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Review

Biomaterials-Based Opportunities to Engineer the Pulmonary Host Immune Response in COVID-19

Bader M. Jarai, Zachary Stillman, Kartik Bomb, April M. Kloxin, and Catherine A. Fromen*

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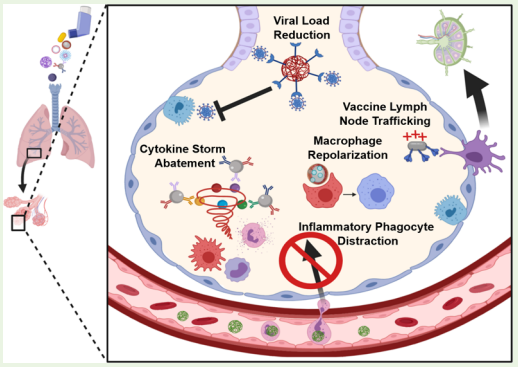
ABSTRACT: The COVID-19 pandemic caused by the global spread of the SARS-CoV-2 virus has led to a staggering number of deaths worldwide and significantly increased burden on healthcare as nations scramble to find mitigation strategies. While significant progress has been made in COVID-19 diagnostics and therapeutics, effective prevention and treatment options remain scarce. Because of the potential for the SARS-CoV-2 infections to cause systemic inflammation and multiple organ failure, it is imperative for the scientific community to evaluate therapeutic options aimed at modulating the causative host immune responses to prevent subsequent systemic complications. Harnessing decades of expertise in the use of natural and synthetic materials for biomedical applications, the biomaterials community has the potential to play an especially instrumental role in developing new strategies or repurposing existing tools to prevent or treat complications resulting from the COVID-19 pathology. Leveraging microparticle- and nanoparticle-based technology, especially in pulmonary delivery, biomaterials have demonstrated the ability to effectively modulate inflammation and may be well-suited for resolving SARS-CoV-2-induced effects. Here, we provide an overview of the SARS-CoV-2 virus infection and highlight current understanding of the host's pulmonary immune response and its contributions to disease severity and systemic inflammation. Comparing to frontline COVID-19 therapeutic options, we highlight the most significant untapped opportunities in immune engineering of the host response using biomaterials and particle technology, which have the potential to improve outcomes for COVID-19 patients, and identify areas needed for future investigations. We hope that this work will prompt preclinical and clinical investigations of promising biomaterials-based treatments to introduce new options for COVID-19 patients.



KEYWORDS: *COVID-19, SARS-CoV-2, biomaterials, nanoparticles, inflammation, immune engineering*

INTRODUCTION

The emergence of the SARS-CoV-2 pathogen in 2019 has prompted the scientific community to work tirelessly in search of therapeutic solutions to slow or stop the COVID-19 pandemic. While significant progress has been made to characterize the effects of SARS-CoV-2 and new information on the pathogen and associated host response continues to emerge daily, there are still outstanding mechanistic questions that have yet to be addressed regarding the COVID-19 pathology and its long-term implications. SARS-CoV-2 is primarily a respiratory infection; however, severe COVID-19 can present with multiple organ involvement including cardiovascular,[1] neurological,[2] and renal[3] damage that is largely driven by dysregulated host immune response.[4] Therefore, successful modulation of the immune microenvironment is a critical therapeutic goal for improving patient outcomes, especially for critically ill COVID-19 patients. Several therapeutic options modulating host immune-specific targets have been developed or repurposed for mitigating COVID-19 symptoms, and many clinical trials are underway; however, current attempts to resolve hyperinflammatory states mostly rely on system-wide immunomodulatory strategies that may benefit from a more targeted approach. Therefore, particle engineering solutions that target the host immune response, particularly in affected organs, are desperately needed to avoid potential off-target effects of potent immunomodulatory treatments.

The goal of this article is to summarize the current clinical understanding of immune response to SARS-CoV-2 along with key host immunological factors implicated in COVID-19 which will inform immune engineering approaches that hold therapeutic potential for mitigating COVID-19 responses occurring in the lung, among other organs. We point to

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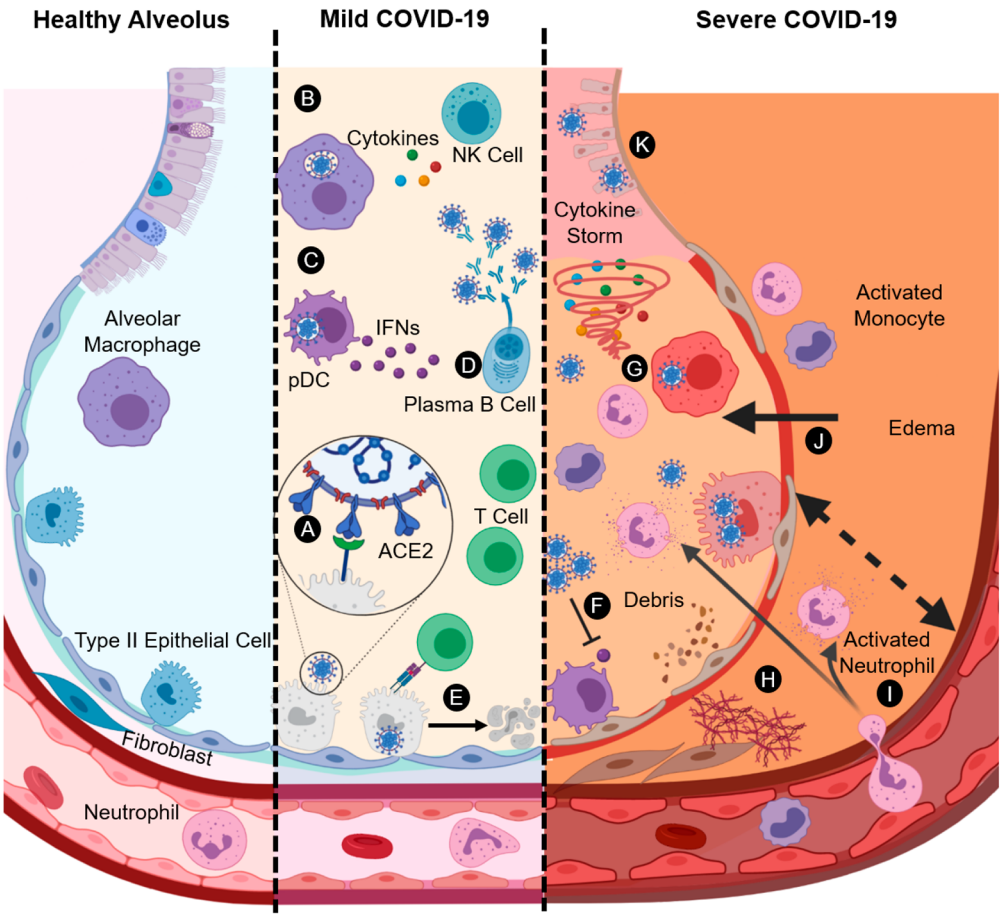

Figure 1. Immune landscape of the alveolar region in healthy, mild, and severe states during COVID-19. A) Infection of type II alveolar epithelial cells with SARS-CoV-2 through the ACE2 receptor. B) Activation of alveolar macrophages following infection/recognition of virus and release of pro-inflammatory cytokines. C) Type I IFN response initiated by plasmatocytoid dendritic cells (pDCs) and recruitment of lymphocytes. D) Plasma B cells producing SARS-CoV-2-specific antibodies following maturation and priming by innate immune cells. E) SARS-CoV-2-specific CD8+ T cells causing apoptosis of infected cells. F) Impaired type I IFN response. G) Cytokine storm by activated macrophages and recruited inflammatory leukocytes. H) Deposition of fibrous strands and extracellular matrix leading to fibrosis and scarring. I) Degranulation of activated neutrophils recruited from the bloodstream. J) Fluid buildup in the alveolus from edemous tissue and widening of interstitium. K) Shedding of ciliated epithelial lining and formation of debris.

lessons learned from therapeutic approaches in the fields of biomaterials and nanomedicine that have demonstrated robustness in inducing anti-inflammatory and immunomodulatory effects, particularly in the context of airway inflammation. Biomaterial-inspired drug delivery designs offer many opportunities for tunable immune modulation as tolerogenic therapeutics or prophylactic/therapeutic vaccines[5] because of their advantageous properties. Engineered particle formulations can be delivered via inhalation or injection with customizable biodegradability that can take advantage of either extracellular or intracellular cues alongside properties including passive or active targeting to lung immune cells, detailed surface functionalization for precise stimulation of innate immune cells, and high loading capacities of cargo with varied properties.[6] Collectively, these considerations lead to highly modular systems capable of meeting the drug delivery and immune-modifying needs of COVID-19-related complications. We provide a potential roadmap for modulating the pulmonary immune response experienced during COVID-19 and seek to answer one key question: *what are untapped immune engineering approaches to control unwanted immune responses in the lung as a result of COVID-19*?

INFECTION, INFLAMMATION, AND HOST FACTORS IN COVID-19 PATHOPHYSIOLOGY

Understanding the structure of the SARS-CoV-2 virus and the mechanism of infection as well as lessons from other closely related coronavirus infections is critical for development of prophylactic vaccine candidates and treatment options for mitigating severe symptoms. Innate and adaptive immune responses play an instrumental role in recovery and disease severity. Furthermore, emerging patterns in biological factors including age, sex, and pre-existing health conditions are reported with regard to their impact on SARS-CoV-2 infection and disease severity. In this section, we give an overview of the SARS-CoV-2 pathogenic mechanism of host cell invasion as well as a summary of immune responses and biological factors that result from infection. We also discuss which of these, based on current understanding, impact the severity of the COVID-19 pathology.

