm are able to bind to the sulfur-bearing residues on the viral envelope. It is proposed that silver's antiviral activity is attributed to the silver nanoparticles physically inhibiting the binding between the virus and the host cell.[137,138] Gold nanoparticles behave in a similar manner by binding to virus particles thereby blocking the cell receptor and preventing the virus from starting the viral cycle. These nanoparticles suppress viral infection by selectively cleaving disulfide bonds, which blocks virus membrane fusion to the cell and prevents viral entry into the host cell (Figure 4a).[139] Gold nanoparticles have also shown to inhibit measles and have low cytotoxicity at viral inhibitory concentrations and may prove useful for viral inactivation for other enveloped viruses.[140] Copper oxide nanoparticles are used to inactivate both enveloped and nonenveloped RNA and DNA viruses.[141] Compared to silver nanoparticles which act as a physical barrier, copper oxide nanoparticles actively damage virus complexes. Copper oxide nanoparticles easily convert between Cu(I) and Cu(II) in vivo, and Cu(II) ions oxidatively damage biomolecules, including viruses.[141] Metal nanoparticles are toxic in vivo causing severe side effects, however by altering the concentration, particle size, or metal coating composition toxicity can be significantly reduced.[142] Mohammadyari, et al. reported that in doses <400 ppm, copper oxide nanoparticles 50 nm in size had no adverse side effects on rat kidney or liver; however, above 400 ppm the particles were toxic.[143] Silver and copper nanoparticles have been incorporated into clothing, wound dressings, and implant coatings due to their antiviral activity.[134] Although incorporation of metal nanoparticles into textiles has been extensively studied, their side effects and toxicity have been less intensively investigated. Due to their small size, nanoparticles can enter the human body through various routes and cause harmful side effects.[144] Further research into metal nanoparticle antiviral activity, toxicity, and cost-effectiveness can further enhance the use of nanoparticles for both in vivo and ex

