

ORIGINAL ARTICLE

Role of Tissue Engineering in COVID-19 and Future Viral Outbreaks

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In light of the current novel coronavirus (COVID-19) pandemic, as well as other viral outbreaks in the 21st century, there is a dire need for new diagnostic and therapeutic strategies to combat infectious diseases worldwide. As a convergence science, tissue engineering has traditionally focused on the application of engineering principles to biological systems, collaboration across disciplines, and rapid translation of technologies from the benchtop to the bedside. Given these strengths, tissue engineers are particularly well suited to apply their skill set to the current crisis and viral outbreaks in general. This work introduces the basics of virology and epidemiology for tissue engineers, and highlights important developments in the field of tissue engineering relevant to the current pandemic, including *in vitro* model systems, vaccine technology, and small-molecule drug delivery. COVID-19 serves as a call to arms for scientists across all disciplines, and tissue engineers are well trained to be leaders and contributors in this time of need.

Keywords: tissue engineering, biomaterials, pandemic, coronavirus, viral

Impact Statement

Given the steep mortality caused by the recent novel coronavirus (COVID-19) pandemic, there is clear need for advances in diagnostics and therapeutics for viral outbreaks. Tissue engineering has the potential for critical impact on clinical outcomes in viral outbreaks. Tissue engineers, if mobilized, could play key roles as leaders in the outbreak, given their ability to apply engineering principles to biological processes, experience in collaborative environments, and penchant for technological translation from benchtop to bedside. In this work, three areas pioneered by tissue engineers that could be applied to the current COVID-19 crisis and future viral outbreaks are highlighted.

Introduction

AS OF APRIL 2020, THE WORLD is facing a pandemic of unfathomable proportions. As per the World Health Organization (WHO) on April 9, more than 1,500,000 patients worldwide have been diagnosed with the novel coronavirus disease 2019 (COVID-2019) caused by a laboratory-confirmed infection of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), with more than 84,000 global deaths at this time.¹ Our hospital systems are rapidly filling with patients suffering from viral illness, and the capacity of resources such as emergency departments, inpatient wards, and intensive care units (ICUs) has become overwhelmed in some regions. There is a dire need for new diagnostic and therapeutic modalities. Early diagnosis is critical in establishing quarantine and limiting the spread of

outbreaks; diagnostics later in the course of an epidemic remain important, particularly in determining established immunity. For those infected, there is a current paucity in validated antiviral therapies, and there is no vaccine at this time, although multiple efforts are under way. Even after the predicted resolution of COVID-19, the increasing frequency of viral outbreaks (including the 2003 Severe Acute Respiratory Syndrome Coronavirus,² 2014 Ebola virus,³ 2015 Middle Eastern Respiratory Syndrome Coronavirus,⁴ and 2015 Zika virus outbreaks⁵) suggests that new mechanisms to combat viral infections are a high priority.

As a convergence science, tissue engineering is uniquely suited to offer solutions to complex clinical questions. Currently, tissue engineering-based technologies are being developed to revolutionize areas in medicine such as high-throughput drug discovery,⁶ personalized cancer therapy,⁷

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immune modulation,⁸ and organ transplantation.⁹ Tissue engineers specialize in the application of engineering principles to biological systems, which facilitates the generation of fundamental knowledge as well as new technologies that could be key in a pandemic. In addition, tissue engineers are well versed in collaborative models,¹⁰ working closely alongside clinicians, biologists, chemists, physicists, mathematicians, veterinarians, and other specialists, which will be critical in a multidisciplinary approach to combating the virus known as SARS-CoV-2. Lastly, tissue engineering as a field has emphasized clinical translation, including creating workflows to optimize bringing the benchtop to the bedside,¹¹ resulting in a \$9 billion market, with 21 companies selling tissue engineering-based products in the United States alone as of 2017.¹² In the current setting of limited clinical data and rising patient morbidity and mortality, tissue engineers would be welcomed and valuable allies in the COVID-19 pandemic.