SARS-CoV-2 Etiology and Host Cell Invasion. Coronaviruses are viral pathogens that belong to the Coronaviridae family and are enveloped, single-stranded, positive-sense RNA viruses with a genome length of ∼30 kb.[7,8] Structurally, coronaviruses have four main proteins including spike (S)

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glycoproteins, small envelope (E) glycoproteins, membrane (M) glycoproteins, and nucleocapsid (N) proteins, along with several other proteins.[9] The spike glycoprotein is a transmembrane, trimeric glycoprotein that facilitates binding and invasion into the host cell.[10] Techniques like electron microscopy have identified SARS-CoV-2 to be a round or oval shaped virus with an approximate diameter of 60−140 nm and a crown-shaped appearance.[11] SARS-CoV-2 is closely related to two other coronaviruses, severe acute respiratory syndrome coronavirus (SARS-CoV-1) and Middle East respiratory syndrome coronavirus (MERS-CoV), both of which have the potential to replicate in the lower respiratory tract and result in fatal pneumonia.[12] SARS-CoV-2 shares 79% genome sequence identity with SARS-CoV-1, another human coronavirus, and has approximately 98% genomic similarity to the bat coronavirus, RaTG13.[13,14]

SARS-CoV-2 is primarily transmitted via exhaled aerosol particulates containing virus that can cause infection following inhalation.[15] Upon infection with SARS-CoV-2, the median incubation period is around 4−5 days[16,17] followed by symptom onset within 11.5 days.[17] Invasion of SARS-CoV-2 into the host cell initiates with viral binding to angiotensin-converting enzyme 2 (ACE2) receptor (Figure 1A).[10,18] Previous studies with SARS-CoV-1 have identified increased ACE2 receptor expression in pulmonary type II epithelial cells, making them likely targets for invasion.[19−21] ACE2 expression decreases when moving deeper into the respiratory tract, from higher expression in the upper airways to lower expression in the lower respiratory tract, with high SARS-CoV-2 infectivity in the nose relative to the alveolar region.[22] The spike (S) protein on the viral surface is comprised of two functional subunits: S1 and S2. S1 subunits facilitate binding with the host cell receptor and comprise an amino-terminal domain and a receptor-binding domain (RBD).[23] The RBD binds to the ACE2 receptor followed by endocytosis of viral components into the host cell.[24,25] Following the binding of SARS-CoV-2 to ACE2 and endocytosis, the spike protein undergoes protease cleavage, exposing the S2 site, which results in membrane fusion and release of viral contents into the cell cytoplasm.[26] Studies have identified increased affinity of the ACE2 receptor with RBD of SARS-CoV-2 relative to SARS-CoV-1, which might explain the greater relative infectivity of SARS-CoV-2.[24,27] The role of the cellular serine protease TMPRSS2 was also identified in promoting host cell entry of the virus in SARS-CoV-2 infections.[28] In addition to TMPRSS2, recent literature has implicated other proteases such as TMPRSS4, Mpro, PLpro, and RdRp, which might play a role in host cell invasion.[29,30]

Host Response to SARS-CoV-2. Both innate and adaptive immune responses are engaged to neutralize the SARS-CoV-2 infection; however, an impaired immune response can result in severe lung pathology and infection manifestations in multiple organs[4] including coagulation abnormalities and thromboembolic events that are common in COVID-19 deaths.[31,32] The severity of initial infection and viral load, combined with the timing and extent of the host immune response, can result in symptoms ranging from asymptomatic or mild to severe pneumonia and acute respiratory distress syndrome (ARDS) with multiple organ failure, as discussed in the following sections. It is critical to increase our understanding of the kinetics, progression, and timing of both healthy and improper host immune involvement prior to developing immune-modifying therapeutics.

Innate Immune Response. The first stage of host immune involvement predominantly comes from the innate immune system. During healthy lung function, the normal alveolar immune landscape mainly consists of alveolar macrophages residing at the air−liquid interface in addition to a small number of granulocytes including basophils and eosinophils.[33] Alveolar macrophages and dendritic cells (DCs) are key antigen presenting cells (APCs) of the local pulmonary innate immune system, with the mucosal lining, epithelial cells, and the complement cascade providing essential barriers to viral infection.[34] As SARS-CoV-2 targets and invades epithelial cells using ACE2 receptors, viral infection spreads, resulting in injury and death of virus-infected cells. Apoptotic cells release pathogen-associated molecular patterns (PAMPs), such as viral RNA, and damage-associated molecular patterns (DAMPs), which are recognized by innate cells using a variety of pattern-recognition receptors (PRRs). Apoptotic epithelial cell components are mainly internalized and cleared by resident pulmonary macrophages and recruited leukocytes to minimize the infection until adaptive immunity is developed.[35] PRR signaling within innate immune cells leads to robust pro-inflammatory signaling and cellular recruitment to the lung (Figure 1B). Pro-inflammatory soluble factors such as interleukin (IL)-1β, IL-8, and IL-6 are elevated in both plasma and bronchoalveolar lavage fluid (BALF[36]) of COVID-19 patients,[37,38] and increased levels of tumor necrosis factor (TNF)-α and granulocyte macrophage-colony stimulating factor (GM-CSF), as well as other cytokines and chemokines, are elevated in plasma.[39] Studies have identified that elevated levels of IL-6 correlate with the severity of the COVID-19 disease,[40] with critically ill patients having IL-6 levels ten times higher than those of severe patients in some cases.[41] Another study complemented these results by demonstrating that risk of respiratory failure for patients with IL-6 levels greater than 80 pg/mL was 22 times higher relative to patients with lower IL-6 levels.[42] Such increased cytokine presence in the lung microenvironment could potentially result in cytokine-mediated lung damage, respiratory distress, and further organ failure.[39] PRR signaling also promotes recruitment of immune cells such as monocytes, neutrophils, and T cells to the site of the infection. Upregulation of chemokines including CCL2, CCL7, and CXCL8 is reported in BALF of COVID-19 patients. These chemokines are critical for the recruitment of monocytes and neutrophils.[37,43]

Importantly, PRR signaling activates production of antiviral type I interferons (IFNs).[44] Recent clinical data support the role of the IFN response as a possible indicator of disease severity.[43] Type I IFNs are produced by plasmacytoid DCs and are critical to antiviral responses (Figure 1C).[44] IFNs activate phagocytosis in macrophages as well as the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway, which is essential in polarizing antiviral helper T cells.[45] With a robust and early IFN response, SARS-CoV-2 infections remain mild or asymptomatic, while a delayed and/or impaired IFN response leads to increasingly severe disease.[46−48] Given the essential antiviral function of IFNs and the JAK-STAT pathway, many viruses have evolved mechanisms to suppress or inhibit functions throughout the IFN and JAK-STAT pathways. Evidence from both SARS-CoV-1 and MERS-CoV viruses implies that SARS-CoV-2 may also have functionality that directly diminishes host IFN response.[43]

APCs specifically provide the bridge between innate and adaptive immune response. Resident pulmonary DCs are likely

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involved with priming the adaptive response through exposure to cytokines and SARS-CoV-2 antigens. There are generally two classes of pulmonary DCs responsible for antigen presentation: CD103+ and CD11b+, where CD103+ DCs are the main migratory subset. Upon infection and activation, DCs migrate to lymph nodes (LNs) and interface with T and B cells to present processed SARS-CoV-2 antigens through immunological synapses.

Adaptive Immune Response. Defense by the innate immune system allows for the initiation of a robust adaptive immune response. In mild COVID-19 cases, patients have not only an early and robust IFN response and highly functional innate response but also a strong, multifaceted adaptive immune response to manage and clear the viral infection (Figure 1D). Virus-specific antibodies generated by plasma B cells and CD8+ (cytotoxic) T lymphocytes are educated by activated DCs draining from the lung to nearby LNs. SARS-CoV-2 neutralizing antibodies are found in plasma of patients and have strong affinity to the RBD of S protein, inhibiting ACE2 binding.[49] Antibodies with specificity to N protein are also detected, and IgA, IgG, and IgM classes of antibodies were found,[50] similar to anti-RBD antibodies.[51] Clinically, a large proportion of the infiltrating adaptive immune cells is T cells, where both CD4+ and CD8+ T cells play a critical role. CD4+ T cells promote B cell activation and immune cell recruitment through cytokine production and are essential for production of neutralizing antibodies. CD8+ T cells are recruited to the airways to trigger apoptosis of infected cells (Figure 1E). Collectively, through robust neutralizing antibody and diverse T cell responses, a proper host immune system is able to clear the SARS-CoV-2 infection and develop robust serological and mucosal immune memory. Recent studies reveal the robust formation of B and T cell memory following SARS-CoV-2 infection, indicating the potential for long-term protection from future infections despite decay in neutralizing antibody titers.[52,53] Detailed clinical studies are needed to investigate whether memory B and T cells are able to protect against SARS-CoV-2 reinfection and prevent severe pathology in the absence of an acute humoral response. Interestingly, computerized tomography (CT) scans of COVID-19 infected patients showed temporal changes and ground glass opacification in the lungs regardless of disease severity,[49] indicating broad pathological impacts even in asymptomatic patients and implying untold long-term implications that may extend past recovery from infection.[54]