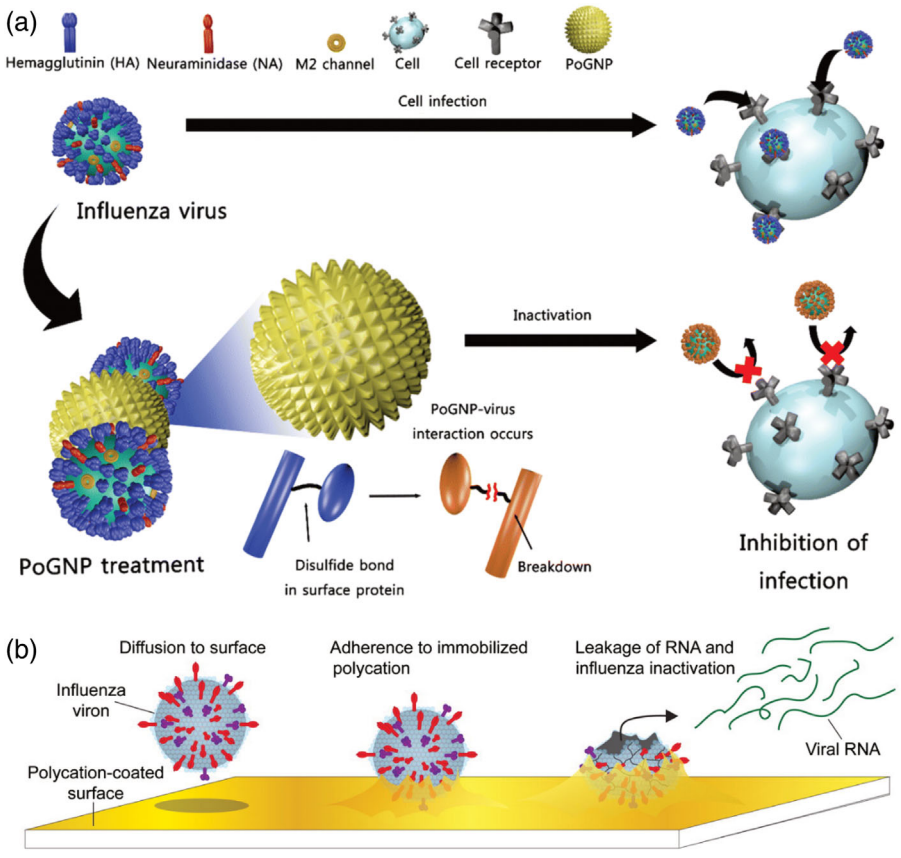

FIGURE 4 Mechanisms of materials to prevent virus spread and inactivation. (a) Use of porous gold nanoparticles (PoGNP) to prevent influenza virus attachment to cell surface; M2- matrix ion channel 2. Reproduced with permission from Kim et al[139] (b) Proposed mechanism of Influenza A virus inactivation by polymer N,N-dodecyl methyl-polyethylenimine (DM-PEI) paint coated on surfaces. Reproduced with permission from Hsu et al.[160]

vivo applications, which can be especially useful for incorporation into PPE. Copper's antiviral abilities have shown to be effective for the deactivation of influenza A virus through an increase in copper ion diffusion through the virus' lipid membrane.[145] Incorporation of Cu(II) held in place by zeolites into cotton textiles significantly increased inactivation of avian influenza H5 subtype virus.[146] Binding cationic copper ions into textiles, latex, and other polymer products during manufacture demonstrated virus inactivation properties for HIV-1.[129] In addition to metals, treating textiles with a boron-triclosan mixture showed efficacy at significantly reducing viral activity of human adenovirus and poliovirus type 1 strains.[147] Virus inactivating gloves are of particular interest in today's pandemic which can serve as a way to increase the safety of hospital workers. Incorporation of an anti-infective agent, chlorhexidine, into the interior of examination gloves to deliver the anti-viral agent within 10 minutes of exposure to a liquid has been patented in the 1990s.[148] However, a large amount of anti-infective agent is required which does not provide a cost-effective material.

Surfactants

Surfactants are chemical species that create self-assembled micelles in solution and contain both a hydrophilic and a hydrophobic group.[149] They are often the common active ingredient in household disinfecting agents and have shown high antiviral activity.[150] The use of surfactants as sanitizing agents for virus inactivation has been recently reviewed by Lin et al.[151] Surfactants can be broken down into cationic—often found in fabric softeners, hair conditioners, antiseptic hand wash, and mouthwash; anionic—often found in detergent and personal-care products; nonionic—often found in foaming and emulsifying agents; and zwitterionic species—often found in laundry and cosmetic products. All are capable of inactivating viruses by solvating and disrupting the lipid-based envelope of the virus or by targeting the capsid proteins.[152-159] Although beneficial as sanitizing agents, surfactants are less commonly used to prepare virus deactivating surfaces. A significant research advancement lies in utilizing these antiviral agents in biomaterials applications. This approach has the potential to minimize the lifespan of viral particles on surfaces thereby minimizing transmission. One method uses surfactants as polymer paints, which can be applied to surfaces to halt the spread of viral infection. Cationic surfactant N,N-dodecyl methyl-polyethylenimine (DM-PEI), a quaternary ammonium compound, has shown to be an antibacterial and enveloped antiviral polymer due to its ability to rupture the cell membranes by interaction with the polycationic chains.[160] The DM-PEI coating acts as an adhesive for the virus particle, which immobilizes the virus, and causes damage from the hydrophobic polycation in DM-PEI (Figure 4b). The virus' genetic material is released leaving residual inactivated virus particle adhered to the substrate surface. Biosurfactants are amphiphilic compounds, mostly produced at the microbial cell surface and are able to accumulate between fluid phases.[161] Similar to chemical surfactants, biosurfactants are used in industrial, agricultural, cosmetic, and pharmaceutical applications.[162] However, biosurfactants can be easily degradable, have a low toxicity, have high availability from raw materials, and often are not affected by environmental factors (pH, temperature, ionic strength).[163] Although mostly used for antimicrobial applications, biosurfactants have been used to inactivate retrovirus, herpes virus, and HIV, among others.[164] Biosurfactants are more commonly used against enveloped viruses due the physicochemical interactions between the virus lipid membrane and the membrane-active surfactant causing viral disintegration.[165] Often biosurfactants are used in preventing biofilm formation and as anti-adhesives in order to prevent bacterial and viral growth.[166] While underdeveloped, the use of surfactants as coatings to achieve antiviral activity has great potential to improve the safety of individuals in high trafficked areas such as airports or in places of high transmission rates such as hospitals.

