Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Molecular Aspects of Medicine xxx (xxxx) xxx

Contents lists available at ScienceDirect

Molecular Aspects of Medicine

journal homepage: www.elsevier.com/locate/mam

In vitro high-content tissue models to address precision medicine challenges

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ARTICLE INFO

Keywords:
COVID-19
Bioprinting
Organ-on-a-chip
SARS-CoV-2
Precision medicine

ABSTRACT

The field of precision medicine allows for tailor-made treatments specific to a patient and thereby improve the efficiency and accuracy of disease prevention, diagnosis, and treatment and at the same time would reduce the cost, redundant treatment, and side effects of current treatments. Here, the combination of organ-on-a-chip and bioprinting into engineering high-content *in vitro* tissue models is envisioned to address some precision medicine challenges. This strategy could be employed to tackle the current coronavirus disease 2019 (COVID-19), which has made a significant impact and paradigm shift in our society. Nevertheless, despite that vaccines against COVID-19 have been successfully developed and vaccination programs are already being deployed worldwide, it will likely require some time before it is available to everyone. Furthermore, there are still some uncertainties and lack of a full understanding of the virus as demonstrated in the high number new mutations arising worldwide and reinfections of already vaccinated individuals. To this end, efficient diagnostic tools and treatments are still urgently needed. In this context, the convergence of bioprinting and organ-on-a-chip technologies, either used alone or in combination, could possibly function as a prominent tool in addressing the current pandemic. This could enable facile advances of important tools, diagnostics, and better physiologically representative *in vitro* models specific to individuals allowing for faster and more accurate screening of therapeutics evaluating their efficacy and toxicity. This review will cover such technological advances and highlight what is needed for the field to mature for tackling the various needs for current and future pandemics as well as their relevancy towards precision medicine.

1. Introduction

Every individual is unique and therefore might respond differently to different therapeutic treatments, and hence, taking individual variability into account in clinical practice is vital (Pereira et al., 2021). Nevertheless, fortunately with today's technological advancements and broad knowledge available (such as the human genome sequence, accurate characterization methods at cellular levels, improved models of human tissues and organs, and powerful computational methods) precision medicine can be possible (Collins and Varmus, 2015). Precision

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https://doi.org/10.1016/j.mam.2022.101108
Received 8 April 2022; Received in revised form 29 June 2022; Accepted 20 July 2022

medicine is about treatment approaches that specifically fit the need of an individual based on features such as genetic, biomarker, phenotypic, or psychosocial characteristics (Jameson and Longo, 2015). The ultimate goal is to improve the efficiency and accuracy of disease prevention diagnosis and treatment, and simultaneously reduce costs, side effects, and unnecessary treatment of those who would not benefit from traditional medicine (Ginsburg and Phillips, 2018).

Nevertheless, in order for precision medicine to truly advance, the challenges with the enormous clinical and research data that precision medicine relies on need to be shared and available without causing any issues with patient confidentiality (Brothers and Rothstein, 2015; Stiles and Appelbaum, 2019). Moreover, high-content or advanced tissue models that are more relevant than current *in vitro* tissue models are needed to provide rich information, recapitulate the *in vivo* microenvironment with more fidelity and accuracy and consequently improve the translation and minimizing the gap between *in vitro* and *in vivo* systems, could promote the advancement of precision medicine even further (Moysidou et al., 2021).

One good example where the area of precision medicine could serve as an enabling tool is in the recent pandemic caused by the coronavirus disease 2019 (COVID-19). To this end, the world has been plagued by one of the worst global pandemics in our history. Emerging at the end of 2019 initially locally, and posteriorly declared a pandemic by the World Health Organization (WHO) in March 2020, the coronavirus disease 2019 (COVID-19) has spread rapidly, causing serious consequences globally with over 180 million confirmed cases worldwide to date (June 2021) (Verity et al., 2020). The alarming growth in the number of confirmed deaths globally due to COVID-19, caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in enormous difficulties in managing this new virus and its variants (Sohrabi et al., 2020).

Some of the main challenges of the COVID-19 outbreak have been the high infectivity and rapid geographical spreading of the virus, insufficient healthcare capacities, the lack of knowledge of the pathogenesis of the disease, and the lack of effective vaccines (before November 2020; since then vaccines against COVID-19 had been successfully developed and vaccination programs already being deployed worldwide) and pharmacological treatments (Cao and Li, 2020). In addition, with limited interventions available, prolonged or intermittent social distancing or other measures under certain scenarios may still be required into the future, which most likely will cause unprecedented humanitarian and economic challenges (Kawohl and Nordt, 2020; Kissler et al., 2020).

In response to the current COVID-19 pandemic, scientists from around the world are racing to develop new methods of prevention, diagnosis, and treatment regimens in an effort to relieve pressures on the healthcare system and reduce the socioeconomic impacts caused by COVID-19 (Ayres, 2020). In this context, animal models have been widely used to study the previous coronaviruses and related lung diseases (Gretebeck and Subbarao, 2015; Sutton and Subbarao, 2015; Yuan et al., 2020a); however, these models still suffer from severe conventional limitations such as species differences, poor predictions, high costs, high regulatory hurdles to conduct animal tests, and ethical issues (Cohen, 2020; Perrin, 2014). On the other hand, bioengineering has surged as a promising approach to overcome these shortcomings and has helped to develop new and effective therapies and tools to understand such a viral disease. To this end, the employment of human-based *in vitro* models mimicking the complex pathophysiology of their *in vivo* counterparts, could provide a facile and convenient tool in combating and understanding this enormous challenge (Tatara, 2020).

Within this framework, *in vitro* models of human tissues applied to viral infections can assist in solving at least three critical points during the current pandemic: (1) understanding the mechanisms of pathogenesis, and enabling high(er)-throughput screening of (2) potential drugs and (3) additional vaccines (Mills and Estes, 2016). However, creating the physiologically relevant human tissue models able to recapitulate the dynamic interactions of the *in vivo* microenvironments within *in vitro* systems is a challenging task (Jackson and Lu, 2016). One of these difficulties include the fabrication of three-dimensional (3D) constructs with geometrical complexities and with a spatial distributions of cells that mimic the native tissues (Mills and Estes, 2016). The essential points and benefits of 3D *in vitro* models ensue despite that two-dimensional (2D) models are still the standard protocols for *in vitro* studies and have contributed immensely to virology research (*e.g.*, studies of pathogenesis and assessment for potential treatments) including that for COVID-19. For instance, 2D culturing of the Vero-E6 cell line has been a powerful tool in research on SARS-CoV-2 infections (Chu et al., 2020; Matsuyama et al., 2020; Wang et al., 2020b), which has allowed for reasonable reproduction of the physiological complexity of living organisms; nevertheless, it does not enable precise recapitulation of the natural infection process *in vivo* and would lead to less reliable and translational results. Compared with 2D models, 3D *in vitro* models are often times more accurate mimicking natural cell proliferation, differentiation, migration, gene expression, and cell-cell and cell-extracellular matrix (ECM) interplay and as a result, 3D systems are able to more accurately simulate the *in vivo* microenvironment providing for more reliable results in the study of infection processes and host responses to viruses and pathogens, *etc.* (Duval et al., 2017; He et al., 2016).

Innovative tissue engineering strategies for *in vitro* tissue model development can be facilitated by bioprinting techniques (Miri et al., 2019a). Bioprinting simultaneously combines cells and/or ECM-like biomaterials through an additive manufacturing process to generate 3D bioengineered living constructs that to a good extent mimic natural tissue properties and characteristics (Saygili et al., 2020). In this work, we have explored the potential applications of bioprinting in COVID-19 and future viral pandemics. An overview of bioprinting for the fabrication of relevant 3D *in vitro* tissue models for use in combating COVID-19 is briefly presented, highlighting how the applications of this promising and emerging technology could contribute to a better understanding of pathogenesis, an improvement of diagnostic tests, and as a platform for drug and vaccine testing and development.

In addition, the use of biomimetic systems in microfluidic culture devices that mimic the microarchitectures and physiological functions of human organs, termed organ-on-chips, is another technology discussed in this review for its potential to address COVID-19 challenges (Wu et al., 2020; Yesil-Celiktas et al., 2018). We also cover current limitations of organ-on-a-chip technology and what is needed for the field to mature to address this and future pandemics. Furthermore, the smooth merging of these two technological platforms may provide unprecedented innovations and solutions, where specific 3D tissue models can be efficiently developed through bioprinting and then be further merged into organ-on-a-chip devices (Parrish et al., 2019; Zhang and Khademhosseini, 2020).

Furthermore, vital 3D *in vitro* organ models termed organoids that are stem cell-derived, self-organized miniature organs will be covered. They have been widely employed in disease modeling and their use in studying SARS-CoV-2 infection will be discussed.

Finally, biosafety is an important aspect to consider when designing and performing various *in vitro* models for SARS-CoV-2 studies. Previous virus-induced epidemic situations could function as an important guideline to quickly design solid and cautious strategies (Herman et al., 2004). In this context, the Centers for Disease Control and Prevention (CDC) and the WHO have provided some guidelines for handling specimens containing SARS-CoV-2 based on previous suggested handling of SARS-CoV and MERS-CoV (Iwen et al., 2020). Further protocols and procedures for the safe collection, handling, and also inactivation of SARS-CoV-2 have been disclosed (Bain et al., 2020; Barrow et al., 2021). Lastly, a comparison between *in vitro* models and animal models for COVID-19 is discussed.

Because of the extensive diversified outcomes of COVID-19, personalized medicine could play a key role in the quest for

eliminating or reducing challenges with the COVID-19 pandemic, but also provide a deeper understanding of individual responses to SARS-CoV-2 infections and potential therapeutics and vaccines (Dopazo et al., 2021). There have been several reports on the huge variations in responses both to the COVID-19 (Choi et al., 2021; Farajallah et al., 2021) and to vaccines for prevention of the disease (Abo-Helo et al., 2021; Barros-Martins et al., 2021; Rubin, 2021). One potential lead that could promote the advancement of precision medicine to address COVID-19 challenges and provide a better understanding for patient susceptibility and responses could be to identify and target specific gene alterations associated with COVID-19 (Zhou et al., 2021).

2. An overview of bioprinting applied towards the generation of *in vitro* tissue models

Bioprinting as defined *vide supra* is an advanced additive manufacturing technological process where a precise controlled, oftentimes layer-by-layer patterning of biological materials into functional structures is performed (Chen et al., 2020b; Murphy and Atala, 2014; Murphy et al., 2020). The essential components for bioprinting are the bioink, a suitable bioprinter and a bioprinting process such as extrusion, droplet, or laser-based bioprinting (Ayan et al., 2020; Leberfinger et al., 2019).