In this work, the potential impact of tissue engineering in improving clinical outcomes during the COVID-19 pandemic and future viral epidemics is explored (Fig. 1). Relevant background information regarding SARS-CoV-2 is briefly reviewed, and pertinent tissue engineering work is highlighted, including development of viral *in vitro* models, drug delivery systems, and vaccine platforms. Given the current state of the pandemic, it may be challenging to mobilize new efforts within the tissue engineering community in time to change practice in health care. New *in vitro* models, diagnostics, and therapeutics will need to be validated prior to safe implementation at the clinical level. In addition, many major academic centers are currently at limited capacity due to precautions to limit the spread of the pandemic. However, COVID-19 can act as a representative outbreak for which tissue engineers can learn from and begin preparations to lead the way to prevent and treat the next viral epidemic better.

Our current understanding of SARS-CoV-2 is evolving and incomplete. The following information is based on current evidence and will likely change as the virus is more closely studied. Given the urgency of the pandemic, some of the references in this work have yet to receive peer review and should be interpreted with caution.

SARS-CoV-2 Background

Coronaviruses, or *Orthocoronavirinae*, are enveloped single-stranded RNA viruses. The virus gets its name from the projections, or “spikes,” emerging from its envelope that appear crown-like on electron micrography. The major components of SARS-CoV-2 are the envelope protein (E), membrane glycoprotein (M), spike protein (S), nucleocapsid protein (N), and its relatively large RNA genome of ~30 kb.^{13,14} Enveloped viruses have a protective lipid bilayer with surface proteins and are generally more vulnerable to harsh environments than non-enveloped viruses. The spike protein is supposed to interact with human angiotensin-converting enzyme 2 (ACE2) membrane protein to induce fusion, endocytosis, and subsequent invasion into the host cell.¹⁵ Coronaviruses escape endosomes to the cytoplasm via acid-dependent cleavage of the S protein.¹⁴ RNA viruses, with few exceptions, replicate in the cytoplasm. The virus takes advantage of host ribosomes to replicate by translation and then assembly in the endoplasmic reticulum directed by M and E protein interactions. Viruses are then released by exocytosis to repeat the cycle of infection. Given this pathophysiology, potential targets being explored as therapeutics agents include blocking ACE2 interactions, altering endosome pH to prevent escape, inhibiting viral and/or host enzymes critical to replication, and downregulating host inflammation, given that an