Immune Manifestations in Severe Disease. A delayed and/or impaired IFN response allows for an initial immunodeficient state (Figure 1F) followed by a hyperresponsive, runaway inflammatory positive feedback loop. This impaired IFN response is characterized by enhanced recruitment of inflammatory infiltrates and can result in a cytokine storm (Figure 1G), with elevated levels of IL-6 and TNF-α being hallmarks and strong predictors of severe COVID-19.[55,56] A hyperinflammatory state may also be responsible for deposition of extracellular matrix and fibrous strands, ultimately leading to fibrosis and scarring (Figure 1H).[57,58] The upregulation of neutrophil chemoattractant IL-8, which may account for the increased neutrophil counts observed in the lungs of COVID-19 patients (Figure 1I), can cause further inflammation through release of neutrophil extracellular traps (NETs) that also induce lung injury.[59] In severe COVID-19, patients show high levels of NET components including cell-free DNA and DNA complexes, as well as citrullinated histone H3.[59,60] Activated neutrophils and high occurrence of prothrombotic autoantibodies that promote clotting events have been implicated in COVID-19 disease severity.[61] The impaired immune response, which includes the cytokine storm, otherwise known as hypercytokinemia, can result in plasma leakage, vascular permeability, and edema, all of which are commonly observed in severe COVID-19 patients (Figure 1J,K). The cytokine storm and the extent of recruitment of inflammatory cells are indicative of the severity of the COVID-19 infection. Elevated levels of inflammatory cytokines, D-dimers, C-reactive protein (CRP), and other inflammatory factors, as well as lymphopenia or depletion of antiviral lymphocytes, are associated with severe COVID-19 infections.[39,62] The cytokine storm in COVID-19 is unique but is similar to that in cytokine release syndrome (CRS),[63−65] which is mainly induced by viral infections and can result in systemic inflammation, hypercytokinemia, and multiple organ failure.

Importantly, T cell numbers are directly correlated with disease severity; lymphopenia, or low lymphocyte counts, have been commonly reported in severe COVID-19 cases.[66] This phenomenon has been attributed to apoptosis caused by the cytokine storm[66] and infection of T cells with SARS-CoV-2, which ultimately leads to T cell death.[67] Furthermore, T cell exhaustion markers were detected in severe COVID-19.[66] However, recent reports show evidence for reversal of lymphopenia after recovery.[68] In addition, reduced natural killer (NK) counts and the emergence of adaptive NK subsets are associated with severe disease.[69] Some clinical data suggest that there may be relatively high antibody titers associated with severe COVID-19;[70] while antibodies have a critical role in neutralizing virus to control infections, activation of Fcγ receptors, degranulation of phagocytes, and priming release of cytokines may also contribute to the cytokine storm. Projections from SARS-CoV-1 studies and some reports with COVID-19 patients show elevated levels of complement components in serum and *post mortem* autopsy lung sections, indicating the potential for complement activation to increase the severity of inflammation and to serve as a host mediator of the resulting ARDS.[71−73]

Lung-resident alveolar macrophages are not thought to be main drivers of inflammation. Instead, infiltrating pro-inflammatory, monocyte-derived macrophages as well as some subsets of wound healing macrophages are found in analysis of BALF cells of COVID-19 patients with varying severity and are expected to contribute to the cytokine storm.[38] Single cell analysis of BALF revealed the presence of inflammatory macrophages in severe COVID-19.[38] Furthermore, studies have observed an increased presence of CD14+/CD16+ inflammatory monocytes and the presence of a highly inflammatory, monocyte-derived FCN1+ macrophage population in COVID-19 patients, which explains the increased pro-inflammatory response observed in the advanced stages of the disease.[74,75] Possible mechanisms of continued cell activation include direct infection and PAMP toll-like receptor (TLR) signaling,[44] inflammasome activation,[76] interaction with immune complex-opsonized virus,[77] and engagement of chemokine and cytokine receptors for soluble factors, as well as delay of Type I IFN response.[46] Collectively, the overabundance of activated innate immune cells (neutrophils, monocytes, macrophages) and the scarcity of antigen-specific T cells (lymphopenia) and NK cells create an ideal environment for a cytokine storm, which may result in sudden clinical deterioration.

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Role of Biological Factors, Pre-Existing Conditions, and Lifestyle in COVID-19 Host Response. The severity of COVID-19 is primarily dependent on the host immune system.[78] Many factors play a role in the background immune state of the host including genetics, pre-existing conditions, environmental factors, and even circadian rhythms.[79−81] We summarize the current state of understanding for each of these factors as they relate to COVID-19 to identify design criteria for therapeutic intervention.

Age quickly emerged as a major biological risk factor linked to increased susceptibility to COVID-19 infections. Large-sample studies in China, as well as other countries, have observed a higher rate of infection in the aged population (65 or older) along with higher mortality rates.[82−85] One potential reason for the increased mortality might be age-related impairment of the innate and adaptive immune systems, termed immunosenescence.[86,87] Type I IFN production in response to viral infection is reduced with age, making aged patients more susceptible to severe COVID-19 infection.[48,88] Furthermore, increased inflammation with age or "inflammaging" may be attributed to a heightened innate inflammatory baseline in older patients, resulting in worse clinical outcomes and increased severity relative to the younger population.[89−92] However, reports of COVID-19 manifestations in children and adolescents have included multisystem inflammatory syndrome and Kawasaki-like symptoms lasting a considerable period after infection, but mechanistic understandings of these phenomena remain unclear.[93,94] Sex disparities have also been found in COVID-19, with increased incidence and mortality in males compared to females.[84,85,95−97] Broadly, females and males have been observed to exhibit differences in immunological responses to foreign and self-antigens, where differences in both genes and hormones are thought to play a role.[98] Increased susceptibility to COVID-19 in the male population could be because of the presence of the ACE2 gene on the X-chromosome and higher circulating ACE2 levels in men relative to women.[99] Males have also been found to demonstrate increased production of pro-inflammatory cytokines such as IL-8 and IL-18 in addition to having worse T cell responses,[100] indicating the potential need for different treatment options based on patient's sex.

Along with biological factors, certain pre-existing health conditions increase infection risk and fatality rates. As the lungs are the primary site of infection for COVID-19, patients with pre-existing health conditions such as asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, and pulmonary fibrosis are also at greater risk.[101] COPD, a chronic inflammation disease associated with limitation in airflow, was identified to increase COVID-19 infection risk by a factor of over 4 times and correlated with increased disease severity.[102−105] Pulmonary fibrosis, a chronic fibrotic disorder resulting in scarring of the lungs, shares similar risk factors associated with COVID-19.[106] ARDS, which is observed in close to 40% of COVID-19 cases, is often linked as a precursor to pulmonary fibrosis.[107] Conversely, pre-existing dysregulated wound healing in idiopathic pulmonary fibrosis can increase the risk of contracting COVID-19 infection.[106] Currently, the functional relationship between chronic pulmonary conditions and COVID-19 remains speculative, and further studies would be required to formally investigate pulmonary fibrosis as a COVID-19 risk factor. Other health conditions including hypertension, chronic respiratory disease, diabetes, and cardiovascular diseases have also been identified as potential risk factors.[102,107,108]

Furthermore, recent evidence suggests that approximately 10% of people diagnosed with COVID-19 experience symptoms months after testing negative for the virus.[109,110] These people, termed "COVID-19 long haulers," experience a wide range of symptoms which, while inconsistent between individuals, include coughing, fatigue, body and joint pain, headache, and brain fog, among many others. The existence of these long haulers potentially implicates permanent changes in the immune response and lung microenvironment, indicating incomplete recovery from the virus.[110,111] One study from Italy found that approximately 87% of recovered COVID-19 patients aged 19−84 reported at least one persistent symptom, particularly fatigue or dyspnea.[112] Another study from a Paris hospital reported a high daily average number of COVID-19 long hauler patients with an average patient age around 40 years and a 4:1 ratio of women to men. Their study suggested that the long-term impacts of COVID-19 may be experienced by people as a function of age, sex, and/or disease severity.[113,114] The reasons for the long-term health impacts of COVID-19 are still not clear; however, permanent organ damage from the cytokine storm,[115] persistent inflammation,[23] and inadequate/variable memory antibody response[116] might contribute to long-term impairment of innate and adaptive immune response in COVID-19 long haulers. A recent study showed higher impairment of natural killer T cells (NKT cells) in individuals recovering from COVID-19 resulting in a reduced immune response.[117] Further, similar phenomena were observed with recovered SARS-CoV-1 patients, who experienced fatigue months or even years after recovery, which was hypothesized to result from persistent low-level inflammation caused by the infection.[118−120] Further studies would be critical in understanding the relationship between COVID-19 and other chronic diseases along with various biological factors, which will help in guiding therapeutic advances toward the COVID-19 disease both in the short and long terms.