The current treatment options to replace damaged tissues and organs are highly dependent on obtaining tissues from transplants or the same individuals. Nevertheless, there are several limitations to these treatment options including the scarcity of donors and long-term problems with surgical reconstructions, where the field of tissue engineering and regenerative medicine are advancing to overcome these challenges (Langer and Vacanti, 1993). Regenerative medicine and tissue engineering in the convergence with advanced materials science and stem cell science, work ceaselessly to produce tissue constructs for the purpose of regenerating complex tissue and organ systems (Atala et al., 2012). With emerging bioprinting technology, it could potentially better tackle the need for tissue and organ replacement, by allowing for the manufacturing of biological constructs with hierarchical architectures similar to their native counterparts as living functional tissues, where stem cells may further be combined (Afewerki et al., 2019; Mandrycky et al., 2016; Murphy and Atala, 2014).

More relevant to the theme of this review, tissue engineering strategies may as well be employed to the engineering of improved *in vitro* 3D tissue models mimicking their corresponding *in vivo* environments, due to their ability to precisely control the properties of the constructs (Moroni et al., 2018). They could be useful for testing drugs, materials, stem cell therapies, and more without necessarily needing time-consuming and sometimes inaccurate animal experimentation. The bioprinting technology is an extended application of rapid prototyping or additive manufacturing techniques to produce tissue constructs usually layer-by-layer printing incorporating living cells, usually along with biocompatible ECM-like materials, especially hydrogels (Arslan-Yildiz et al., 2016). The quality of the final bioprinted constructs is influenced by their cellular responses and tissue microenvironment formation (Derby, 2012). The bioink (*e.g.*, cellular components often times encapsulated within biomaterials) is used in obtaining an optimally bioprinted construct/tissue model, where it should display properties such as improved biocompatibility and desired biodegradability with appropriate mechanical properties, structural integrity, and promotion of cell growth as well as other cellular behaviors (*e.g.*, migration, proliferation, and differentiation) (Afewerki et al., 2021; Jang et al., 2018; Ying et al., 2018).

Among the various biomaterials, hydrogels are the most attractive for bioprinting applications, and are 3D networks of polymeric chains with the ability to maintain a large volume of water (Afewerki et al., 2020; Zhang and Khademhosseini, 2017). This class of biomaterials have gained significant interest due to their resemblance to the ECM of natural tissues (Kopeček, 2007).

Bioprinted complex human tissues (such as the liver (Kryou et al., 2019), heart (Birla and Williams, 2020; Qasim et al., 2019; Zhang et al., 2016), and blood vessels (Gong et al., 2020; Hoch et al., 2014; Pi et al., 2018)) have been created in which they are primarily used to evaluate the efficacy and toxicity of drugs. Such systems could eliminate or reduce animal testing, which often fails in predicting human responses, in addition to minimizing ethical concerns, complexity in studies, expenses, and overall reduces delays in commercializing such drugs (Shanks et al., 2009; Van Norman, 2019).

The fundamental strategy with these models is their use for improved investigation in cell cultures and more accurate screening of drugs *in vitro* (Castilho et al., 2014; Vanderburgh et al., 2017). As an example of creating a 3D organ or tissue for *in vitro* tests, lung cancer-associated fibroblasts (CAFs) and non-small cell lung cancer (NSCLC) cells have been 3D-bioprinted with biomaterials composed of sodium alginate and gelatin for the high-throughput screening of drugs (Mondal et al., 2018).

Another exemplary application of this concept is the use of a human liver decellularized ECM (dECM) bioink to bioprint liver tissues, obtaining information on the biology of liver diseases and the study of the delivery and screening of drugs and potential use in 3D hepatic tissue transplantation (Tomaz et al., 2018). In fact, since the dECM embodies the complexity of the natural ECM, a wide range of organ and tissue dECM has been employed as bioinks for bioprinting *in vitro* tissue models (Jo et al., 2021; Kim et al., 2017), such as those derived from adipose, cartilage, or heart tissues (Pati et al., 2014). For example, Jang and colleagues used porcine heart, liver, and colon dECM and further fabricated these into light-sensitive bioinks and further bioprinted them into microtissues with controllable sizes (Kang et al., 2022). In another report the same group employed porcine colon dECM to bioprint a tubular intestine model to recapitulate the human intestinal system *in vitro* (Han et al., 2022).

Furthermore, 3D bioprinting has been employed for COVID-19 research to design biomimetic models (Akter et al., 2021) useful for drug toxicity tests and for the study of the fundamental mechanisms of infection (Chakraborty et al., 2020; Kabir et al., 2021) (Fig. 1). This strategy would make it possible in the near future to accelerate our understanding of unprecedented infectious diseases but also minimize the need for animal models, fasten the drug development process of therapeutics and vaccines (Papi et al., 2022), and hopefully minimize the total costs required (Singh et al., 2020; Yi et al., 2021). In this context, 3D bioprinting could be used to print an *in vitro* model for the upper and lower respiratory tracts, providing a system to study SARS-CoV-2 infection, its entry, and the corresponding immune responses (Fig. 1a). Furthermore, we bioprinted 3D hepatic microtissues for drug safety screening against COVID-19 (Coban et al., 2021). A total of 15 potential candidate compounds against COVID-19 were tested on the bioprinted liver microtissues for toxicity, which demonstrated that none of these compounds exhibited significant signs of toxicity (Fig. 1b).

3. An overview of organ-on-a-chip models applied towards the generation of *in vitro* tissue models

The use of *in vitro* tissue models has advanced into organ-on-a-chip models where cutting-edge 3D microtissues are combined with microscale fluids that allow for the temporal and spatial control of cellular microenvironments and the manipulation of small amounts of fluids (Low et al., 2021; Meyvantsson and Beebe, 2008). In other words, organ-on-a-chip models are microphysiological systems encompassing microfluidic devices combined with dynamic cell cultures to mimic tissue and organ systems (Esch et al., 2015; Wang et al., 2022; Wang et al., 2021b; Zhang et al., 2018). This strategy would mimic and translate the structure, function, physiology, and pathology of human organs in a better way, into practical *in vitro* models, and overcoming some key limitations of current planar or static *in vitro* models and animal models (Sasmal et al., 2018). The concept of the organ-on-a-chip can be improved by integrating additional relevant fabrication tools

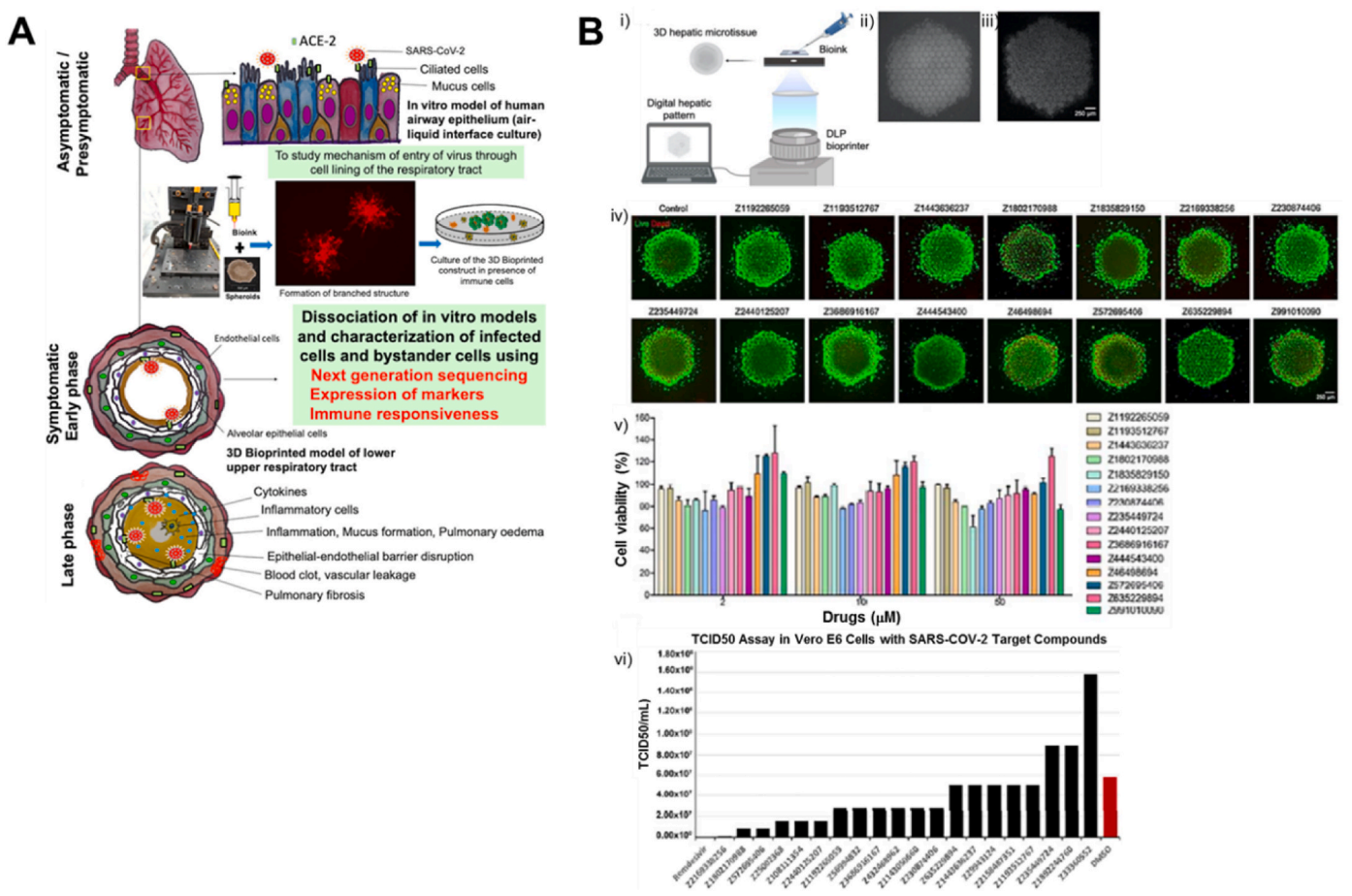

Fig. 1. Examples of bioprinted tissues used for COVID-19 research and drug testing. **A)** Image demonstrating the evaluation of viral infection mechanism on 3D-bioprinted disease tissue models of the human airway epithelium and lower upper respiratory tracts in the presence of immune cells. Reproduced with permission (Chakraborty et al., 2020). Copyright 2020, American Chemical Society, Chakraborty et al. **B)** i) Scheme demonstrating the process for the 3D bioprinting of human hepatic microtissues and the bright-field image of the printed construct ii) in the absence of cells and iii) with HepG2-C3A cells. iv) Fluorescence images of stained cells treated with the various compounds. v) The quantification of metabolic activity and vi) of the TCID50 assay when treated with Remdesivir, DMSO, or the various SAR-CoV-2-targeting compounds. Reproduced with permission (Coban et al., 2021). Copyright 2021, Coban et al. Licensed under A Creative Commons Attribution License (CC BY).

such as chemical gradients, mechanical forces, and electrical stimuli, depending on the organ of interest (Huh et al., 2012b). These systems can be enabling *in vitro* platforms for the evaluation of drugs and delivery vehicles including their efficacy and toxicity, and tissue-engineered implants and medical implants, all potentially in a personalizable manner (Ronaldson-Bouchard and Vunjak-Novakovic, 2018; Sharifi et al., 2019; Zhang, 2019). In the context of the current COVID-19 pandemic, very recently, Ingber and colleagues devised a human organ-on-a-chip technology as a tool to study SARS-CoV-2 infections and immune responses by using a pseudotyped virus to test cellular entry, and further screen approved drugs as potential therapeutics for the inhibition of the entry of the pseudotyped SARS-CoV-2 virus into the host cells (Si et al., 2020). Through their device comprising of human lung epithelial cells, which can express high levels of angiotensin-converting enzyme 2 (ACE2) (Ma et al., 2020) and transmembrane protease, serine 2 (TMPRSS2) (Gkogkou et al., 2020) and several clinically approved drugs were evaluated. The study showed that the malaria drug amodiaquine and breast cancer drug toremifene significantly reduced pseudotyped SARS-CoV-2 replication (Si et al., 2020).