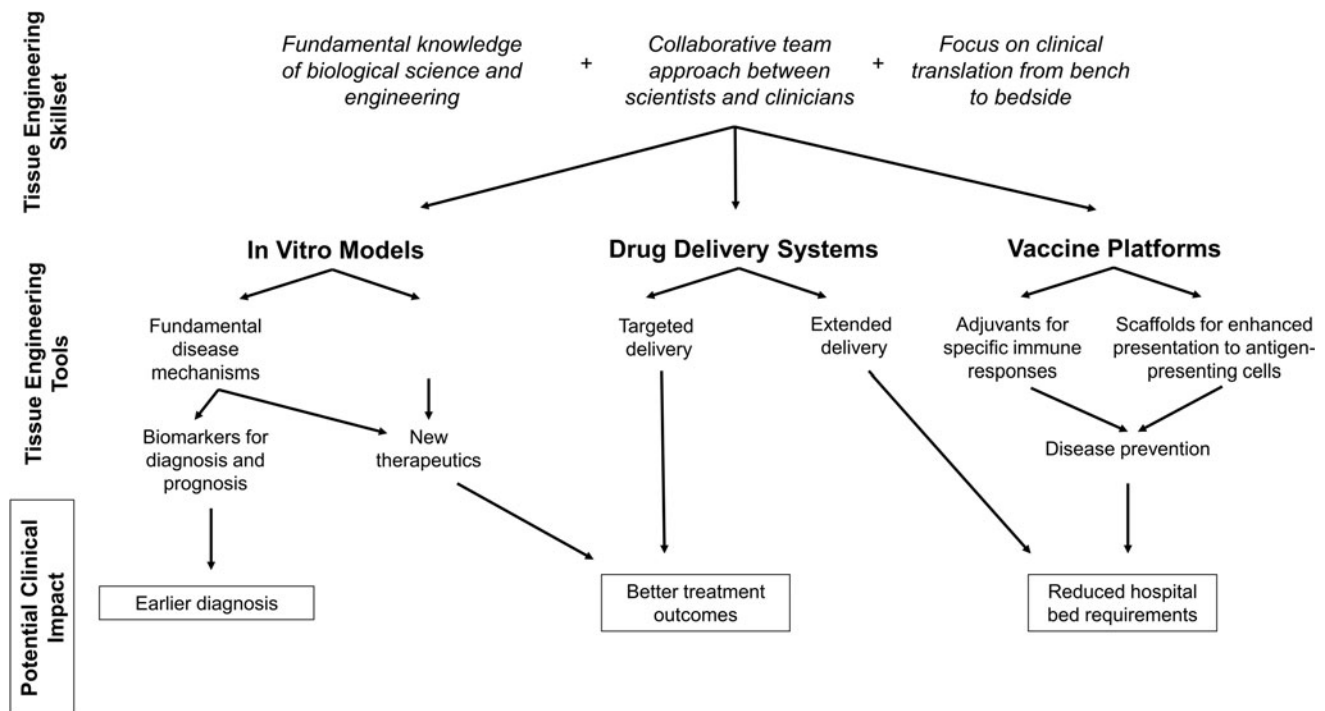


FIG. 1. Examples of how tissue engineering skills and tools may be leveraged to have an impact on clinical practice in the setting of a viral outbreak.

overexuberant response may lead to acute respiratory distress syndrome (ARDS).¹⁶

SARS-CoV-2 has the highest viral burden in the nares rather than the throat and is thought to be spread during coughing and aerosolization of droplets.¹⁷ Compared to SARS-CoV-1, spread of the virus appears to be more rapid due to higher asymptomatic carrier rates and a longer incubation time prior to symptom onset.¹⁸ Initial symptoms commonly include fever, cough, and fatigue and, less commonly, gastrointestinal manifestations.¹⁹ Current biomarkers suggestive of infection include elevated lactate dehydrogenase, ferritin, D-dimer, erythrocyte sedimentation rate, C-reactive protein, and absolute lymphopenia.²⁰ In the United States, the most widely available diagnostic test is polymerase chain reaction based, although antibody-based assays are in development and are available in other countries.²¹ The virus primarily affects the lungs, causing ARDS in up to 5–10% of infected patients,^{22,23} although it has also been causing myocardial injury suspected to be due to high concentrations of ACE2 in cardiac tissue.¹⁵ Mortality is estimated to be 3–4%.¹⁸ Given the extreme global morbidity and mortality caused by the pandemic, there is a dire need for a better understanding of molecular mechanisms of host–virus interaction, more rapid methods to screen potential therapeutics, and platforms to facilitate safe clinical translation. These are all areas in which tissue engineers are primed to make significant contributions for COVID-19, the next coronavirus epidemic, or other future viral outbreaks.

In Vitro Models

Development of physiologically representative *in vitro* models of viral disease can assist in two critical roles during a pandemic: (1) better characterization and understanding of the host–pathogen interface and mechanisms of infection; and (2) as a platform for high-throughput screening of potential therapeutics. Currently, it is challenging and clinically necessary to predict the course of patients infected with SARS-CoV-2. Profiling biomarkers may allow for better risk stratification and resource allotment.²⁴ More accurate *in vitro* modeling to understand host response as well as viral mechanisms for transmission and replication is critical for the identification of biomarkers to pursue as hypothesis-driven diagnostic and therapeutic targets. In addition, a physiologically relevant *in vitro* model has the potential to fill the critical need for improved drug candidate screening.