CURRENT THERAPEUTIC PARADIGM IN PULMONARY HOST MODULATION

There are numerous methods being explored for the prevention of SARS-CoV-2 infection that are related to the manners in which the disease accesses cells, triggers host inflammation, and avoids detection. While several specific SARS-CoV-2 antiviral therapeutics have been studied throughout the course of the pandemic, to date, limited efficacy has been demonstrated in mitigating SARS-CoV-2 spread or improving outcomes for COVID-19 patients. Therapeutic targets specific to viral function have included inhibitors of viral fusion (Chloroquine, Hydroxychloroquine), viral proteases (Lopinavir, Ritonavir), and viral polymerases (Remdesivir, Favipiravir). Of these, some promising results of Remdesivir usage have been reported,[121] with placebo-controlled trials ongoing; however, conflicting reports of efficacy, especially in severe COVID-19 patients, have also emerged,[122] and questions of achieving critical concentrations in the airways have been raised.[123] Given the challenges associated with controlling viral entry, the high infectivity of the SARS-CoV-2 virus, and the emergence of COVID-19 pathology despite declining viral load, therapeutic approaches capable of modulating the host response are imperative to halting disease progression and reversing the impacts of SARS-CoV-2 pathology.[23] Here, we provide examples of the current

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therapeutic platforms for managing COVID-19 infections and the resultant inflammation and point the reader to excellent reviews with more exhaustive discussions of treatment options and clinical trials.[124−126]

Corticosteroids. Corticosteroids have been widely used for inflammatory and autoimmune diseases in addition to treating pneumonia symptoms and other respiratory conditions, such as asthma and COPD, and can be administered through oral, intravenous, or inhalable routes.[127−129] Corticosteroids exert anti-inflammatory effects through glucocorticoid receptor binding and interference with inflammatory gene transcription factors (e.g., NF-κB).[130] Because of the hyperinflammatory state caused by the SARS-CoV-2 infection and other viruses causing pneumonia and ARDS, corticosteroids have been proposed to mitigate pulmonary and systemic inflammation caused by cytokine storm. However, the delivery of corticosteroids has had mixed results, with studies indicating that the dosage, timing, and type of corticosteroid used may be important to achieving positive outcomes.[131−133] Corticosteroids have previously been evaluated in SARS-CoV-1 and MERS-CoV; treatment showed limited success with some possible harmful effects in SARS-CoV-1 patients,[134] while some improvement was observed with methylprednisolone treatment in patients with ARDS.[135] There is a strong case against the use of certain corticosteroids for COVID-19 complications based on clinical data from MERS-CoV and SARS-CoV-1, with patients receiving corticosteroids becoming more likely to be placed on mechanical ventilation and showing delayed recovery relative to patients that had not received corticosteroid treatment.[136] Several studies investigating methylprednisolone, including a randomized, double blind, placebo-controlled trial, found no significant prevention of deaths or improvement of clinical outcomes following a short-course treatment,[132,137,138] while others showed modest improvement.[139] Budesonide has recently been shown to reduce the number of deaths in patients with severe COVID-19 as compared to untreated patients.[140,141] A recent study with a relatively greater number of participants has shown efficacy with dexamethasone with a 6 mg daily oral or intravenous dose reducing the number of deaths and requirement of invasive mechanical ventilation in hospitalized COVID-19 patients relative to those not receiving dexamethasone.[142] While these results indicate the potential for some corticosteroids improving outcomes for COVID-19 patients, more studies are required to elucidate the mechanism of dexamethasone compared to other corticosteroids in preventing clinical deterioration in COVID-19. Because of the widespread availability of corticosteroids and the potential utility by physicians for COVID-19 patients, caution must be exercised to avoid undesirable and potentially harmful side effects. The main concern with systemically administered corticosteroids is the immunosuppressive effects that could hinder the host's innate antiviral responses. In some studies, 50% of nonsurviving COVID-19 patients had secondary infections,[102] indicating that broad immunosuppressive strategies may be detrimental to the host's ability to fight infections. While evaluation of corticosteroids in SARS-CoV-1, MERS-CoV, and, in many cases, SARS-CoV-2 has shown disappointing results partly because of the lack of randomized and properly controlled trials, the recent, promising results with dexamethasone treatment emerging from a thorough design and a large number of participants have sparked cautious optimism and pushed dexamethasone toward becoming the current standard of care for treating COVID-19.[141] More studies are required to confirm these preliminary results and investigate critical factors such as dosage, frequency, route of administration, and timing of treatment.

Pro-Inflammatory Cytokine Blockade and Pathway Inhibition. Given the overabundance of pro-inflammatory signaling molecules, approaches to dampen or regulate the immune response and prevent the cytokine storm have been attempted in various clinical trials. Unlike corticosteroids, blocking specific cytokine targets and pathway does not risk broad immunosuppression and will likely mitigate individual pro-inflammatory responses without impairing the host's ability to clear the SARS-CoV-2 virus. It is important to point out that most of these treatments are still under investigation for potential COVID-19 complications, and further trials are required before approval.

IL-6 has been identified as a primary pro-inflammatory marker in COVID-19 and represents a key therapeutic target. Tocilizumab is a recombinant monoclonal antibody (mAb) formulation designed to block both membrane-bound and soluble forms of the IL-6 receptor (IL-6R). It has previously been used for rheumatoid arthritis[143] and is approved in the United States for treatment of the cytokine storms that occur as a result of CAR-T cell therapy.[144] In studies of patients with severe COVID-19, intravenous or subcutaneous administration of tocilizumab resulted in some improvements, reducing the frequency of invasive mechanical ventilation or death,[145] while simultaneously normalizing body temperature, lymphocyte counts, and C-reactive protein (CRP) levels, indicating the potential for IL-6R blockade to improve clinical symptoms in severe COVID-19.[146] However, more studies are needed to determine proper dosage and examine the effectiveness of treatment for different levels of disease severity. Preliminary studies with sarilumab, an anti-IL-6Rα mAb, had mixed results, with some studies showing clinical improvements,[147,148] while others did not observe significantly improved outcomes when compared to standard of care.[147] These studies highlight the importance of dosage and timing of administration, two factors that must be investigated to thoroughly evaluate the efficacy of IL-6R blockade for COVID-19. In addition to IL-6R blockade, siltuximab, a mAb against IL-6 itself, has been preliminarily investigated in COVID-19 patients with respiratory failure. A reduction in serum CRP levels and likelihood of death was observed following one or two treatments of siltuximab.[149] Results showing lower than expected efficacy could potentially signal the need for localized treatment to the lung, as opposed to systemic IL-6 or IL-6R blockade, in an effort to relieve local hyperinflammatory regions at the primary SARS-CoV-2 infection site. More randomized, placebo-controlled studies are required to validate these findings and further elucidate the role of IL-6 neutralization in mitigating the effects of the cytokine storm and ARDS. Furthermore, with IL-6 serving a role in fighting infections, total hindrance or blockage may harm the host's ability to clear the SARS-CoV-2 infection, indicating the need for more studies to optimize dosage, route of administration, and timing of treating with IL-6 and IL-6R blocking strategies.[150]

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a cytokine responsible for maintaining homeostasis in the lungs through regulation of proliferation and differentiation of immune cells, especially macrophages and neutrophils.[151] GM-CSF targeting has emerged as a possible therapeutic strategy because of the high numbers of infiltrating

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inflammatory cells in the lungs and elevated blood levels of GM-CSF in severe COVID-19.[39] Aberrant GM-CSF levels may enhance the activation of inflammatory phagocytes and exacerbate the cytokine storm by stimulating the secretion of other pro-inflammatory cytokines.[152] A study investigating mavrilimumab, a mAb against the GM-CSF receptor (GM-CSFRα), has shown promising results in patients with severe COVID-19.[153] Some of these improvements include faster recovery of respiratory function and better clinical outcomes as well as reduced CRP levels after a single intravenous dose. Furthermore, administration of three doses of lenzilumab, a mAb targeting GM-CSF itself, has shown notable improvements including lower CRP and pro-inflammatory cytokine levels and higher absolute lymphocyte counts, indicating potential recovery.[154]

Inflammasome activation as a result of the SARS-CoV-2 infection results in increased secretion of IL-1β, which has been observed in severe COVID-19.[76] Anakinra is a mAb with specificity to the IL-1 receptor (IL-1R) and blocks the binding of IL-1α and IL-1β, thereby preventing the propagation of pro-inflammatory cascades, including the expression of IL-6 as a result of IL-1β secretion.[155] High-dose intravenous administration of anakinra, in combination with antivirals, promoted higher survival and lower risk for invasive mechanical ventilation in addition to improvement in CRP levels and respiratory function.[156] However, in the same study, a subcutaneously administered, lower dose was not associated with any indicators of better clinical outcomes, and, as a result, the subcutaneous administration study was ended prior to completion. Another study investigating daily intravenous anakinra treatment without the use of antivirals found a rapid response characterized by sharp reduction in fever and CRP within 48 h of administration.[157]

In addition to IL-1β, TNF-α is present in blood and lungs of patients in severe cases of COVID-19 and is a common inflammatory agent in the cytokine storm. Anti-TNF-α mAbs have been widely used to alleviate inflammation in many autoimmune and inflammatory diseases.[158] Infliximab, an anti-TNF-α mAb, was used to treat a Crohn's disease pediatric patient suffering from Kawasaki-like symptoms as a result of severe COVID-19.[159]

The Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway is responsible for the transcription of multiple pro-inflammatory cascades[160] and is hypothesized to be activated as a result of the SARS-CoV-2 infection.[161] JAK inhibitors such as ruxolitinib have been used to treat hemophagocytic lymphohistiocytosis,[162] an inflammatory disease caused by the cytokine-mediated hyperactivation of immune cells and is similar to the inflammatory profile in severe COVID-19.[163] Therefore, the use of JAK inhibitors has been proposed to control the runaway inflammation in severe COVID-19. Baricitinib, a potent and specific inhibitor of JAK 1 and 2, has shown promising signs of clinical improvement in a preliminary, noncontrolled, retrospective study with a resolution of fever and a reduction of CRP levels,[164] indicating potential for expansive investigation of baricitinib to treat COVID-19 complications. In addition to disrupting transcription of pro-inflammatory cytokines, baricitinib is hypothesized to block the cellular entry of SARS-CoV-2, although robust clinical evidence is required to support this hypothesis.[165] Another small, noncontrolled study supported similar conclusions, where baricitinib treatment was shown to promote improvements in respiratory function and led to reduction of CRP levels within 1−2 weeks of treatment.[166] Ruxolitinib, another potent JAK1 and JAK2 inhibitor, has also been investigated for mitigating the effects of the cytokine storm in severe COVID-19 patients. In a small study without a randomized control group, researchers investigated compassionate use of ruxolitinib in older and high risk COVID-19 patients. Treatment showed notable improvement in respiratory function and led to eventual discharge of a large majority of patients.[167] Furthermore, higher lymphocyte counts and lower expression of serum inflammatory cytokines were observed 14 days after treatment, and a majority of patients tested negative for SARS-CoV-2 at the end of the study. These results were supported by another small study that reported a sharp decrease in CRP and IL-6 levels as well as a general recovery in lymphocyte counts after treatment with ruxolitinib.[168] A single-blind, randomized controlled study with a 5 mg daily, oral dose of ruxolitinib showed significant recovery from lymphopenia and reduction in levels of pro-inflammatory cytokines including IL-6,[169] which supports the conclusion from the other studies discussed here. Albeit small in sample size, the study is the first randomized controlled trial evaluating ruxolitinib for severe COVID-19.

Overall, preliminary results of various cytokine blockades are promising, and more studies, including placebo-controlled studies with larger sample sizes, are warranted to confirm the observed trends and investigate potential systemic and pulmonary immunomodulatory effects of blocking these targets. A major concern regarding the use of inhibitors is the broad suppression of the expression of other pro-inflammatory cytokines including IFNs;[170] specific cytokine targets must be thoroughly investigated to avoid these undesirable side effects. Administration at incorrect timing could also disrupt the host antiviral response and impair the ability to clear the SARS-CoV-2 infection, while increasing susceptibility to secondary infections.[171] Current evaluations are often limited and have small sample sizes. Additionally, general impact on antiviral IFNs and host safety must be evaluated in larger cohorts to determine whether there should be wider use of these inhibitors for severe COVID-19 treatment.

Exogenous Interferons. Because of the impaired type I IFN response in severe COVID-19, IFN administration has been proposed as a possible therapeutic strategy to overcome viral immune evasion and promote immune-mediated antiviral pathways. In a prospective noncontrolled trial with a small cohort, severe COVID-19 patients that received subcutaneous injections of a type I IFN (IFN-β-1a) showed some improvements in fever, viral clearance, and reduction in airway pathology in chest X-rays and CT scans.[172] However, another study found no significant improvement in survival in severe COVID-19 patients receiving subcutaneous IFN-β-1b with or without hydroxychloroquine or other protease inhibitors relative to the control group.[173] In a third randomized, open-label trial without placebo groups, subcutaneous administration of IFN-β-1b in combination with protease inhibitors yielded significantly faster viral clearance and suppression of IL-6 levels relative to the control group receiving protease inhibitors only. Relative to the aforementioned studies, this trial showed encouraging results at earlier stages of the disease, indicating the importance of early intervention with antiviral therapies and IFNs. These conflicting results warrant the investigation of factors that affect treatment, especially disease severity and timing of treatment, because the strength of the

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early IFN response may determine the severity of the disease and affect clinical outcomes.[174] Inhalable IFN-α-2b has preliminarily demonstrated potential in enhancing viral clearance and reduction of IL-6 and CRP levels in moderate COVID-19 patients,[175] indicating that the route of administration may be important in the efficacy of immunomodulatory treatments.

Immunoglobulins and Convalescent Plasma. Intravenous immunoglobulins (IVIGs) are used to intercept cytokines, antibodies, and inflammatory factors especially in autoimmune diseases and other inflammatory dysfunctions through nonspecific interactions.[176] IVIGs are also used to block Fcγ receptors on macrophages and other phagocytic cells to prevent involvement of inflammatory cells.[177] Some hypotheses are suggesting that a possible route for immune cell infection with SARS-CoV-2 is through Fcγ receptor-mediated internalization of active SARS-CoV-2 bound to antibodies or immune complexes, which could ultimately result in infection and activation of macrophages and inflammatory cells.[178] Therefore, there is potential for using IVIGs to block Fcγ receptors on infiltrating inflammatory cells in the lung while simultaneously depleting some aberrant cytokines that contribute to the cytokine storm. High dose IVIG in three patients with severe COVID-19 resulted in a rapid drop in fever and recovery of respiratory function;[179] however, a retrospective trial did not find significant improvement in survival or inflammatory response as a result of IVIG treatment,[180] although it is unclear whether the lack of effectiveness was a result of the treatment or more severe disease in the IVIG cohort. A study investigating timing of IVIG administration showed evidence suggesting that early treatment (within 48 h of admission) resulted in better survival than delayed treatment in severe or critical COVID-19 patients.[181] Altogether, the conflicting studies from IVIG treatment warrant more robust and larger controlled studies to elucidate conclusions for treatment effectiveness and safety in COVID-19.

Unlike IVIG, which provides nonspecific protection, convalescent plasma is derived from plasma of patients with high titers of antibodies specific to SARS-CoV-2 and has recently emerged as a possible therapeutic avenue for COVID-19.[182] In an open-label randomized trial of severe and critical COVID-19 patients, convalescent plasma treatment did not result in significant clinical improvement or survival within 28 days, possibly because treatment was initiated at least 14 days after onset of symptoms, indicating the potential importance of early clinical intervention for more effective results.[183] A larger, multicenter, open-label study demonstrated strong evidence for improved outcomes for patients receiving convalescent plasma treatment within 3 days or a delayed administration after 4 days of COVID-19 diagnosis, with a significant improvement in survival associated with earlier administration.[184] Furthermore, the study evaluated the effect of antibody titers and showed higher survival in patients receiving plasma with high antibody titers as compared to those receiving plasma with lower titers, indicating a concentration-dependent effect on recovery and showing no evidence of worsening because of antibody-dependent enhancement (ADE). These promising results must be validated in randomized, placebo-controlled trials to further assess effectiveness as well as quantify secondary clinical outcomes including systemic inflammation and respiratory function.

Prophylactic Vaccine Strategies. No discussion of immunotherapies for COVID-19 could be complete without acknowledging the heroic effort behind the highly accelerated SARS-CoV-2 vaccine development. An impressive number of potential SARS-CoV-2 vaccine candidates are currently being investigated in accelerated clinical trials.[185−187] Several SARS-CoV-2 vaccine formats are currently in development including whole virus, subunit, and nucleic acid vaccines.[85] Formats involving whole viruses under investigation include live-attenuated virus vaccine,[188] inactivated virus vaccine,[189,190] and adenovirus-based vaccines.[191,192] Subunit vaccines have also had promising results with some progressing to ongoing clinical studies.[193] Nucleic acid-based vaccines have recently come into the spotlight with both Moderna and Pfizer's mRNA vaccines showing promising results[194] and progressing rapidly in the development pipeline. Other nucleic acid-based (both mRNA and DNA) candidates are also currently under investigation.[195] Although there is much optimism surrounding the rapid vaccine development and early positive results, caution is warranted to avoid taking shortcuts. Robust clinical trials must be performed to ensure that vaccines promote protective and proper immune responses in healthy individuals of all ages, genders, races, and genetic backgrounds and avoid potential ADE from non-neutralizing antibodies that exacerbates cell activation and inflammatory response.[196,197]

BIOMATERIALS AND PARTICLE-BASED IMMUNE ENGINEERING OPPORTUNITIES FOR COVID-19

Though the previously mentioned therapeutics are making inroads in the treatment of COVID-19 and the alleviation of its symptoms, there are many areas of improvement that can enhance these treatments, including reducing off-target effects, more effectively directing immune modulation, and promoting localized action to affected regions. Employing lessons from the fields of drug delivery, biomaterials, and particle engineering offers opportunities to enhance or augment the current treatment paradigm. Utilizing biomaterial therapeutics takes advantage of tailorable building blocks that can favorably interact with immune cells and simultaneously deliver cargo directly to the lungs to avoid off-target effects. One of the primary advantages of particle engineering with biomaterials is that they can be synthesized to fall into the ideal size range for cellular targeting and internalization for critical cellular targets for COVID-19 therapeutic treatment, including innate immune cells, in addition to having controlled release properties.[62,198] Particle engineering can leverage a wide range of formulation compositions, with polymers and lipids allowing for design flexibility (Figure 2A) and size selection during synthesis and processing.[199,200] This tailorability also extends to surface functionalization, which can be used to add active targeting ligands or stimulus-responsive moieties in addition to antibodies or drugs for interfacing with target cells or proteins (Figure 2B).[201−203] Engineering particle properties including size, shape, and porosity can also be used to control delivery to the lungs via either pulmonary inhalation or vascular delivery (Figure 2D).[204,205] Furthermore, many biomaterials including poly(lactic-*co*-glycolic acid) (PLGA),[206] poly(ethylene glycol) (PEG),[206] and lipids,[207] among many others,[208] have inherent low cytotoxicity and high biocompatibility, essential attributes for translation to COVID-19 treatment.[23]