It is important to highlight that despite the fact that the pseudotyped SARS-CoV-2 virus has been widely used to study the native virus, it has several limitations worth considering, since it can only mimic the upstream cellular entry and cannot trigger the downstream immune responses within infected cells like the native virus, hence it is not suitable for studies involving immune responses (Kruglova et al., 2021).

4. High-content tissue models toward personalized medicine for COVID-19

The prediction of disease susceptibility of a person by characterizing specific individual immune-genomics and use of knowledge to promote innovative tailor-made treatments, termed personalized medicine, has gained significantly increased attention as of late (Hamburg and Collins, 2010). This would allow one to overcome the variability in treatment responses from various individuals due to genetic variations (Lee and Morton, 2008). In this context, COVID-19 has proven the importance of personalized medicine, where heterogeneity in treatment response is a great challenge that could possibly cause disease enhancement or efficacy variability in various individuals groups (Visvikis-Siest et al., 2020), for instance elderly individuals that are more susceptible to infection and death (Guilger-Casagrande et al., 2021; Pereira et al., 2021). Therefore, personalized medicine for COVID-19 would transform healthcare and clinical practice providing a better preparation and technological platform for future unexpected pandemics (Dopazo et al., 2021).

The genetic background of various patients has led to variations in drug effectiveness and toxicity in the pursuit of better COVID-19 infection treatments (Cascella et al., 2021). A further important aspect of

personalized medicine in the context of COVID-19 infection is the wide range of mutations of the SARS-CoV-2 virus observed to date (Aleem et al., 2021; Conti et al., 2021), where different individuals respond differently to the various mutations (La Rosa et al., 2021) and whether the already successfully developed vaccines will provide the same efficacy on new mutations or will they lead to some side effects or ineffectiveness (Cines and Bussel, 2021; Jia and Gong, 2021).

The personalized medicine strategy would promote essential levels of care for all and could potentially overcome variations both from the individuals and pathogens point of view (Carta et al., 2020). One approach to further promote the innovations from and development of personalized medicine for COVID-19 that match every individual towards a more precise and effective treatment could be through the employment of an organ-on-a-chip model (Ma et al., 2021). As *vide supra* highlights, therapeutics evaluated through 2D cell cultures and animal models sometimes fail in functioning in humans due to the lack of recapitulating *in vivo* environment in the first model and whilst the second one due to species differences and therefore poorly reconstruct the human pathophysiology (Ashammakhi and Elzagheid, 2018). The selection of appropriate cells or tissues from a patient, for instance the induced pluripotent stem cells (iPSCs), could serve as a cell source to generate the desired organ or tissue and further be linked to an organ-on-a-chip model for the development of a personalized disease model or for drug screening (Ma et al., 2021). Despite that several reports have demonstrated the use of organ-on-a-chip models towards improving personalized medicine (Ellis et al., 2017; Vatine et al., 2019), to our knowledge, to date, no examples of personalized medicine for COVID-19 by using organ-on-a-chip platforms have been reported. Nevertheless, this is a very interesting and highly important research topic that we hope will boosted in the near future. Moreover, within the framework of personalized medicine for COVID-19, several aspects have to be considered in order to design a suitable and translational organs-on-a-chip model that could be used for the said applications, such as personal samples and health data of the patients must be obtained, and also the patient's results in order to corroborate the results obtained from the organ-on-a-chip studies (van den Berg et al., 2019). This strategy would most likely provide a protocol and approach verifying the potential of organ-on-chips for personalized medicine in the battle for COVID-19 challenges (Ingber, 2022).

Furthermore, 3D bioprinting could function as a prominent tool for generating high-content tissue models for personalized medicine, in particular for infectious disease research and drug development, through a rapid and automated production (Kim et al., 2021; Yi et al., 2021). Within this framework, Perez et al. demonstrated this strategy successfully by printing tissues for a personalized treatment for neurological diseases 3D bioprinting of adipose tissue-derived mesenchymal stem cells using a fibrin-based bioink (Restan Perez et al., 2021).

The future advancement of organ-on-a-chip and 3D bioprinting for engineering high-content tissue models towards personalized medicine for infectious diseases will most likely play a key role in how well-prepared and how smoothly we can handle future unexpected pandemics (Chakraborty et al., 2020).

Recently there have been several examples on how precision medicine could fruitfully be employed towards addressing COVID-19 challenges and also initiatives promoting the inventiveness towards this goal. One initiative that potentially could facilitate and promote the use of precision medicine towards tackling COVID-19 is the creation of the open-access database named the COVID-19 Genomics and Precision Health database (COVID-19 GPH) by the Genomics and Precision Public Health at the CDC, providing important information such as pathogenic information and the contribution of genomics (Yu et al., 2022). To date, current COVID-19 therapeutics have never undergone multifactorial drug-gene interactions; within this framework, it has been suggested that these therapeutics should undergo evaluation for their genetic associations of relevant metabolic or transporter genes, which would allow for the evaluation of their safety and effectiveness and also promoting precision COVID-19 therapeutics (Biswas et al., 2022). Another strategy that has been investigated in personalized medicine for COVID-19 patients is the use of autologous peripheral blood stem cells and plasma (Balzanelli et al., 2022). Nevertheless, an immunomodulatory therapy approach using patient-specific immunophenotyping might be an additional option for precision medicine due to the great variability of immune responses from COVID-19 patients (Fang and Schooley, 2021; Hall et al., 2020).

5. *In vitro* tissue models and technologies for COVID-19 applications

5.1. Development of tissue models

Human tissue models have been developed using various methods, such as planar and 3D models (Elliott and Yuan, 2011; Liaw et al., 2018; MacGregor et al., 2001; Mironov et al., 2009; Wrzesinski and J Fey, 2015), specially designed chambers (Transwell) (Heydarian et al., 2019) and others (Schanz et al., 2010), yet reproducing the complex architectures of the human tissues is still a challenge (Benam et al., 2015; Doryab et al., 2019). The combination of the conceptual strategy of bioprinting and organ-on-a-chip techniques would promote the engineering of suitable microenvironments to better represent the complexities of human tissues, thus mimicking their true functions, which would increase the reliability of pre-clinical tests. Moreover, bioprinting technologies can be used to devise *in vitro* models allowing for better characterization and understanding of the mechanisms of viral infections (Saygili et al., 2020). Additionally, the merging of bioprinted tissue models with chip devices could provide an important combination taking the two separate concepts into synergistic fruitful outcomes (Zhang and Khademhosseini, 2020). This combined strategy could perhaps lead to better representative models that not only feature volumetric structures but also, compartmentalization and dynamic flows.

Moreover, tissue models such as 3D human lung tissue models have been developed and used to study the pathogenesis of *Mycobacterium tuberculosis*, *Staphylococcal pneumonia*, and *Andes hantavirus* (Mairpady Shambat et al., 2015; Mills and Estes, 2016; Parasa et al., 2014; Sundström et al., 2016). Despite that the models demonstrated promising outcomes, they still encountered some limitations such as the use of cells to make them more realistic to *in vivo* conditions (especially, inclusion of neutrophils and lymphocytes), the absence of vascularization, and the lack of several important proteins and components found in the native ECM (Braian et al., 2015).

Several studies have already demonstrated the successful engineering of *in vitro* models for investigating coronaviruses by combining human bronchial tracheal mesenchymal cells (HBTCs) with adenovirus-12 SV40 hybrid virus transformed bronchial epithelial (BEAS-2B) cells (Albright et al., 1990) or by using pulmonary Oct-4+ stem/progenitor cells (Ling et al., 2006; Suderman McCarthy et al., 2006), influenza A by using A549 human alveolar epithelial cells and a hydrogel comprising of Matrigel, alginate, and gelatin or by employing primary human small airway epithelial cells (HSAEpCs) in combination with a chitosan-collagen scaffold (Berg et al., 2018; Bhowmick et al., 2018), and other respiratory system-related viruses (Gardner and Herbst-Kralovetz, 2016; Huh et al., 2012a; Miller and Spence, 2017; Nichols et al., 2013). Taking the lead from these studies, using the proper tissue types and by making additional efforts, 3D models suitable for the study of the SARS-CoV-2 virus represents an excellent opportunity to quickly understand the disease, rather than waiting for animal models – in fact, mature animal models for SARS-CoV-2 infection are rarely available.

5.2. Understanding the mechanisms of pathogenesis

To date, our knowledge of the SARS-CoV-2 virus is limited.

Nevertheless, the vast pool of recent literature proposes a plausible understanding of the pathogenesis of the novel coronavirus (Hoffmann and Pöhlmann, 2021), where it is reasonable to assume that epithelial cells and macrophages are the primary targets of the virus (Andersen et al., 2020; Hoffmann et al., 2020; Lai et al., 2020; Walls et al., 2020). Due to a comparable sequence of the receptor-binding domain of the SARS-CoV-2 spike proteins to that of the corresponding spike proteins on SARS-CoV, it is proposed that the virus enters the host cells via the envelop spike glycoprotein and binds to its cellular receptor termed ACE2 (Onweni et al., 2020), which is expressed in epithelial cells of the lung (Inde et al., 2021), intestine, kidneys, heart, vessels, and brain (Li et al., 2020b; Liu et al., 2020b), followed by fusion with the cell membranes (Li et al., 2003; Wan et al., 2020). After the virus enters the cells, the RNA genome is released into the cytoplasm and the viral genome begins to replicate (Perlman and Netland, 2009). Additionally, while the virus enters the cells, its antigen will bind to antigen-presentation cells (APCs), which is a central part of the body's anti-viral immunity. The APCs stimulate the body's humoral and cellular immunity (Arunachalam et al., 2020; Vick et al., 2021), and as a result, one of the humoral responses is associated to the production of a large number of cytokines. Thus, high quantities of cytokines may trigger a violent attack by the immune system to the body, causing the so-called "cytokine storm" (Kuri-Cervantes et al., 2020), as well as acute respiratory distress syndrome (ARDS), thrombotic complications (Connors and Levy, 2020; Klok et al., 2020; Zuo et al., 2020), and multiple organ failures, which are the main causes of death of COVID-19 (Chen et al., 2010; D'Agnillo et al., 2021; Huang et al., 2020; Liu et al., 2010; Xu et al., 2020).