Naturally derived products

Many naturally derived products have been used to prevent virus transmission; cellulose has been used in meat products and as the wax coating on fruits and vegetables.[167] Antiviral coatings have been approved for use on food items and packaging to prevent the spread of human noroviruses and hepatitis A virus, among others.[168] These coatings are often made from polysaccharides, cellulose, starch, pectin, alginate, lipids, or other natural polymers and are generally termed safe for ingestion.[169] Active compounds derived or extracted from grape seed, green tea, *Aloe vera*, Eriobotryae folium, and cinnamaldehyde are a few naturally derived compounds used in active packaging against marine norovirus.[170-172] Catechins present in green tea extract contain antioxidant, anticarcinogenic, anti-inflammatory and antimicrobial properties and have recently been shown to exhibit antiviral activity against the food-borne pathogens hepatitis A and murine norovirus.[173,174] Cyclodextrins are another group of naturally occurring macrocyclic molecules that have been used for their virucidal activity.[175] These naturally occurring products are most commonly used in food packaging applications and have not been translated to applications outside of the food industry.

2.3.2 | Viral filtration

To prevent the spread of human-to-human transmission, face masks have become mandated in many countries when traveling, shopping, or when simply leaving the house. Face masks have received significant review since the beginning of the pandemic; which fabrics are the best for particle filtration, can masks be reused, what are their utility lifespans, and what happens with the extra waste produced when they are discarded. One commonality most often agreed upon is that they are necessary to help filter aerosolized droplets from the air to minimize viral transmission. Existing filtration strategies see more regular clinical use, especially in the context of negative pressure isolation rooms and face masks. Currently they strive to capture viral particles from the air, but do not deactivate the particles. As a result, air filtration devices such as respirators and masks must be changed frequently when exposure to virus is suspected, a practice that contributes to ongoing PPE shortages and contributes to the generation of nondegradable waste. Biomaterials strategies can be employed to develop novel filtration devices capable of capturing and deactivating SARS-CoV-2 and other viruses.

Face masks

The most commonly used viral filtration devices are face masks. Masks are a necessary component for the health and safety of individuals who are exposed to aerosolized virus particles; however, not all masks are designed for virus filtration.[176] The most common masks used are (a) surgical masks which are capable of filtering 98% of 3 μm particles making them effective in blocking large-particle droplets, but not able to filter aerosolized particles transmitted by coughs or sneezes; and (b) performance level face masks such as N95 masks which are capable of filtering 95% of 0.1–0.3 μm particles.[177-179] To reduce the spread and transmission of viruses, it is important to design masks that have a minimum porosity threshold of an individual virus particle—20–300 nm.[180,181] There is an abundance of current research focusing on chemically modifying masks to provide viral deactivation properties, which would allow for multiple uses, reducing PPE shortages, and nondegradable waste generation. Most masks are made from non-biodegradable, non-renewable petroleum-based polymers that are already contributing to environmental pollution worldwide.[182,183] To reduce this and future pandemics' environmental impact, it is important to design masks that are made from biodegradable materials or can be multi-use. Ideally, these masks would also have antiviral activity and be more effective at filtering virus particles. One example of a virus-functionalized mask is by Tiliket et al. who chemically modified the mask layers by incorporating DM-PEI functionalized Kimwipes® Lite (non-woven cellulosic fiber filter) layers into a low-cost commercial medical mask which improved the affinity for trapping airborne influenza virus A (H5N2).[180] Other approaches to modify masks for viral filtration efficacy include the incorporation of natural extracts from green tea (QR-435, catechin, theaflavin) into the masks layers, which successfully block the passage of virus or inactivate viruses by inhibiting viral replication; impregnating copper oxide into N95 respiratory masks to mitigate viral titer recovery of influenza virus; and incorporating sialic acid, which mimics human cell receptor sites, to create an affordable, easy-to-produce filter capable of removing viruses such as influenza.[184-188] Due to more strict requirements to wear a face covering, Konda et al. studied the efficacy of different commonly available fabrics for preventing the inhalation of aerosol particles.[189] They found that tighter weaves with low porosity (i.e., high thread count cotton sheets) are ideal for mechanical filtration whereas natural silk, chiffon, and flannel provide high electrostatic filtering capabilities. A hybrid mask incorporating both cotton with silk or chiffon had increased filtration efficiency. Designing and implementing a mask that is able to filter or deactivate virus particles, is cost effective, is environmentally degradable, and has the potential to change the rate of virus spread worldwide.