Particle engineering approaches can be used for treatment strategies including synthetic vaccines, virus decoys, cytokine

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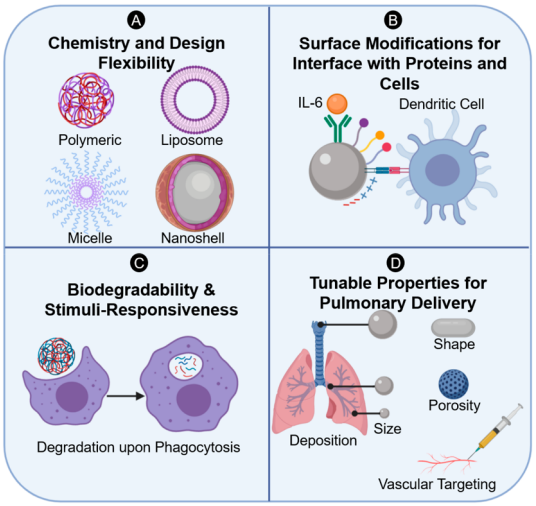

Figure 2. Potential particle engineering features for host immune modulation in COVID-19. A) Tailorability of design and building blocks to accommodate a wide range of applications and cargo loading and ensure biocompatibility. B) Modular surface design with functional ligands and receptors that are capable of interacting with high specificity with lung immune cells or proteins. C) Controlled degradation and cargo release in low pH environments upon internalization by lung phagocytes. D) Tunability of nanomaterial properties for optimal deposition in the airways and targeting through vasculature.

sequestration, macrophage repolarization, and immune cell distraction, as discussed in the following section. They can also promote the delivery of therapeutics to treat COVID-19, including those listed in the prior section. In this section, we highlight recent advances that improve drug delivery to the lung, identify particle engineering approaches to regulate immune pulmonary responses, and point to untapped opportunities for the use of biomaterials and particle engineering for the development of novel COVID-19 therapies. While these immunomodulatory, particle-based strategies represent a promising avenue for regulation of COVID-19 inflammation, significant preclinical and clinical studies considering specific aspects of SARS-CoV-2 and the COVID-19 inflammatory landscapes will be needed for clinical translation.

Localizing Therapeutics to the Lung. Orchestrating the host response in the lung requires consideration of the unique pulmonary microenvironment as well as physiological barriers that arise from both the air and vascular sides of the lung. Delivery of agents which need to act in the lung can be accomplished by systemic delivery (primarily oral or intravenous)[209,210] and diffusion into the tissue. This delivery is nonspecific, and delivery to the lungs likely should be enhanced through the use of active targeting ligands to aid in crossing the endothelium into lung tissue.[211] Efforts to target nanoparticle drug carriers to the inflamed pulmonary vasculature intravenously can be achieved with ligand functionalization that targets upregulated receptors in the leukocyte adhesion cascade occurring during pulmonary infiltration and by tuning carrier modulus.[212,213] Certainly, vascular delivery of nanoparticles offers unique opportunities to address adverse coagulation events that occur during COVID-19 through targeting of clot components, blocking of autoantibodies, and delivery of clot dissolution agents, as reviewed elsewhere.[214,215]

Alternatively, high drug concentrations can be achieved through oral inhalation via aerosols, reducing off-target effects associated with systemic delivery routes while increasing the effective dose to affected lung tissue.[6,216] Here, particle size dominates in terms of effect on deposition location and therapeutic efficacy.[204] Particles with aerodynamic diameters significantly smaller than 1 μm or larger than 5 μm will have deposition fractions below 0.5 in the alveolar region of the lung, our primary therapeutic target region for treatment of COVID-19.[204,217] Accordingly, it is critical to achieve aerodynamic particle sizes within the 1 to 5 μm range, along with low dispersity, for effective, consistent dosage.[204] In the case of aerosol delivery, the delivery device also can be impactful on delivery because of the formulated particle size and patient compliance. For the case of COVID-19 treatment, nebulizers have the advantages of delivering large dosages without particular breathing techniques or coordination by patients that may have difficulty breathing and also allow for ease of formulation chemistry, as the nebulizer will generate aerosols in the desired size range.[6,218] Other delivery devices such as dry powder inhalers and metered dose inhalers have the advantages of higher delivery efficiency and lower cost but have drawbacks of potential aggregation, which could cause reduced deposition in the alveoli, and requirement of coordinated inspiration by the patient along with additional regulatory hurdles.[218] Regardless of the delivery method, pulmonary delivery of biomaterials can offer great advantages in increasing dosage to the lungs and avoiding off-target, systemic effects, while simultaneously targeting immune cells in the lung through size and charge considerations or avoiding clearance through the same parameters;[219,220] smaller (50 to a few hundred nm) nanoparticles will be preferentially internalized by alveolar macrophages, while larger (greater than 10 μm) particles will be more likely to avoid internalization. However, to induce immunomodulatory effects and achieve high delivery efficiency to diseased areas and immune cells, pulmonary delivery of therapeutic particles must overcome mucosal and epithelial barriers.[221] Hydrophilic and neutral/positively charged moieties may be incorporated in the particle design to avoid entrapment by mucus and promote localization to APCs.[222] Because of the tailorability of biomaterial-based particles, these parameters can be factored into their design and increase the effectiveness of potential therapeutic treatments of COVID-19.

Biomaterials in Vaccine Development. Nanoparticles and microparticles have distinct advantages in terms of delivery of vaccines, as they can be passively targeted to immune cells because of their size and can either codeliver adjuvants or act as their own adjuvants.[223,224] Furthermore, the modular nature of many nanoparticles, whether liposomes, polymer nanoparticles, or others, allows for the design of smart materials to actively target immune cells[225] and be biodegradable.[206] Some nanovaccines, termed as virus-like particles, utilize components or structures of viruses to achieve effective vaccination owing to their size and ability to enter cells effectively to deliver vaccine components.[226] Several virus-like particle vaccines for COVID-19 are rapidly progressing through the pipeline.[227] Nanovaccine formulations can have controlled degradation based on nanoparticle properties such as swellability and modulus[228] and adjusted immunogenicity and localization as a function of particle properties such as charge and density of antigen for efficient dendritic cell association and lymph node trafficking (Figure 3A).[229−231] Nanoparticles, such as those

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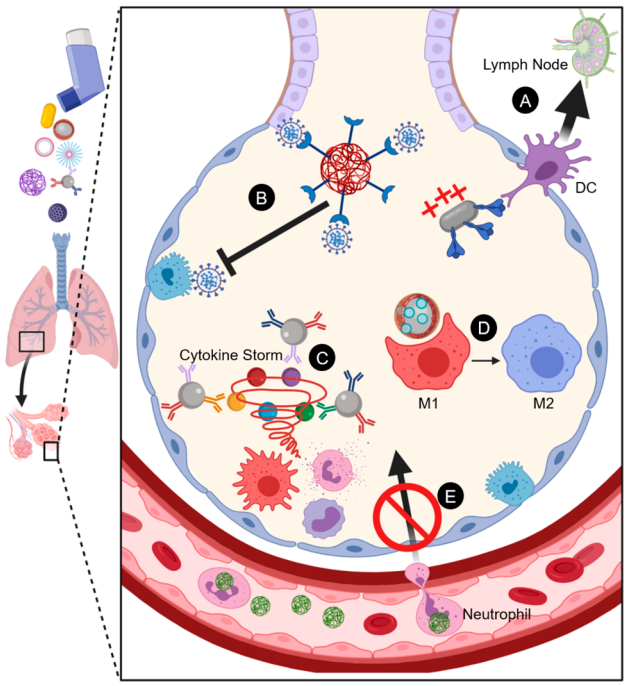

Figure 3. Summary of potential particle-based pulmonary immune engineering approaches for COVID-19. A) Engineering nanoparticle vaccines for enhanced association with migratory dendritic cells and increased lymph node trafficking to prime adaptive immunity. B) Nanoparticles as viral decoys displaying ACE2 to bind SARS-CoV-2 and inhibit infection of alveolar cells. C) Nanoparticles with functional ligands to sequester pro-inflammatory cytokines and prevent the cytokine storm. D) Use of nanoparticles and loaded cargo to drive polarization of inflammatory M1 macrophages toward anti-inflammatory M2 macrophages. E) Phagocyte distraction with injected nanoparticles.

based on gold,[232] lipids (liposomes),[233] PLGA,[225] and HPMA/NIPAM[234] among many others, have been used previously for vaccine approaches. These approaches have been described in-depth in previous reviews regarding the use of biomaterials for vaccine applications.[221,225,235−240] Additionally, we point readers to excellent works reviewing other considerations in design of particle-based vaccines.[241−243]

Particle-based formulations are rising to the forefront of vaccine approaches to combat COVID-19, with Moderna's lipid nanoparticle-formulated mRNA vaccine currently in Phase III clinical trials, having shown significant promise in nonhuman primates.[244] The vaccine delivers mRNA in a four-lipid nanoparticle which encodes for the SARS-CoV-2 spike glycoprotein in its prefusion conformation.[194,245] In addition, other leading vaccine candidates including the Pfizer and BioNTech formulations also utilize mRNA technology with lipid nanoparticle designs.[246] Respiratory infections like SARS-CoV-2 could benefit from inhalable vaccine strategies to achieve high mucosal immunity in the lungs, the primary target for SARS-CoV-2. Therefore, particle-based, inhalable formulations could be a significant, untapped opportunity that could improve current vaccines in development.