The main pathogenesis of COVID-19 infection as a respiratory system targeting virus is severe pneumonia (Cheon et al., 2021; Zhao et al., 2021), RNAemia, combined with the incidence of ground-glass opacities, and acute cardiac injury (Perez-Bermejo et al., 2021). Nevertheless, neurological complications such as stroke, neuromuscular disorder, and anosmia (Melo et al., 2021a) have also been linked to acute COVID-19 (Spudich and Nath, 2022). Furthermore, significant levels of cytokines and chemokines were noted in patients with COVID-19. Other clinical manifestations include fever, non-productive cough, dyspnea, myalgia, and fatigue (Huang et al., 2020; Peiris et al., 2004). Moreover, a damaging inflammatory response (Mudd et al., 2020; Vella et al., 2021) is associated with severe COVID-19, and the mechanism is linked to the early non-neutralizing afucosylated anti-spike IgG response (Larsen et al., 2021). Since this antibody plays a role in the inflammatory pathogenesis of diseases, the authors suggested this as a potential key component in the early detection of patients with high risk of the infection (Brunet-Ratnasingham et al., 2021; Chakraborty et al., 2022).

Several indications and linkages of the mechanism of pathogenesis for patients with severe COVID-19 have been reported such as an increased number of suppressive myeloid cells in their blood (Mann et al., 2020; Reyes et al., 2021), generation of robust $CD8^+$ T cell memory responses (Kusnadi et al., 2021), a higher level of "armed" natural killer (NK) cells with elevated cytotoxic proteins (Maucourant et al., 2020), and the link of type I interferon to systemic immune alterations (Paludan and Mogensen, 2022; Wijst et al., 2021).

Furthermore, the direct infection of the epithelial cells in the gut because of their high level of the ACE2 and TMPRSS2 expression has been associated with gastrointestinal symptoms such as nausea, vomitting, belly pain, appetite loss and diarrhea besides respiratory symptoms (Roy et al., 2021). The COVID-19 pathogenic mechanism has also been linked to liver disease cirrhosis leading to increased systemic inflammation, cirrhosis-associated immune dysfunction, coagulopathy, and intestinal dysbiosis (Marjot et al., 2021).

This mechanistic pathogenesis understanding could pave the way for the engineering of tissue models, e.g., perfectly replicating epithelial cells models, where ACE2 is expressed in various organs in order to gain a further detailed understanding and screening of potential antiviral drugs or vaccines.

5.3. Therapeutic development

Currently. there do exist treatments/vaccines (before November 2020) for the prevention of COVID-19, but there are very few and their development remains inadequate due to the limited knowledge regarding the detailed molecular mechanisms of and interactions between SARS-CoV-2 and human cells during infection.

To date, vaccines against COVID-19 have been successfully developed by several companies and vaccination has already being employed worldwide (Lopez-Cantu et al., 2022). Despite that vaccination has already progressed significantly, it will most likely require some additional time before it is available to everyone, and therefore, several approaches have been suggested to control its spreading such as keeping social distancing and supportive care for severe cases will most likely continue to endure for a while. Furthermore, many researchers have been studying and suggesting plausible approaches to treat this disease (Christie et al., 2021; Gordon et al., 2020). A lack of efficient *in vitro* and *in vivo* models that represent and predict the human immune responses certainly makes it difficult to understand and investigate infectious agents that cause human diseases.

Although a vast number of various vaccines have been developed since the start of the pandemic, the most successful are probably the messenger ribonucleic acid (mRNA)-based vaccines (BNT162B2 (Pfizer/BioNTech) and mRNA-1273 (Moderna)) that provoke immune responses and further generate neutralizing antibodies against spike proteins in SARS-CoV-2 (Lopez-Cantu et al., 2022; Sadarangani et al., 2021).

Therefore, the development of essential tools for the study and manipulation of pathogens would facilitate and motivate faster responses to future pandemics and invention of vaccines, drugs, therapeutics, and host-targeted immunotherapies. Researchers have managed to clone, label, and express 26 of the 29 SARS-CoV-2 proteins in human cells and thereby study virus interactions with human proteins (Shang et al., 2020; Wang et al., 2020c). This understanding could provide fundamentals for the invention of suitable drugs (Xu et al., 2020). Screening of promising antiviral agents has confirmed two mechanisms of action, the inhibition of mRNA translation and the regulation of some cell receptors (Gordon et al., 2020). Other reports have demonstrated the repurpose of remdesivir, a drug used in the Ebola treatment that functions as an immediate RNA chain terminator (Hillen et al., 2020; Yin et al., 2020).

In fact, several other drugs and potential drug combinations based on the repurposing strategy considering their virus-host protein interactions have been proposed (Zhou et al., 2020c). Moreover, a novel human monoclonal antibody has also been developed that neutralizes the virus rather than acting through receptor-binding inhibition (Wang et al., 2020a). Since COVID-19 has been linked with thrombotic complications (Giannis et al., 2020), the use of heparin in COVID-19 patients can decrease mortality rates (Negri et al., 2020; Thachil, 2020).

Different from conventional drugs, the development of vaccines is based on the human immune response, and the mechanism of action entails exposing the body to an antigen that will trigger an immune response without causing the disease, but causing the immune system to further block or kill the true virus. In the context of COVID-19, specialized APCs bind to SARC-CoV-2 (Liu et al., 2020a), which further leads to the activation of T-helper cells and further activates B cells that target the virus for destruction or blocking it from infecting other cells (Callaway, 2020). Some of the vaccine candidates developed against COVID-19, comprise the whole virus, or are protein-based and nucleic acid-based (Ahmed et al., 2020b; Chen et al., 2020a; Gurwitz, 2020; Prompetchara et al., 2020).

However, the first step to accelerate such research and development is the pre-clinical phase, where the vaccine is tested in *in vitro* and *in vivo* animal models. Here, bioprinting has a strong potential to be employed to create disease models quickly, where cells combined with biomaterials can be bioprinted at necessary spatial resolutions and with desirable shapes and structures (Datta et al., 2017; Sasmal et al., 2018;

Zhang et al., 2019).

Unfortunately, the potential of bioprinting to create models for viral infection studies has not yet been fully explored (Berg et al., 2018; Saygili et al., 2020). This technology can also provide the opportunity to study the variances between human and animals tissues, which is important for tackling the next pandemic due to a better understanding of potential pathogenic virus infections from animals to humans, or the translation of the therapeutics during the development process (Cui et al., 2019; Di Paola et al., 2020; Pierson and Diamond, 2020).

A virtuous example of the employment of bioprinting in viral infection studies has been demonstrated. A 3D model of the human alveoli was created by bioprinting a bioink consisting of A549 alveolar epithelial cells, and subsequently the bioprinted model was infected with influenza A virus (Berg et al., 2018). Interestingly, a clustered infection pattern was observed in the lungs along with viral replication and common immune cell reactions, which were also observed in animal models, thus validating such an *in vitro* system. It is often the lack of *in vivo* validation, or even attempt at such validation, of *in vitro* systems, either those bioprinted or based on organ-on-a-chip platforms, or their combinations, that prevents regulatory agencies (such as the United States Food and Drug Administration (FDA)) from embracing such technologies.

5.4. Lung-on-a-chip models

The challenges with organ-on-a-chip strategies merging with bioprinting is the high complexity and the lack of non-standardized protocols that have been developed (Shrestha et al., 2019, 2020). More specifically, the organ-on-a-chip platforms consist of continuously perfused microfluidic chips with micro-sized channels filled with living cells, and in some cases with components providing stimuli to the systems as well as in-line sensors (Bhatia and Ingber, 2014; Mandenius, 2018; Wu et al., 2020). Due to the possibility of fabricating and manipulating the systems at the microscale, it allows for the replication of the complex microenvironment, dynamic tissue interactions, as well as biomechanical and biochemical functions *in vivo* in a more representative way, for instance compared to traditional cell culture, potentially also at a high(er) throughput (Huh et al., 2011). In addition to a more accurate representation of the physiological functions *in vivo*, the technology provides several other significant advantages, such as better control of physical and chemical properties, fewer samples needed, lower reagent consumptions, enhanced cost-effectiveness, higher sensitivity, and more rapid turnaround times (Shrestha et al., 2020). Consequently, the organ-on-a-chip approach has become an enabling *in vitro* platform to study pathologies and to perform drug development and testing, and therefore, is a good candidate as a future replacement and/or reduction of experimental animal models (Reardon, 2015).

Furthermore, even though researchers have already developed organ-on-a-chip systems for emulating several human body parts (*e.g.*, heart (Kitsara et al., 2019; Sakamiya et al., 2020), liver (Banaeiyan et al., 2017; Jang et al., 2019; Lauschke et al., 2019), kidney (Lee and Kim, 2018; Wilmer et al., 2016), and intestine (Bein et al., 2018; Guo et al., 2018)) including the lung (Benam et al., 2016; Huh et al., 2010; Jain et al., 2018; Shrestha et al., 2019; Xu et al., 2013), and demonstrated promising results, most of these technologies are only at the research stage. The eminence of some of the developed organ-on-a-chip models could be improved, for instance, through the fabrication of multiple compartments, employment of appropriate bioprinting methods and bioinks, and consequent validation against *in vivo* systems already used clinically to approve drug or vaccine development (Ma et al., 2018; Miri et al., 2019b).

Although the bioprinting of tissues/organs combined with microfluidics has already been investigated for several applications (Ma et al., 2018; Park et al., 2018), to our knowledge, no report has been presented towards an integrated strategy comprising bioprinting and organ-on-a-chip technologies addressing the current prodigious challenges with COVID-19. Therefore, we aim to highlight how this technology could be employed providing an improved understanding through the development of better models and diagnostics, which hopefully will help the scientific community in innovating solutions to the current pandemic and prevent future ones. In this context, a great scientific foundation has already been established for bioprinting and organ-on-a-chip models. However, the challenges are connecting the right strategies together in finding appropriate solutions.

Several studies have demonstrated important progress in the development of viral infection models both through organ-on-a-chip devices (Kang et al., 2017; Sodunke et al., 2008; Villenave et al., 2017) or bioprinting technology (Berg et al., 2018; Hiller et al., 2018; Kang et al., 2018), as also briefly mentioned above. Nevertheless, all of the above examples have used bioprinting and organ-on-a-chip models separately. Here, the convergence of the findings in these studies associated with an existing scientific basis on *in vitro* lung models, both lung-on-a-chip and bioprinted lung models together can represent a significant strategy in inventing solid technological solutions in the search for the effective treatment of and solid diagnostics for COVID-19, and overall in the battle against the current and future pandemics (Sun et al., 2021).