The current gold standard for screening antiviral therapeutics is based on static monolayer culture of Vero cells, an interferon-deficient aneuploid line of kidney epithelial cells originally isolated from an African green monkey.^{25,26} In a recent study, Vero cells were exposed to a library of 3000 drugs approved by the Food and Drug Administration and the Investigational New Drug program and then infected with SARS-CoV-2 to screen for potential therapeutics.²⁷ Because Vero cells lack interferon, they are highly susceptible to viruses and allow for replication, and so they have been an attractive vehicle to screen compounds. However, interferon itself is an important regulator of host binding proteins involved in SARS-CoV-2.²⁸ In general, the relevance of a drug's ability to inhibit viral infection of a malignant non-human primate (NHP) kidney cell lacking interferon production is uncertain. For example, while the antidepressant

sertraline was found to have potent *in vitro* activity against Ebola in the Vero cell model,²⁶ later testing in an *in vivo* NHP model failed to show protection against Ebola.²⁹ Static cultures of xenograft monolayers fail to replicate many of the conditions facing viruses *in vivo*, including realistic extracellular matrix (ECM), three-dimensional cell–cell interfaces, and shear forces. Coronaviruses and other respiratory viruses, for example, can bind to the ECM components such as sialic acid to assist in infection of the host.³⁰

In the last decade, tissue engineering has made significant advances regarding *in vitro* human cell culture models. Developments of induced pluripotent stem cells, CRISPR-Cas, microfluidics, 3D printing, and biomaterials have led to technologies such as tissue-on-a-chip and advanced bioreactor models containing co-cultures of cells from ectodermal, mesodermal, and endodermal lineages. These models, utilizing human cells, have been able to mimic complex pathophysiology such as generation of pulmonary edema upon exposure to inflammatory signals such as interleukin-2.³¹ For example, in a model to study influenza A virus, 3D tissue-engineered constructs more accurately recapitulated the host morphology of cultured human epithelial airway cells compared to 2D culture, and infection with major influenza strains resulted in upregulation of proinflammatory cytokines.³² One coronavirus-specific example of a tissue-engineered platform in which respiratory viruses have been studied is the rotation wall vessel bioreactor. These models simulate low physiologic shear stresses and frequently incorporate multiple pulmonary cell types, including co-culture of human mesenchymal bronchial tracheal cells and human bronchial epithelial cells, challenging them against respiratory syncytial virus and SARS-CoV-1.³³ Unfortunately, SARS-CoV-1 did not replicate in this study.³⁴ In another model, human pulmonary epithelial progenitor cells were grown on a collagen matrix in a serum-free media with a mesenchymal stroma and exposed to virus. It was demonstrated that stem cells were targeted by SARS-CoV-1, which may suggest why normal lung regeneration following viral infection is challenging.³⁵

There are a number of exciting tissue-engineered human *in vitro* lung models currently available that could be leveraged for studying viral infection^{36,37} and established *in vivo* models for respiratory viruses, including NHPs, already in use.^{38–40} Elements that may improve the relevance of *in vitro* models include: (1) human rather than animal cell lines; (2) co-culture of multiple pulmonary cell lines; (3) 3D scaffolds that mimic native pulmonary architecture; and (4) culture methods that permit generation of ECM prior to viral inoculation. Additional head-to-head studies will need to be performed to determine if these components are necessary to capture the pathophysiology of viral infection. These platforms will be important in conducting hypothesis-driven research to understand the host–pathogen interface. Scaling these models to allow for high-throughput drug screening will offer important advantages over the current Vero-based methods to identify therapeutic candidates for *in vivo* translation rapidly during major infectious outbreaks.

Drug Delivery Systems

During the COVID-19 pandemic, one of the most significant strains on the health-care system has been the need

for inpatient beds, both on general wards and in ICUs.⁴¹ As discussed previously regarding *in vitro* drug screens, there are currently limited therapeutics that have clear clinical evidence of improving outcomes such as days of hospitalization required, need for ICU stay, and need for intubation/ventilation. As new small molecule-based therapies come through the pipeline, tissue engineers can continue to design drug delivery systems to (1) target medications to specific organ systems to increase bioavailability, and (2) extend the release of medications so that frequent administration is not necessary.