Engineered Viral Decoys. Engineered particles offer opportunities as novel antivirals by blocking SARS-CoV-2 binding to host ACE2 receptors through host-cell mimicry.[141] Delivery of free ACE2 is currently being pursued in clinical trials,[247] which would occupy the RBD to limit viral binding to host cells. This decoy approach would benefit from nanoparticle-mediated delivery, particularly to the lung, to prevent or abate infection. Nanoparticles can be decorated with ACE2-mimicking moieties that will bind to SARS-CoV-2 RBD and limit viral binding to host cells (Figure 3B). Engineered biomaterials are an ideal class of materials for this purpose, as they can be delivered to the pulmonary space and can be designed to display high densities of ACE2.[248,249] For example, PLGA polymer nanoparticles could be functionalized and decorated with the aforementioned ACE2 receptor proteins. Recently, Zhang et al. developed a method to distract SARS-CoV-2 and reduce infectivity using PLGA nanoparticles coated with membranes from alveolar epithelial cells and macrophages, respectively.[250] Both of the membrane-coated nanoparticles were able to neutralize infectivity of SARS-CoV-2 in a dose dependent manner up to ∼80% at treatments of 5 mg/mL of the nanoparticles in an infection model using Vero E6 cells using authentic SARS-CoV-2 viruses.[44] Other promising attempts include using extracellular vesicles containing ACE2 as decoys to block infection by a lentivirus containing SARS-CoV-2 spike protein[251] or gene delivery approaches that package ACE2 mRNA inside lipid nanoparticles.[252] Collectively, these nanoparticle platforms perform critical host-mimicry to distract the SARS-CoV-2 virus from host binding.

Drug Delivery Approaches to Cytokine Sequestration and Cytokine Storm Abatement. As mentioned previously, a number of cytokines and factors have been identified as contributors to the inflammation and severe symptoms of COVID-19 including IL-1β, IL-2, IL-6, IL-18, and granulocyte colony-stimulating factor (G-CSF), among others.[23,141] Treatments have been proposed for the sequestration of IL-6, IL-18, and IL-1β through the use of systemically delivered antibodies.[141,253,254] One significant possible downside of this approach may be the lack of specificity to the lung space, leading to body or system-wide immune suppression, reducing the recruitment of antiviral immune cells in other instances in which it is desired or necessary. Accordingly, localized delivery to the lung and efficient sequestration of inflammatory cytokines is a potentially untapped opportunity for pulmonary delivery of biomaterials and therapeutic particles. Similar to some of the prophylactic treatments in which ACE2 can be conjugated to the surface of a biomaterial-based nanoparticle, antibodies against one or multiple inflammatory molecules involved in the cytokine storm can be conjugated to the surface of the biomaterial-based nanoparticles to allow for efficient and effective removal of the markers to alleviate the burden caused by the cytokine storm (Figure 3C). Some previously employed strategies have included chitosan and hyaluronic acid-based, PLGA-based, and mesoporous silica nanoparticles to sequester IL-6,[255−257] all of which can be adapted for delivery to the lung. The mesoporous silica nanoparticles in particular were designed for aerosol delivery for an asthma model and may have capacity to be translated to the cytokine storm abatement during SARS-CoV-2 infection.[257] The incorporation strategies, including carbodiimide conjugation of antibodies and formulation of nanoparticles with loaded antibodies, can be utilized in addition to other synthetic strategies, such as thiol-Michael click chemistry to incorporate antibodies into nanoparticles for delivery.[255−257] Simultaneous incorporation of multiple ligands or cues is a secondary advantage of the use of nanoparticulate biomaterials, which is possible through the conjugation of multiple antibodies to sequester cytokines, inclusion of active-targeting moieties, and codelivery of anti-inflammatory agents to limit activated macrophage polar-

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ization.[225,258−261] All of these strategies could improve COVID-19 treatment through more efficient, localized delivery, reduction in off-target effects, and simultaneous delivery of anti-inflammatory agents alongside particles sequestering inflammatory molecules.

Delivery of Anti-Inflammatory Agents for Repolarization of Immune Cells. Another approach of promise for the treatment of the COVID-19 pathology is the repolarization of inflammatory macrophages to prevent or abate their cytokine contributions. Macrophages fall along a spectrum of activation, traditionally described as skewing toward either classically activated pro-inflammatory (M1) or alternatively activated anti-inflammatory (M2) phenotypes,[262] although the reality of macrophage phenotype is much more fluid. M1 macrophages are abundant in the SARS-CoV-2-infection following monocyte infiltration and cell differentiation in the lung. When present, they cause the further release of inflammatory cytokines including IL-6 and exacerbate existing inflammation.[95] Accordingly, therapeutic strategies that aid in the repolarization of macrophages from the M1-like phenotype toward the M2 phenotype (Figure 3D) could be useful in the treatment of COVID-19 symptoms by abating the cycle of inflammation caused by release of the aforementioned cytokines and further recruitment of inflammatory leukocytes.[107] M2 macrophages not only reduce secretion of inflammatory cytokines such as IL-6, TNF-α, and IL-1β[263] but also promote secretion of anti-inflammatory factors such as IL-10 that may restore the microenvironment homeostasis.[262] When introduced at the right time during COVID-19 host response, macrophage repolarization at the air−liquid interface using inhaled, engineered particles may allow for local restoration of host immune response and mitigation of subsequent inflammatory airway pathologies.

Biomaterials are particularly suited for this purpose because they often do not persist in the body, can deliver cytokines and other materials to aid in polarization, can be targeted to immune cells like macrophages, and can, themselves, repolarize macrophages.[263] A plethora of strategies has been developed to influence inflammatory macrophage response. Some examples include an alginate-based nanoparticle system developed to deliver IL-10 plasmid DNA to repolarize M1 macrophages to M2 macrophages;[264] polyethylenimine nanoparticles used to deliver the gene for CD163, an M2 macrophage marker;[265] and PLGA nanoparticles used to mimic apoptotic bodies via a phospholipid membrane coating supplemented with phosphatidylserine to trigger the memory of uptake of apoptotic bodies, inducing an M2 polarization.[266] All of these strategies led to decreases in the release of inflammatory cytokines including IL-6, IL-1β, IFN-γ, TNF-α, and MCP-1 and led to the repolarization of macrophages toward the M2 phenotype. These materials and methods were used *in vitro*, but their resultant reduction in the release of inflammatory cytokines and macrophage repolarization indicates their potential to be used to reduce or eliminate the inflammation induced by macrophages during SARS-CoV-2 infection.

Another way in which biomaterials could be used for the therapeutic treatment of COVID-19 is the delivery of anti-inflammatory cytokines such as IL-4, IL-10, and IL-13. IL-4 has previously been administered both *in vitro* and *in vivo* via conjugation to gold nanoparticles[267] and within mesoporous silica nanoparticles.[268] Both treatments led to an increase in the population of M2 macrophages alongside a corresponding reduction in the population of M1 macrophages. The silica nanoparticles would also have the benefit of larger aerodynamic diameters than their 180 nm geometric diameter, making them good candidates for pulmonary delivery of IL-4 for the treatment of COVID-19, which, as noted previously, would aid in minimizing off-target effects and increasing efficacy of treatment.[216,268,269] Other studies have also indicated that mesoporous silica nanoparticles can themselves stimulate the immune system, leading to the production of IFN-γ, IL-2, IL-4, and IL-10, and are preferentially internalized by M1 macrophages.[270,271] This may lead to greater efficiency of treatment relative to other materials, as the M1 macrophages, primary drivers of inflammation and thus key therapeutic targets, will internalize the silica nanoparticles more than other cells, which are less desirable targets. Similar treatments with IL-10 have been developed using nanoparticles including the previously mentioned alginate nanoparticles that deliver genes encoding for IL-10[264] and nanoparticulate polyester (PLGA and PEG) polymers nanoprecipitated with IL-10.[272] Many of these studies have demonstrated efficacy *in vivo*, giving more credence to their potential for combatting COVID-19. Many of the nanoparticles have potential for pulmonary delivery as well, which would make them even better candidates for combating the inflammation associated with COVID-19.

Delivery of corticosteroids can also impact macrophage polarization and thus is another category of therapeutics that may be of use for COVID-19 treatment. A primary concern of corticosteroid use is systemic immunosuppression, which could lead to impaired antiviral response.[141] In this regard, pulmonary drug delivery could be advantageous, as particle platforms have already been developed for corticosteroid delivery and can likely be adapted to the use of particular steroids proven to be effective, such as budesonide and dexamethasone.[273] For example, budesonide has been loaded into PLGA nanoparticles with 90% encapsulation efficiency and high drug loading of relevant sizes for cellular internalization.[274] Similarly, metal−organic framework (MOF) nanoparticles were loaded with dexamethasone and evaluated for pulmonary delivery.[275] Some other methods that have been developed to deliver corticosteroids include delivery of solid lipid nanoparticles loaded with budesonide for pulmonary drug delivery[276] and dexamethasone for potential lung targeting,[277] itraconazole nanoparticle-based dry powders for aerosol delivery of budesonide,[278] cross-linked copolymers of methyl methacrylate, *N*,*N*-dimethylaminoethyl methacrylate, and butyl methacrylate monomers designed to load hydrophobic corticosteroids.[279] Notably, dexamethasone-loaded PLGA microparticles were utilized to polarize macrophages toward an anti-inflammatory phenotype and resulted in a significant suppression of pro-inflammatory genes and TNF-α secretion.[280,281] All of these methods may be viable options to deliver these anti-inflammatory agents, especially if they can be formulated and delivered directly to the lungs to reduce or preclude systemic immunosuppression that may result in worse outcomes for patients treated with corticosteroids.