The use of lung-on-a-chip technology for the study of various viruses and infectious diseases has previously been disclosed by several reports (Fig. 2) (Nof et al., 2022; Saygili et al., 2021; Si et al., 2019; Tang et al., 2020; Thacker et al., 2021; Zhang et al., 2021). For instance, the models have been used to investigate the drug-resistant evolution of the influenza virus and identification of new resistance mutations by viral genome sequencing (Fig. 2a) (Tang et al., 2020; Si et al., 2019). Zhang and coauthors devised a microengineered 3D human alveolus chip for a SAR-CoV-2 infectious study, which showed mimicking lung injury and immune responses, and the study also demonstrated that treatment with remdesivir could inhibit viral replication (Fig. 2b) (Zhang et al., 2021). Similarly, the human lung-on-a-chip comprising alveolar epithelial cells, microvascular endothelial cells, and circulating immune cells has been engineered for the assessment of a model respiratory viruses and immune responses (Fig. 2c) (Saygili et al., 2021; Zhang et al., 2020). Moreover, Nof and coauthors devised a multi-compartment respiratory tract-on-chip model containing nasal-, bronchial-, and acinar airways to study SARS-CoV-2 infections and its transmission from the nose to pulmonay acini (Fig. 2d) (Nof et al., 2022). The presented platform allows for the evaluation of the transmission pathway, infectious pathogenesis and host-pathogen interactions and could possibly be employed for drug screening. The use of a human lung-on-a-chip model and further inducing SARS-CoV-2 infection demonstrated rapid endotheliitis and vascular damage (Fig. 2e) (Thacker et al., 2021).

Despite that several organ-on-a-chip models such as gut-on-a-chip (Shin and Kim, 2022), intestine-on-a-chip (Bein et al., 2021), and airway-on-a-chip (Gard et al., 2021; Si et al., 2021), have been devised as a potential model to study SARS-CoV-2 infections, and a vein-on-a-chip model to study COVID-19 induced thrombosis (Pandian and Jain, 2022), the lung-on-a-chip models for SARS-CoV-2 are probably the most emerging and frequently reported to date, most likely because the lung is the primary target for SARS-Cov-2 infection (Baddal and Marrazzo, 2021; Cao et al., 2022; Grant et al., 2021). In this context, Deinhardt-Emmer et al. designed a human alveolus-on-a-chip model engineered by using epithelial, endothelial, and mononuclear cells for the study of SARS-CoV-2 infections (Deinhardt-Emmer et al., 2020). The authors demonstrated that the epithelial cells were infected with a high viral load and inflammatory responses, and interferon expression. Nevertheless, the authors noticed that after a prolonged infection, the adjacent endothelial cells were also infected and damaged (Deinhardt-Emmer et al., 2020). Moreover, we have recently disclosed a reversed-engineered functional human lung-on-a-chip model mimicking the pulmonary alveoli with the ability to demonstrate the breathing activities as a potential model to study SARS-CoV-2 infections (Huang et al., 2021).

Very recently, Fisher and coworkers disclosed the first fruitful report

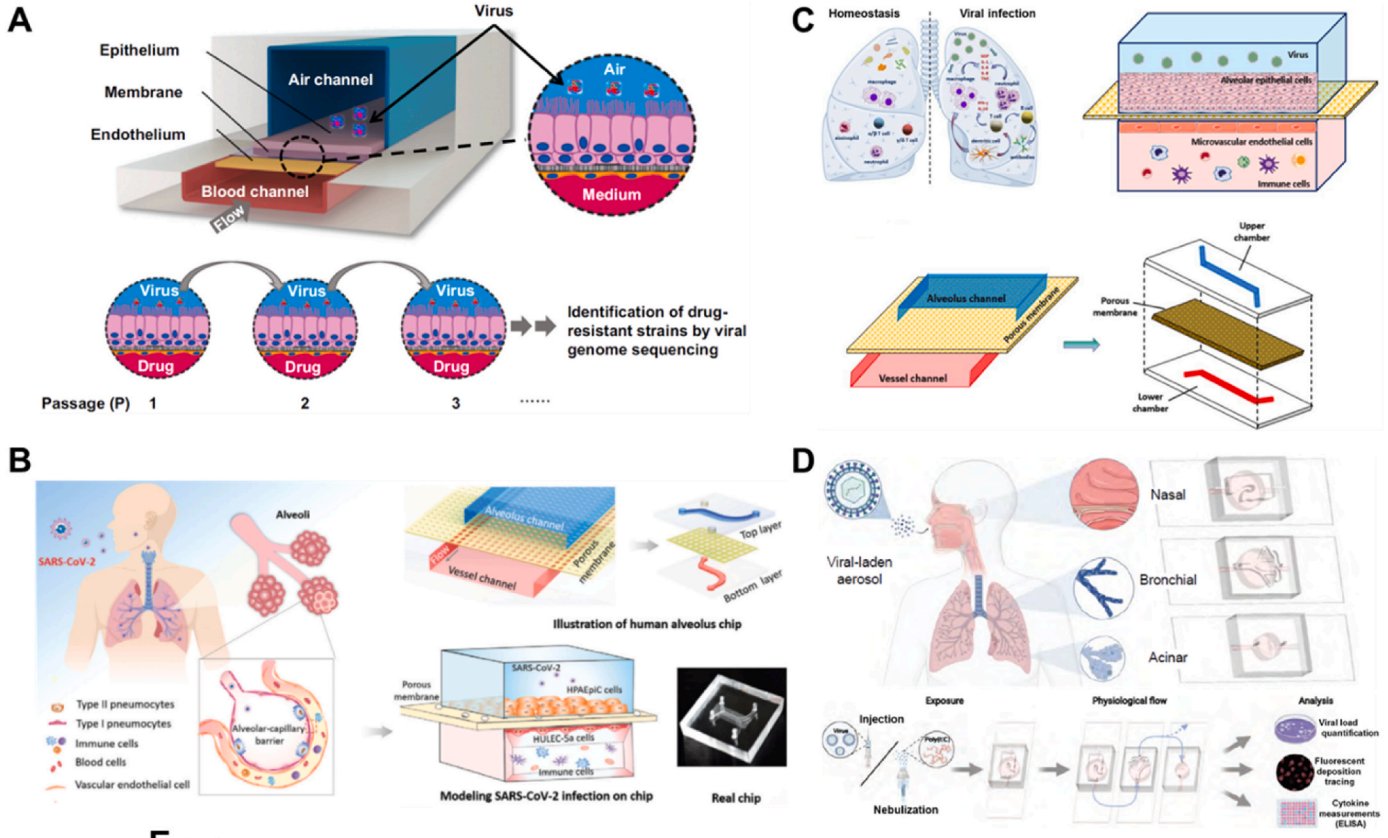

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Fig. 2. Examples of virus infection on lung-on-a-chip models. A) Human lung-on-a-chip model for the investigation of influenza drug-resistance development and the characterization of drug-resistant virus strains using the technology. Reproduced with permission (Tang et al., 2020). Copyright 2020, Elsevier, Tang et al. B) A 3D human alveolar-capillary barrier *in vivo* and biomimetic human alveolus chip infected with SARS-CoV-2. Reproduced with permission (Zhang et al., 2021). Copyright 2021, John Wiley & Sons, Inc. Zhang et al. C) Hung homeostasis and immune response under normal conditions and after viral infection in the respiratory system. A Human alveolus-on-a-chip designed by combining upper alveolar epithelial channels and lower microvascular endothelial channels and a porous membrane acting as a barrier. Reproduced with permission (Saygili et al., 2021). Copyright 2022, AIP Publishing LLC. Saygili et al. D) Multi-compartment respiratory tract-on-chip model comprising nasal-, bronchial-, and acinar airways for human host-pathogen interaction studies. Reproduced with permission (Nof et al., 2022). Copyright 2022, Nof et al. Licensed under A Creative Commons Attribution License (CC BY). E) i) SARS-CoV-2 infection in a human lung-on-a-chip model; ii)−iii) labeling of actin, CD31, and TJP-1; and iv)−x) characterization of the markers ACE2, TMPRSS2, and NRP1 expression levels and SARS-CoV-2 entry. Reproduced with permission (Thacker et al., 2021). Copyright 2021, John Wiley and Sons. Thacker et al.

on SARS-CoV-2 infection and viral replication by a human tissue lung-on-a-chip model (Fisher et al., 2021). The presented technology could function as an important model for screening new therapeutics and vaccines in a high-throughput manner.

Zhang and coworkers reported an attempt to build a human alveolar infection model on chip induced by SARS-CoV-2. This was performed by the coculture of the human alveolar epithelium, microvascular endothelium, and circulating immune cells under fluidic flow (Zhang et al., 2021).

Correspondingly, Thacker et al. prepared a vascularized lung-on-a-chip infection model comprising human alveolar epithelial cells and lung microvascular endothelial cells (Thacker et al., 2021). Various methods were used to elucidate the viral infection damage such as quantitative reverse transcription polymerase chain reaction (qRT-PCR), RNAscope, immunofluorescence, and enzyme-linked immunosorbent assay (ELISA) analyses. The investigation showed persistent infection, loss of endothelial integrity, low viral replication, and inflammatory responses. It has also been observed that the viral infection leads to noticeable morphological changes and destruction of intestinal villus (Guo et al., 2020).

In addition, researchers have taken the organ-on-a-chip strategy to the next level by exploring multi-organ-on-a-chip models, thus approaching closer to designing integrated vital organs (Park et al., 2019; Zhao et al., 2019). These *in vitro* models would provide better predictions of human pathophysiology and responses and a better understanding of the interplay between the various organs (Zhang and Khademhosseini, 2015). For instance, this strategy have been employed for the evaluation of efficacy and toxicity of anticancer drugs by using both liver and cardiac models (McAleer et al., 2019). Another study reported that the merging of lung, heart, and liver models and by using bioprinted spheroid-laden hydrogel bioinks managed to integrate the multisystem in a closed circulatory perfusion system to create inter-organ interactions (Skardal et al., 2017). Several other reports on multi-organ-on-a-chip platforms have also been disclosed such as the human heart-liver-on-chips platforms (Zhang et al., 2017).

5.5. Organoids as 3D in vitro models

Another important category of 3D models used to understand underlying biology and study various diseases includes organoids which are miniaturized 3D self-organized tissue cultures derived from stem cells that mimic the multicellular complexity of organs and tissues (Park et al., 2019; Takebe and Wells, 2019).