Classes of molecules that have been suggested as possible therapies include repurposed small-molecule drugs, monoclonal antibodies, and oligonucleotide strategies.⁴² For example, based on a small clinical study,⁴³ the combination of hydroxychloroquine (a small molecule traditionally used to treat malaria and lupus) and azithromycin (a macrolide antibiotic with anti-inflammatory properties) has been suggested as a means to reduce SARS-CoV-2 viral load, although these results are controversial.⁴⁴ Poly(lactide) and poly(lactide-co-glycolide) (PLGA) microparticles can deliver azithromycin for up to 60 days with zero-order release kinetics.⁴⁵ There are also formulations using fumaryl dike-topiperazine microparticles to deliver azithromycin via intratracheal insufflation directly to the lungs, resulting in higher local concentrations in a murine pneumonia model compared to oral and intravenous routes of delivery.⁴⁶ Given that the half-life of hydroxychloroquine is >40 days, extended drug delivery options may not be warranted.⁴⁷ However, there have been successful delivery systems constructed from PLGA nanoparticles for specific cell targeting.⁴⁸ While the efficacy of hydroxychloroquine and azithromycin in the prevention and treatment of SARS-CoV-2 remains an area of active study, the above examples serve to show that tissue engineers and biomaterials scientists have been working on drug delivery for decades with a variety of vehicles available for small molecules in general.

In addition to small molecules, monoclonal antibodies are an exciting class of medication, given their success in the treatment of Ebola virus.⁴⁹ Antibodies are a natural part of humoral immunity and can be engineered to block specific ligands or receptors vital for viral function. These therapies generally need to be delivered intravenously to be successful. In the Ebola virus studies, for example, patients required one to three infusion sessions, depending on the antibody. A human monoclonal antibody was developed against SARS-CoV-1 and was demonstrated to be effective in a ferret model.³⁸ Researchers have screened monoclonal antibodies designed against SARS-CoV-1 and have discovered cross-reactivity of at least one of the antibodies against SARS-CoV-2.⁵⁰ Systems designs for the controlled extended release of antibodies may be advantageous over multiple infusion sessions for clinical practice. Nanoporous scaffolds coated with allylamine-based polymer were capable of releasing rituximab, a monoclonal antibody against B cells, for up to 30 days.⁵¹ Similarly, an alginate-based drug delivery system was able to deliver a human immunoglobulin G1 (IgG1) monoclonal antibody in a rat model for at least 28 days with a single dose of the system.⁵² In addition to the possibility of reducing administration to single dosing by extended release, there has also been development of ingestible injection systems to deliver biomacromolecules

through autoinjection during gastric transit. These allowed for insulin delivery in a porcine model and may facilitate oral delivery of medications previously only efficacious in intravenous form.⁵³

Lastly, short interfering RNA (siRNA) has also been explored as both prophylaxis and therapy for coronavirus infection.⁵⁴ For sequences specific to SARS-CoV-1, siRNA was effective in a NHP model,³⁹ resulting in diminished viral load and alveolar damage. Four intranasal doses were required over 5 days in treatment arms. The researchers reported not using additional vehicles to deliver their siRNA such as polyethylenimine due to the possibility of carrier-induced lung inflammation. However, more complex vehicles have since been developed by the field specifically for pulmonary usage, including mesoporous silica nanoparticles⁵⁵ and cationic liposomes.⁵⁶ As siRNA sequences, specific antibodies, and small molecules are identified that specifically mitigate SARS-CoV-2, tissue engineers and biomaterials scientists can continue their work in designing vehicles to target areas of high viral load specifically and extendedly. Even if this work may not come to fruition during the current pandemic, these vehicles may serve vital roles during future viral outbreaks.