Air filtration

A similar avenue of research is based on the use of ventilators which typically are fitted with an inhalant and an expiratory filter. However, the chemical make-up of these filters is of extreme importance. When placed on mechanical ventilation, infected patients can contribute to the spread of the virus through the expiratory valve aerosolizing droplets into ambient air. Several filters, PALL Ultipor® 25, Ultipor® 100, and BB50T among others, are available for use on the expiratory limb of ventilators that have shown to filter >99.999% of H1N1 virus.[190,191] Most filters fitted on respirators are high efficiency particulate air (HEPA) filters which are adequate for bacterial, dust, pollen, mold filtration, and other particles larger than 0.2 μm in size; however they are not sufficient for virus particle filtration.[32,191] It is important to design a filtration device that can be attached to ventilators to mitigate the spread of aerosolized virus particles. Simultaneously, it is important to filter building air, especially in a hospital setting where aerosolized virus particles can be at a high concentration. Buildings are often fitted with HVAC systems that have a filter for airborne pathogens.[192] Robust filters also exist for virus filtration that involve carbon-fiber ionizers designed to generate air ions and charge aerosolized virus particles which allows for the filter to capture the virus particles.[193] Home filter devices have been designed to inactivate common airborne viruses through the use of palladium-titanium dioxide catalysts with vacuum ultraviolet irradiation.[194] It is important to implement these virus filtration systems in high traffic areas or areas with a high virus concentration to create a constant airflow and deactivate virus particles. It has been shown that when virus particles become electrostatically charged, they are attracted to an oppositely charged surface.[195,196] Hagbom et al. developed a small-scale device using charged surface technology to both inactivate and filter Influenza A and H1N1 virus particles by placing the device between an infected and healthy individual.[197] It was proposed that reduced virus infectivity is caused by damaging the viral lipid envelope through peroxidation reactions between the reactive oxygen species and the lipid and protein. When the ionizing device was placed between two guinea pig cages, one infected with Influenza A and one healthy, none of the exposed guinea pigs tested positive for influenza-specific immune response serum compared to 75% in exposed guinea pigs where an inactive ionizing device was present. Such a device, if scaled up appropriately, has the potential to be either used in hospital settings where hospital personnel are closely interacting with infected patients or to create a highly sensitive device to capture virus particles to help in the detection and identification of novel viruses. Similar virus filtration and inactivation systems (filtration, microfiltration, hydrophobic or ionic surface modifications) have been studied for their ability to trap viruses during water filtration.[198] Of particular interest is the use of previously mentioned DM-PEI as a polyelectrolyte coating on commercially available microfiltration membranes which not only remove but also inactivate hepatitis E surrogates.[199]

3 | CONCLUSIONS

Much of our current knowledge stems from the previous viral outbreaks, SARS and MERS, but COVID-19 has transcended those in overall mortality, prevalence, and social and economic impact. This review has described several specific opportunities for the biomaterials community to contribute significantly in the fight against the COVID-19 pandemic. Importantly, this is not an exhaustive list but

serves to illustrate a variety of recent advances and future directions for biomaterial research. Given how universal this outbreak has been, global readiness and scientific collaboration are imperative.

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