These models have been suggested as a prominent platform to gain a fundamental understanding of viral infections such as COVID-19 (Basanthakumar, 2021; de Melo et al., 2021; Deguchi et al., 2021; Harb et al., 2022; Kronemberger et al., 2021; Lv et al., 2021; Ramani et al., 2021; Sia et al., 2022; Sourimant et al., 2022; van der Vaart et al., 2021; Wang et al.; Yu, 2021; Zech et al., 2021) and could be a good alternative to facilitate the development and discovery of new therapeutics and vaccines (Clevers, 2020; Raimondi et al., 2020). To date, various types of organoid-enabled 3D models have been employed to study and understand SARS-CoV-2 infection such as the brain organoid (Ramani et al., 2020), lung organoid (Ekanger et al., 2022; Salahudeen et al., 2020; van der Vaart et al., 2021; Wang et al., 2021a), intestine organoid (Dickson, 2020), as well as liver ductal organoid and bile duct organoid (Zhao et al., 2020a) (Fig. 3). Information from these 3D models has provided the research field with the understanding that the SARS-CoV-2 infection not only affects the respiratory system but also additional tissues and organs (Huang et al., 2020; Li et al., 2020b; Liu et al., 2020b; Peiris et al., 2004).

5.5.1. Brain organoid models

Raman et al. reported that SARS-CoV-2 enters the human brain and causes neurotoxic effects by using 3D human brain organoids (Ramani et al., 2020). The group used induced pluripotent stem cell (iPSC)-derived human brain organoids and isolated SARS-CoV-2 (SARS-CoV-2 NRW-42) from an infected patient through nasopharyngeal and oropharyngeal swabs. The authors observed an altered Tau localization into the somas in SARS-CoV-2-positive neurons and therefore an enhanced level of Tau, which might indicate a potential neuronal stress reaction. This discovery could be a possible initial approach to obtain some insights and understanding of the neurological symptoms associated with SARS-CoV-2 infections (Ahmed et al., 2020a). Furthermore, Mesci et al. demonstrated that SARS-CoV-2 could target the human brain by the design of human brain organoids, which showed that the virus could infect and kill neural cells and cortical neurons (Mesci et al., 2020). The authors also investigated the FDA-approved antiviral drug Sofosbuvir as a potential candidate treatment. The study demonstrated that Sofosbuvir could ease COVID-19-related neurological symptoms such as neuronal death and impaired synaptogenesis. Several other research groups have in addition, confirmed the impairment of neurological functions using *in vitro* brain organoids (Smirnova et al., 2021) or *in vivo* experiments (Song et al., 2020; Yi et al., 2020; Zhang et al., 2020). Since neuronal infection is believed to proceed by the entry of SARS-CoV-2 through the ACE2 receptor, viral infection was managed by blocking ACE2 with antibodies or by administering cerebrospinal fluid from a COVID-19 patient (Song et al., 2020). Interestingly, brain organoids showed susceptibility to SARS-CoV-2 infection but not SARS-CoV infection (Zhang et al., 2020). Additional research has demonstrated that SARS-CoV-2 infects the brain choroid plexus and disrupts the blood-cerebrospinal fluid interface in human brain organoids leading to leakage across this important protective barrier (Pellegrini et al., 2020).

5.5.2. Lung, airway, and intestinal organoid models

Despite that COVID-19 pathophysiology includes several organs such as the lung, the gut, the liver, the heart, and the pancreas, one of the main characteristics includes respiratory failures, which means that the lung and the respiratory systems are the regions impacted to a larger extent (Raimondi et al., 2020). Therefore, modelling the lung and the airways (Elbadawi and Efferth, 2020; Sachs et al., 2019) in organoid models would provide more profound and more fundamental understanding of this type of infectious disease (Chen et al., 2017). Consequently, the various types of cells in the airways system could be used to engineer lung organoids for COVID-19 research and drug screening, and to better understand the impact from SARS-CoV-2 infection on various regions (Fig. 3a). (van der Vaart et al., 2021). In this context, lung, airway, and alveolar organoids have been designed to study the effects of SARS-CoV-2 infections (Duan et al., 2021; Huff et al., 2021; Lamers et al., 2022; Meng et al., 2022; Pei et al., 2020; Pia and Rowland-Jones,

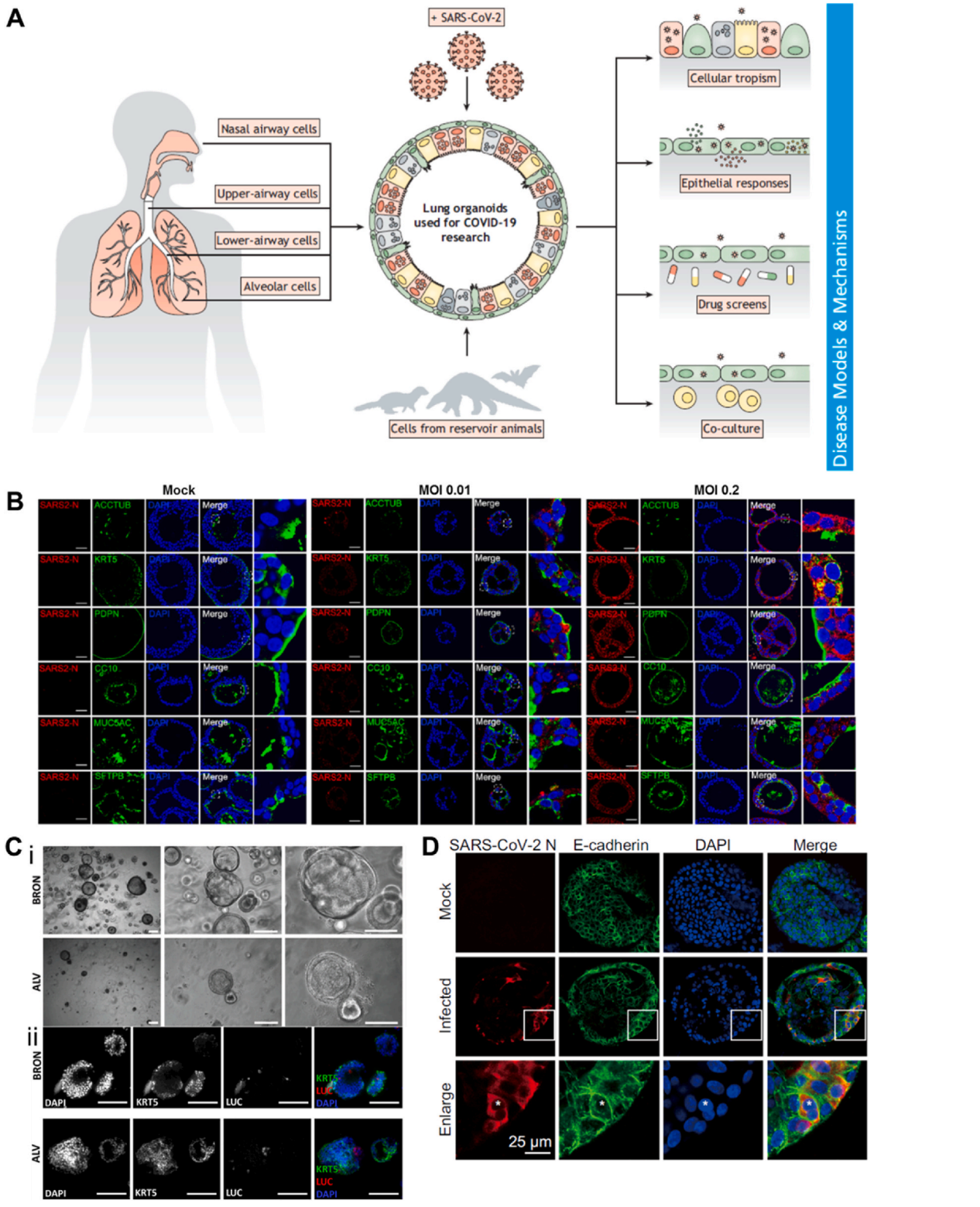

Fig. 3. Examples of virus infection of lung organoid models. A) Scheme demonstrating the use of lung organoids for COVID-19 research. Reproduced with permission (van der Vaart et al., 2021). Copyright 2021, The Company of Biologists Ltd, van der Vaart et al., Licensed under A Creative Commons Attribution License (CC BY). **B)** SARS-CoV-2 infections of human distal lung organoids and its cellular responses by immunofluorescence staining different cell markers and SARS-CoV-2-N antibodies in mock or SARS-CoV-2 infected human distal lung organoids at dpi at MOI = 0.01 and 0.2. Scale bars are 50 μm. Reproduced with permission (Wang et al., 2021a). Copyright 2022, Springer Nature, Wang et al., Licensed under A Creative Commons Attribution License (CC BY). **C)** i) Human lung organoids of bronchiolar and alveolar differentiation. Magnifications are 4x left, 10x middle and 20x right and the scale bars are 250 μm. ii) Detection through immunostaining of cells infected by influenza pseudo H5N1 and viral replication by H7N1 of infected organoids. Scale bars are 100 μm. Reproduced with permission (Ekanger et al., 2022). Copyright 2022, Frontiers Media S.A., Ekanger et al., Licensed under A Creative Commons Attribution License (CC BY). **D)** SARS-CoV-2 infections in human liver ductal organoids. Reproduced with permission (Zhao et al., 2020a). Copyright 2020, Springer Nature, Zhao et al., Licensed under A Creative Commons Attribution License (CC BY).

2022; Salahudeen et al., 2020; Warrier et al., 2022; Xu et al., 2021). Prominently, this viral infection caused more cell death in the alveolar organoids than in the airway organoids. The authors observed that the virus targeted the ciliated cells, alveolar type 2 (AT2) cells, and the rare club cells. The drugs remdesivir, camostat (a serine-protease and TMPRSS2-inhibitor), and bestatin were used to investigate their efficacies against the inhibition of SARS-CoV-2 replication. Remdesivir was shown to inhibit SARS-CoV-2 replication in the lung organoids (Pei et al., 2020). Moreover, Wang and coauthors devised human distal lung organoids infected with SARS-CoV-2 to understand the serial cellular responses as a result from the infection through immunofluorescence staining (Fig. 3b) (Wang et al., 2021a). The authors demonstrated that their disclosed model could mimic the pathological changes in COVID-19 patients, and the study showed cellular responses such as a downregulation of keratinization, a metabolic switch from oxidative phosphorylation to glycolysis, decreased lysosomal function, and apoptosis, among others (Wang et al., 2021a). Ekanger and coauthors established human adult stem cell-derived organoids as a model for the upper respiratory airways and lungs, and demonstrated that the model was permissive to infection by influenza and SARS-CoV-2 viruses (Fig. 3c) (Ekanger et al., 2022).

Another study designed an organoid-derived bronchioalveolar model based on alveolar cells, basal cells and rare neuroendocrine cells and further infected the organoids with SARS-CoV-2 (Lamers et al., 2021). The authors observed the infection targeted mainly the surfactant protein C-positive alveolar type II-like cells. By further treating the infected organoids with interferon lambda 1, a reduction in the viral replication was demonstrated.

In addition, Tsuji et al. used bronchial organoids to show that SARS-CoV-2 infection triggers paracrine senescence, which results in the senescence-associated inflammatory response (Tsuji et al., 2022).