Vaccine Platforms

The ability to vaccinate against specific pathogens has played a major role in preventative medicine for the last century. Vaccines exist both for respiratory viruses such as *Influenzavirus* and for bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae*. While the success of respiratory viral vaccines varies from season to season, data suggest influenza vaccination generally results in lower probability of complications, including ICU stay, mechanical ventilation, and severe outcomes, especially in patients with comorbidities such as chronic obstructive pulmonary disease.^{57–59} Work is already underway to develop vaccines effective against SARS-CoV-2 to prevent disease and mitigate transmission.⁶⁰

Successful vaccination against pathogens relies on presenting antigens and stimulating specific elements of the immune system to build recognition and memory in both humoral and cell-mediated branches. With advances in immunology, biomaterials and tissue engineering are being leveraged to elicit specific host immune responses to augment vaccination strategies.^{8,61} In many of these systems, the biomaterial acts as the drug delivery vehicle for the vaccine as well as the adjuvant. Furthermore, the field is characterizing how the size, shape, and other physicochemical properties of biomaterials affect the behavior of immune cells.^{62–64} The goals of many of these systems are to target antigen-presenting cells such as macrophages and dendritic cells and to drive specific responses such as Th1 or Th2 (different helper T classes). For example, conjugation of different receptors to protein-based particles can individually tune Th1 or Th2 response in a murine model.⁶⁵ Biodegradable polymers, one of the primary workhorses as scaffold material in tissue engineering, have also been explored. PLGA nanoparticles drive Th1 immune response compared to no carriers and other biomaterials in a vaccine against Chagas disease in a murine model⁶⁶ and have also been explored for targeted delivery to specific immune

populations.⁶⁷ PLGA microparticles in combination with a chitosan/peptide conjugate coating have also been used as a delivery system to target specific mucosal cells and to deliver a swine dysentery vaccine with elevated IgA and IgG production in mice.⁶⁸ In another murine model, chitosan nanoparticles enhanced T-cell response for a *Mycobacterium tuberculosis* DNA vaccine.⁶⁹ When chitosan was mannosylated to promote endocytosis, an intranasal vaccine increased IgG levels in a murine model.⁷⁰ For influenza, chitosan has also been modified to create a thermoresponsive intranasal murine vaccine against H5N1.⁷¹ Silver nanoparticles have also been used to deliver inactivated influenza vaccine locally with some specificity to lung immune cells, resulting in greater IgG titers and reduced mortality in a murine model.⁴⁰ While there are currently fewer studies regarding coronavirus vaccines, there has been some success in mice in which nanoparticles were prepared from a SARS-CoV-1 peptide sequence, and subsequent sera was successful in preventing infection of Vero cells.⁷²

In addition to various particle-based platforms, tissue engineering strategies have been harnessed to create scaffold systems for vaccination enhancement. With specific physicochemical properties, such as pore size, and profile of released recruitment signals such as granulocyte-colony stimulating factor, scaffolds of PLGA^{73,74} and mesoporous silica rods^{64,75} have been used to recruit and concentrate antigen-presenting cells to vaccine components. This strategy has primarily been applied to tumor vaccines and has demonstrated efficacy in animal models against melanoma and intracranial gliomas.^{73,76} It is currently undergoing a Phase I clinical trial of 23 patients with melanoma, which is estimated to complete in June 2020 (NCT01753089; ClinicalTrials.gov). This platform of scaffold-based vaccination has also shown efficacy against bacterial pathogens in porcine and murine models.⁷⁷ Other examples of scaffold-based vaccine systems include those generated from respiratory syncytial virus that were effective in mice as well NHPs.^{78,79} These particle-based and scaffold-based vaccine systems may be promising in translation against SARS-CoV-2. However, the majority have only been studied in mouse models at this point in time, and significant translational efforts will need to be undertaken for clinical trials. Modular platforms in which different antigens can be plugged in⁷⁷ may be very useful for rapid vaccine development in future pandemics.

Conclusion

The world faces a global health-care crisis of unheralded magnitude. The rate of infection and mortality from COVID-19 make it unlike any virus seen in this century. Physicians and scientists are banding together to combat the threat of SAR-CoV-2. Tissue engineers have a rare set of tools and can make substantial contributions to our understanding of viral disease and contribute toward the critical development of diagnostic and therapeutic platforms. Together, we can overcome this current pandemic and work to prevent and mitigate future viral outbreaks.

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