In addition to the delivery of anti-inflammatory agents, biomaterials themselves can be used to either induce or reduce inflammation. Their properties of immune skewing, particularly of macrophages, depend on the size, surface chemistry, and hydrophobicity of the material, in addition to other properties.[263] In particular, larger materials (greater than 10 μm in at least one dimension) tend to induce an M1 phenotype in macrophages because of frustrated phagocytosis

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that occurs when macrophages are unable to effectively engulf the large particles.[282] Accordingly, smaller particles would be desired for treatment of COVID-19 to reduce inflammation, as was the case for folate-conjugated silicate and calcium-based nanoparticles[283] and RGD-conjugated gold nanorods,[284] which both utilized sub-250 nm sized nanoparticles and showed anti-inflammatory properties of the respective nanoparticles. In both of these cases, surface modifications were necessary to aid in M2 polarization; however, there are instances demonstrating nonfunctionalized materials aiding in the polarization toward M2 phenotypes, such as nonfunctionalized PLGA nanoparticles and microparticles that reduce the expression of M1 markers and the secretion of pro-inflammatory cytokines, including IL-6, *in vitro*.[285,286] It has also been shown that titanium implants with calcium and strontium surface modifications and a particular nanotopography can induce an M2 immune response, as were some titania nanoparticles,[287] which may be another material type that could be explored to reduce inflammation in the form of titanium or titania nanoparticles containing these ions.[288] Any of the aforementioned systems could be used to aid in inducing anti-inflammatory phenotypes in macrophages as part of COVID-19 treatment, though they lack distinct advantages over polymeric biomaterials capable of delivering anti-inflammatory agents and ensuring intracellular degradation. In both cases, active targeting ligands for macrophages may be beneficial to ensure uptake or to increase their anti-inflammatory effects. For example, clustering mannose receptors on macrophages through carbohydrate inclusion in nanoparticle formulations can aid in macrophage M2 polarization,[289] while conjugation of dextran ligands can target M1 macrophages for delivery of cargo and re-education toward an M2 phenotype.[290] Functionalization with molecular "markers of self," such as CD47 or phosphatidylserine, can also promote macrophage polarization for localized immune modulation.[291,292]

Phagocyte Distraction. Neutrophils, in addition to macrophages, serve as part of the innate immune response to SARS-CoV-2 infection, contributing significantly to the aforementioned cycle of inflammation and cytokine storm.[23] A potential approach to abating the cycle of inflammation in COVID-19 is to direct inflammatory phagocytic cells away from the lung and reduce the number of recruited leukocytes from vasculature or surrounding tissue (Figure 3E). Vascular drug delivery systems have previously been used to distract neutrophils from sites of inflammation, including previous work, which demonstrated that intravenous injections of 2 and 0.5 μm carboxylated polystyrene nanoparticles can distract neutrophils from infiltrating into the lung as part of an acute lung injury model.[231] Instead, the neutrophils were diverted to the liver, reducing the pulmonary inflammation associated with their response. In addition, negatively charged 500 nm polystyrene and PLGA particles were used to limit trafficking of inflammatory monocytes to inflammation loci in several murine inflammation models including West Nile virus encephalitis.[293] Similar methods have been employed for the distraction of monocytes and neutrophils using intravenous injections of PLGA nanorods and nanoparticles.[294,295] PLGA-based nanorods have been shown to be preferentially internalized by neutrophils, which can be used to distract said neutrophils during inflammation to improve pathogenesis, while PLGA nanoparticles have been used to reduce the recruitment of both monocytes and neutrophils to the site of injury using a spinal cord injury model.[294,295] In the latter case, the recruitment of all innate immune cells at the site of injury was reduced by 75%, allowing for much more rapid recovery from injury. Recent work has shown that asymmetric lysozyme-dextran nanogels and cross-linked albumin nanoparticles with agglutinated proteins in amorphous nanostructures particularly target neutrophils during lung injury as demonstrated both *in vivo* in mice and also using human lungs, which could be critically valuable for selective treatment and/or distraction of neutrophils during COVID-19.[296] These examples demonstrate that inflammation can be reduced and innate immune cells can be redirected from the sites of injury, which could be very valuable for the therapeutic treatment of COVID-19, especially in light of increased neutrophil-lymphocyte ratios found in 80% of patients infected with SARS-CoV-2.[102] These distraction methods can also potentially be used in tandem with previously discussed drug delivery approaches, leveraging vascular targeting.

Opportunities for Biomaterials-Based Model System Development for Addressing Long-Term Effects of COVID-19. As noted above, COVID-19 can have long-term health implications in addition to short-term difficulties. These effects are attributed to permanent changes in the lung microenvironment and altered innate and adaptive immunity. These long-term issues can be further exacerbated by age, pre-existing health conditions, and COVID-19 severity.[114] While there is a push to find vaccine candidates and clinical treatments for COVID-19 in the short term, there is also an emerging need to better understand the long-term ailments associated with COVID-19 and develop therapeutics for persistent health conditions for millions of recovering patients worldwide. Screening and developing such new therapeutics will require advances in mechanistic understanding of the resultant multicellular crosstalk involved in COVID-19 resolution as well as novel testing platforms able to recapitulate these effects. Traditional *in vitro* culture models (i.e., tissue culture plastic systems)[297] and *in vivo* models (*e.g.,* murine animal models)[298] may be useful for initial hypothesis testing and translation of winnowed drug candidates; however, such systems alone may limit the development of effective therapeutics for COVID-19 long haulers because of anatomical inaccuracies, lack of complexity, and/or species-related differences. In that vein, biomaterials-based model systems that integrate human cells, including those from each sex, allow for an interesting opportunity to recapitulate the permanent changes in the lung microenvironment such as increased tissue stiffness, altered extracellular matrix composition, and a modified cellular microenvironment. These model systems would enable hypothesis testing in more physiologically relevant conditions that could help in understanding aspects of how the immune response is altered in the long term and consequently allow for the development and testing of therapeutics. Work from several groups, including ours, is utilizing such biomimetic model systems to reproduce key aspects of pulmonary fibrosis, which shares similar pathophysiology to COVID-19, which both cause organ damage and dysregulated wound healing.[299−304] Additionally, there exist underlying opportunities in utilizing organ-on-a-chip model systems to study the effects on other organs systems in recovered COVID-19 patients.[305−308] Utilizing these model systems with primary cells derived from recovered patients would facilitate a hypothesis-based approach to understand post-COVID-19 symptoms and recovery in a physiologically relevant manner and could allow for prescreening of

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therapeutics in a microenvironment resembling that of COVID-19 long haulers.

OUTLOOK

This work is intended to be a guide to the biomaterials community to the potential application of biomaterials-based principles toward COVID-19 and other pulmonary inflammations. We hope that the immune engineering strategies highlighted in this review will lead to more preclinical and clinical investigations of emerging biomaterials and particle-based therapies for COVID-19 and other infections that contribute to pulmonary and systemic inflammations. While the main focus of this review was to highlight opportunities for COVID-19-specific pathologies and complications, the proposed therapeutic strategies could certainly be applicable to other infections and diseases that cause inflammation in the lung. As indicated in various instances in this review, thorough clinical investigations are needed to reveal and characterize the involvement of key immune players in SARS-CoV-2-related infection, inflammation, and immunity. Additional biomaterials and particle-based therapeutic options may also be proposed and investigated as a more detailed, mechanistic understanding of COVID-19 pathophysiology is discovered. As prophylactic vaccines are developed, particle-based designs, as well as the pulmonary route of administration, should be considered to enhance the safety and efficacy of the desired response. However, it is imperative to characterize potential disadvantages associated with the proposed novel strategies including side effects, toxicity, long-term fate, and cost prior to clinical translation. As seen in current clinical studies, "clean" study designs with adequate sample sizes will be needed to fully determine the efficacy of these emerging technologies. Finally, approaches suggested for COVID-19 may find significant translation to other respiratory pathogens and are worthy of pursuit as platform technologies to mitigate the global burden of respiratory viral infections.

AUTHOR INFORMATION

Corresponding Author

Catherine A. Fromen − *Department of Chemical and Biomolecular Engineering, University of Delaware, Newark, Delaware 19716, United States;* orcid.org/0000-0002-7528-0997; Phone: (302) 831-3649; Email: cfromen@udel.edu

Authors

Bader M. Jarai − *Department of Chemical and Biomolecular Engineering, University of Delaware, Newark, Delaware 19716, United States;* orcid.org/0000-0001-7099-2461

Zachary Stillman − *Department of Chemical and Biomolecular Engineering, University of Delaware, Newark, Delaware 19716, United States*

Kartik Bomb − *Department of Chemical and Biomolecular Engineering, University of Delaware, Newark, Delaware 19716, United States*

April M. Kloxin − *Department of Chemical and Biomolecular Engineering, University of Delaware, Newark, Delaware 19716, United States; Department of Materials Science and Engineering, University of Delaware, Newark, Delaware 19716, United States;* orcid.org/0000-0002-4594-2953

Complete contact information is available at: https://pubs.acs.org/10.1021/acsbiomaterials.0c01287

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Notes

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