In the quest of modeling a personalized and precise recapitulation of the human lung, Tindle et al. designed an adult stem cell-derived human lung organoid complete with both proximal and distal airway epithelia, where the proximal airway cells are vital for viral infectivity and the distal epithelia for mimicking the host response (Tindle et al., 2021). The transcription factor farnesoid X receptor (FXR) was suggested as a novel therapeutic target against SARS-CoV-2 after observing upregulation of ACE2 transcription in organoids from primary cholangiocyte, as well as pulmonary and intestinal organoids (Brevini et al., 2021). Another study using lung organoids demonstrated the use of interferons as a potential therapeutic to eliminate the replication of SARS-CoV-2 by adopting the lung organoids (Ianevski et al., 2021). Hence, interferons alone did not show any activity, but in combination with other drugs such as remdesivir and camostat it demonstrated high efficacy (Ianevski et al., 2021). Moreover, Suzuki et al. disclosed an approach to devise human bronchial organoids (hBOs) from cryopreserved adult human bronchial epithelial cells (hBEpC) as a model to study SARS-CoV-2 (Suzuki et al., 2020). The authors demonstrated that SARS-CoV-2 infected the hBOs that led to the inducement of type I interferon and interferon-stimulated gene expression. They also demonstrated that the treatment with camostat suppressed viral replication (Uno, 2020). Moreover, Zhou et al. designed human airway organoids to study SARS-CoV-2 infection and found out that ciliated cells and basal cells were infected. Interestingly, they compared the infection degrees of SARS-CoV-2 and SARS-CoV and demonstrated that the first one presented higher infectiousness and evasion of interferon responses (Zhou et al., 2020a). Similarly, airway epithelial models of nasal or bronchial tissues could be generated to study the efficacies of remdesivir and the combination of remdesivir and diltiazem as a potential therapeutic against COVID-19 (Pizzorno et al., 2020).

Recently, it was demonstrated that the broad-spectrum antiviral drug ribonucleoside-analog β-D-N4-hydroxycytidine (NHC; EIDD-1931) inhibits SARS-CoV-2 in human airway epithelial cell cultures and also further in mice infected with SARS-CoV (Sheahan et al., 2020). An example of using organoid models was demonstrated by Han et al., where FDA-approved drugs such as imatinib, mycophenolic acid, and quinacrine dihydrochloride were evaluated as potential inhibitors of SARS-CoV-2 (pseudotyped) entry through a high-throughput screening using both lung and colonic organoids (Han et al., 2021). The same authors also employed colonic organoids to screen 1,280 FDA-approved drugs, where the authors identified mycophenolic acid and quinacrine dihydrochloride to inhibit SARS-CoV-2 entry (Duan et al., 2020). These findings were also corroborated with *in vivo* experiments using humanized mice (Han et al., 2021). Other studies have engineered colonic organoids to assess the association of hypertension and SARS-CoV-2 infections since hypertension is one of the most common comorbidities in COVID-19 patients (Li et al., 2020a). Human intestinal organoids infected with SARS-CoV-2 were used as a model to study infection in the gut (Wang et al., 2022; Zhou et al., 2020b), which demonstrated that the gut is also another target organ since ACE2 is highly expressed on enterocytes (Becker et al., 2022; Lamers et al., 2020). These discoveries could be an explanation to the common gastrointestinal symptoms observed in COVID-19 patients such as diarrhea (Ye et al., 2020). Moreover, the virus could also be detected in the stool of COVID-19 patients (Zhou et al., 2020b).

5.5.3. Miscellaneous organoid models

The human liver ductal organoid model has been used to recapitulate SARS-CoV-2 infection, and through the model, the authors could detect that the virus impairs the barrier and bile acid transportation function of cholangiocytes (Fig. 3d) (Zhao et al., 2020a). Furthermore, the organoid technology has been used to mimic the 3D structures and functions of the kidney to study the potential of SARS-CoV-2 to infect the kidney (Helms et al., 2021a, 2021b; Monteil et al., 2020; Vanslambrouck et al., 2021). Nevertheless, it was also demonstrated that human recombinant soluble ACE2 significantly reduced the infection (by a factor of 1,000–5,000) of the kidney organoids by inhibiting the attachment of the virus to the cells (Monteil et al., 2020). Furthermore, Jansen et al. employed human-induced pluripotent stem cell-derived kidney organoids to verify that SARS-CoV-2 infects the human kidney and stimulates profibrotic signaling which promotes fibrosis (Jansen et al., 2022). The study also demonstrated that a protease blocker could inhibit SARS-CoV-2 infection. Rahmani et al. demonstrated the use of losartan (an angiotensin II receptor blocker) can weaken SARS-CoV-2 infection by reducing ACE2 internalization in human kidney organoids (Rahmani et al., 2022).

Despite that COVID-19 patients are profoundly affected in the lungs due to the higher levels of ACE2 expressed in this region, additional organs and tissues such as pancreatic endocrine cells, liver, cardiomyocytes, and dopaminergic neurons have also been demonstrated to be affected (Monteil et al., 2020). Moreover, a study demonstrating a clear association between COVID-19 and diabetes has also been disclosed (Ardestani and Maedler, 2020).

Recently, Wagar et al. developed tonsil organoids that model human adaptive immune responses for vaccine development (Wagar et al., 2021). To our knowledge this was the first example of using a 3D organoid model to test SARS-CoV-2 vaccine candidates. The disclosed protocol could be an important model to gain a deeper mechanistic understanding of the variable human immune response to the current SARS-CoV-2 and therefore provide a profounder fundamental knowledge promoting the development of vaccines with broad protective immunity.

Interestingly, human pluripotent stem cell-derived skin organoids containing hair follicles and the nervous system have also been employed to study SARS-CoV-2 infections, which demonstrated that an association between COVID-19 and hair loss might be evident (Ma et al., 2022).

Rajan et al. engineered human nose organoids and further infected them with SARS-CoV-2 as a model to study respiratory viruses and test therapeutics that could function as an alternative model to lung organoids (Rajan et al., 2022). To study potential audiovestibular dysfunction as a result from SARS-CoV-2 infection, Jeong et al. prepared human

air organoids that successfully expressed the important components of ACE2, TMPRSS2, and FURIN cofactors for SARS-CoV-2 entry (Jeong et al., 2021). Through their models, the authors could demonstrate the association between audiovestibular dysfunction and COVID-19.

6. Translational aspects of 3D bioprinting, organ-on-a-chip, and organoid technologies

Despite the great advantages and scientific advancement in various technologies, unless they are clinically translated into useful applications in their respective areas, their true potential and positive impact will go wasted. In the context of 3D bioprinting, despite that 3D-printed orthopedic devices have been used in patients, when it comes to bioprinted tissue constructs, there are significant challenges remaining. In light of this, Murphy and coauthors disclosed an insightful perspective regarding the translational challenges within 3D bioprinting (Murphy et al., 2020). Some important aspects to consider when designing solid and functional 3D-bioprinted tissue constructs are: 1) imitating the native tissues, 2) possessing suitable mechanical properties, 3) containing necessary components, and 4) mimicking the function of their corresponding tissues of the organ. Further challenges in translating 3D living constructs includes the cost-effectiveness of the manufacturing and scaling, limitations with biomimicry, and potential challenges integrating with larger tissues and organs, regulatory hurdles, as well as a lack of defined regulatory pathways, and absence of standards for 3D bioprinting and their respective logistics (Murphy et al., 2020). Additional challenges that need to be overcome for smooth translation are the ability to bioprint multi-cellular and vascularized tissues with high resolution, and the laborious procedures to fabricate complex biomimetic tissues (Heinrich et al., 2019). The preparation of bioinks is also an important aspect to bioprint stable structural constructs with defined biological function and to promote efficiency, reproducibility, and a solid translational approach (Gu et al., 2022).

When it comes to organ-on-a-chip technologies, some reports have already confirmed positive *in vitro* to *in vivo* translation (Ingber, 2022); however, to promote their translational applications further technical, standardization, and regulatory advancements and authorization are needed such as more cost-efficient fabrication and mass-production of organ-on-chips, using biomimetic materials and adding more components to mimic the complexity of native organs and their functions (Liu et al., 2016), technological maturity, additional successful *in vitro* to *in vivo* validation, and a solid mechanism for commercialization practicability (Allwardt et al., 2020). To date, organ-on-chips lack specific regulatory classification; therefore in order to promote and facilitate their translational applications, regulatory agencies need to create suitable standard guidelines for their validation (Singh et al., 2022).

On the other hand, limitations of organoids that need to be overcome to promote their translational applications are for instance, reproducibility, consistency, controllability, and ethical issues, but also technical issues such as high cost and lack of solid scale-up manufacturing (Zhang et al., 2022). Similarly, organoids generally lack *in vitro* to *in vivo* validation and standardized processes; nevertheless, by creating biobank libraries, clinical-grade organoids, and standardized pathways for regulatory and commercial procedures, the gap between basic science and industrial applications could be narrowed (Nguyen et al., 2020; Takebe et al., 2018).

7. *In vitro* tissue models versus animal models for COVID-19

Some of the limitations with *in vitro* models could be the lack of precise mimicking of the *in vivo* environment since they rely on isolation of a minor piece of tissue sample, nevertheless by the strategic design of 3D *in vitro* models, these limitations can be overcome (Duval et al., 2017; He et al., 2016). On the other hand, animal models sometimes display greater challenges and limitations as mentioned above, such as species differences, lack of representing the human *in vivo* environment such as the essential features of human adaptive immunity, sometimes poor prediction, high costs, high regulatory hurdles, and ethical issues (Cohen, 2020; Jameson and Masopust, 2018; Perrin, 2014). In particular, studying COVID-19 infectious disease is even more challenging due to the extreme variability in human immune responses (Buchbinder et al., 2008; Jameson and Masopust, 2018; Tameris et al., 2013; Watkins et al., 2008). To overcome the challenges with species differences, researchers have developed genetically manipulated and inbred animal models, such as humanized mouse models (Sefik et al., 2021); nevertheless, these models still encounter limitations such as lack of precisely recapitulating human immunity (Kalnin et al., 2021; Wagar et al., 2018). The challenges with using mouse models for studying COVID-19 infections is the absence of appropriate receptors to initiate viral infection, the virus binds through the ACE2 and the same receptor in a mouse does not bind to the virus (Muñoz-Fontela et al., 2020; Zhao et al., 2020b).

Dinnon et al. demonstrated the use of a mouse model to study COVID-19 infection by reverse genetics allowing the S protein of the virus to bind to the murine orthogonal ACE2 (mACE2) for entry (Dinnon et al., 2020). In the study, the authors observed age-related pathogenesis, as we have seen from COVID-19 infection in humans. Despite that a vast number of animal models have been developed for COVID-19 research (Abdelnabi et al., 2022; Baum et al., 2020; Bewley et al., 2021; Camell et al., 2021; Israelow et al., 2021; de Melo et al., 2021; Nambulli et al., 2021; Nanishi et al., 2022; Nouailles et al., 2021; Qiao et al., 2021; Rice et al., 2021; Rosenke et al., 2021; Salguero et al., 2021; Schepens et al., 2021; Sourimant et al., 2022; Speranza et al., 2021; Yuan et al., 2020b), most of them only recapitulate some minor patterns of human COVID-19, for instance no severe illness being linked with mortality (Ehaideb et al., 2020). However, in this quest, important lessons can be taken from the previous corona viruses, where animal models have been successfully developed (Bolles et al., 2011; Corey et al., 2020; Graham, 2020; Haynes et al., 2020; Huang et al., 2007).

Nonhuman primate models are probably the closest to the human and have fruitfully been used as models of human viral infections (Corbett et al., 2021; Estes et al., 2018; Klasse et al., 2021; Natoli et al., 2020). Here, Rockx et al. demonstrated the use of a nonhuman primate model (cynomolgus macaques) to study the pathogenesis of COVID-19 and showed that the SARS-CoV-2 triggered COVID-19-like diseases (Rockx et al., 2020).

Takayama presented in a review an introduction to the *in vitro* models such as cell lines and organoids, and *in vivo* animal models that are currently employed in COVID-19 research, their limitations and advantages, and also selection guide based on research intention (Takayama, 2020). For instance, it is more preferable to use ferrets and cats over pigs since the latter one cannot replicate SARS-CoV-2 (Shi et al., 2020).

Overall, several reports have demonstrated the wide gap between COVID-19 in humans and animal models, whilst they might mimic mild patterns of humans, generally they lack severe illness linked with mortality (Ehaideb et al., 2020).

To date, several animal models specific to COVID-19 have been developed (Le et al., 2020), nevertheless, there are limitations and strengths with the animal models. For instance, Macaque are phylogenetically related to humans, but display more advanced cognition and they do not develop acute lung injury; mouse models are cost-effective, easy to handle and are permissive, but major differences exist in lung and immune physiology when it comes to SARS-CoV-2 infection (Casel et al., 2021; Veenhuis and Zeiss, 2021; Zeiss et al., 2021). Therefore, to design the optimal animal model, a combination of several animal models might be needed for overcoming the limitations with each one (Cleary et al., 2020; Kumar et al., 2020; Lakdawala and Menachery, 2020). Nevertheless, an optimal and practical model must consist of a combination of both *in vitro* and animal models before clinical trials on humans are initiated (Hewitt et al., 2020; Pandamooz et al., 2022). Such a strategy has been successfully demonstrated and suggested by several

reports for addressing the COVID-19 challenge (Blasi et al., 2020; Cathcart et al., 2021; Chaves et al., 2021; Deng et al., 2020; Li et al., 2021; Liu et al., 2021; Murray et al., 2021; Owen et al., 2021; Rosa et al., 2021; Song et al., 2021; Stoddard et al., 2021; Ye et al., 2021).

8. Conclusions and remarks

The combination of organ-on-a-chip and bioprinting technologies might provide great tools for quickly addressing sudden pandemics or crises. This strategy would provide the possibility to develop technologies, devices, and diagnostics in a facile way, and therefore understand the pathogenesis leading to the development of effective therapeutics and drugs. For instance, in the current COVID-19 pandemic, through an approach incorporating a lung-on-a-chip and a liver-on-a-chip, or even additionally a lymph node-on-a-chip as well as a bone marrow-on-a-chip, the platform could be used for addressing the challenges and inventing solutions rapidly (Fig. 4) (Balkhi, 2021). In particular, this would allow researchers to investigate the interaction of the human innate immune system with SARS-CoV-2 and provide a deeper fundamental knowledge and hopefully a better understanding of the variability of the immune system and heterogenicity of the COVID-19 outcomes and responses (Schultze and Aschenbrenner, 2021; Shah et al., 2020). Pharmacokinetics and pharmacodynamics might be further refined in such multi-organ-on-a-chip setups.

Moreover, the strategy of convergence approaches has been demonstrated for the bioprinting of organoids (Brassard et al., 2021) or for the development of organoid-on-a-chip technology (Park et al., 2019). For instance, the synergistically merging of the two concepts of organ-on-a-chip and organoid approaches would potentially allow for unprecedented engineering of *in vitro* technologies, where the two approaches complement each other rather than interfering, thus strengthening and broadening their capacities (Park et al., 2019). The organoids recapitulate many of the *in vivo* characteristic structures and functions (Garreta et al., 2021), whilst the organ-on-a-chip technology is employed to mimic and model human organs *in vitro* primarily from the engineering perspective. Similarly, the combination of organoids with bioprinting has demonstrated improved reproducibility, scalability, and throughput (Humphreys, 2021). All these reports demonstrated the great impact of convergence approaches; therefore, we believe that the synergistically merging of bioprinting and organ-on-a-chip strategies could possibly function as a prominent tool in addressing the current and future pandemics.

In the context of recent advances of iPSCs into disease modeling, regenerative therapy and drug discovery could potentially facilitate and promote the adoption of these strategies into precision medicine applications (Sayed et al., 2016). Patient-derived iPSCs could be valuable for identifying new biomarkers that could be useful to design tailor-made therapeutics specific to the patient. Another important strategy for disease modeling that could endorse the field of precision medicine is biopsy-derived cells that could generate specific tissue models from the patient's own tissues and cells (Kasendra et al., 2018). The outcomes from these models could directly be linked to the patients' own responses for diagnostic and other practices.

Notably, these newer *in vitro* models perhaps could never replace *in*

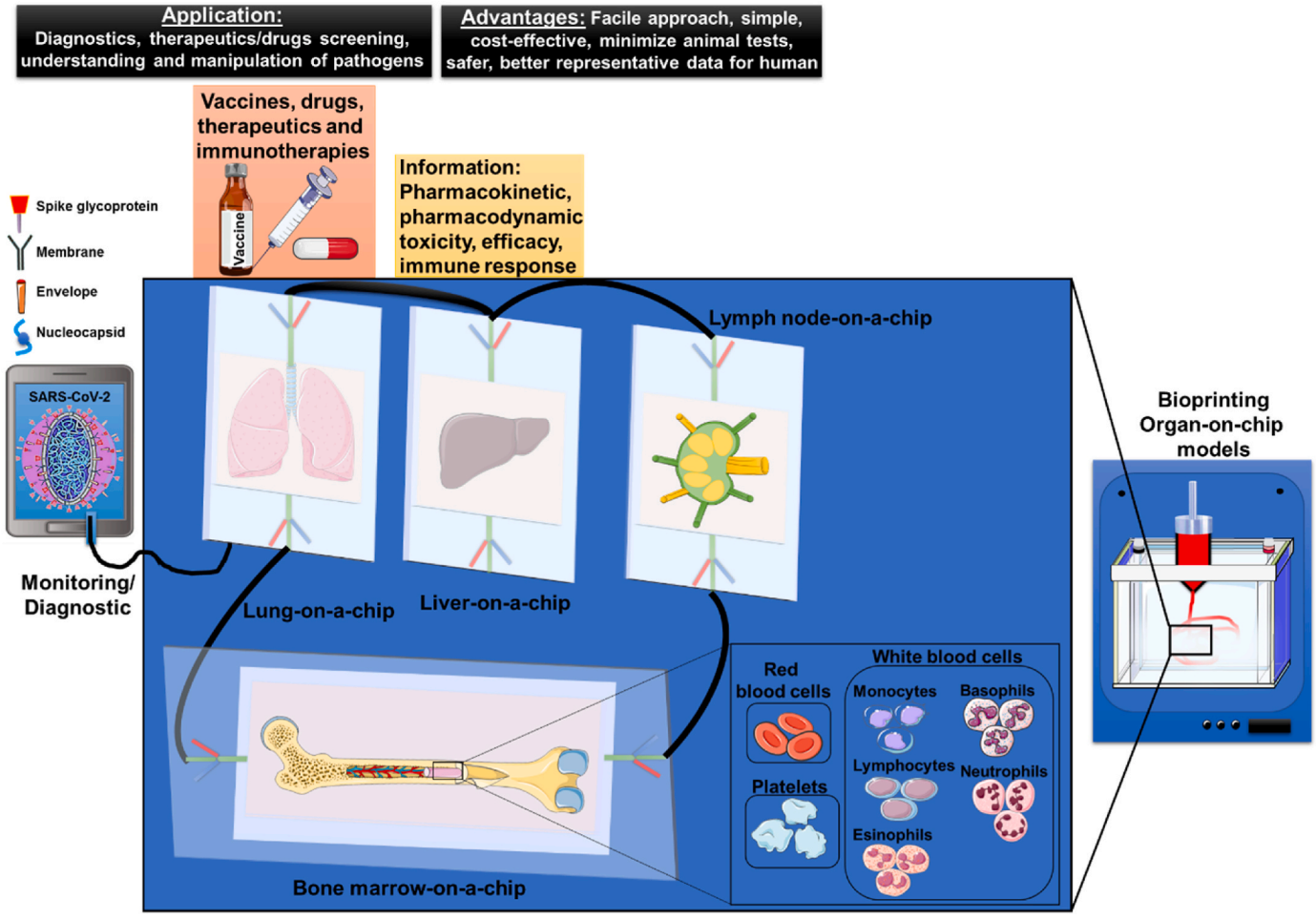

Fig. 4. Overview of merging the technological concept of *in vitro* models produced by bioprinting, organ-on-a-chip, or their combinations in addressing the challenges associated with the current COVID-19 pandemic.

vivo testing in humans; however, they would certainly facilitate developing new drug candidates if appropriately validated through currently supported animal models and would avoid/minimize some unnecessary animal testing, providing more representative information for humans since human tissues will be employed for more accurate and safer evaluations. Despite the fact that 3D bioprinting and microfluidic technologies have advanced and several promising strategies and protocols have been disclosed, more effort is still needed to make them scientifically valid, solid, translational, and commercially viable. Future endeavors should focus on the development of new biomaterials with good printability, biocompatibility, and ability to promote various cellular mechanisms and activities, and bioprinting methods providing the possibilities of bioprinting complex biomimetic microarchitectures and functional tissues, at high resolution, fast speeds, and scalability. Moreover, strategies to directly combine bioprinting with organ-on-a-chip devices are necessary to achieve seamless integration of volumetric and the dynamic features. In addition, the possibility of creating several tissue/organ models linked together would enable a more physiological representation of the multi-dynamic and multifunctional *in vivo* microenvironments needed for COVID-19 studies and future pandemics. The importance of continuing the effort and development of solid, practical, and translational *in vitro* tissue models suitable to address COVID-19 challenges and gaining a more fundamental understanding has been shown in the vast number of new mutations of the SARS-CoV-2 virus and also of the reinfection of individuals despite being vaccinated. These cases demonstrated the lack of fully understanding the current virus and its possibility to continue causing undesirable damages. Therefore, *in vitro* high-content tissue models could promote the precision medicine strategy towards addressing challenges associated with COVID-19, other infectious diseases, as well as future pandemics in a precision medicine manner.

Author contributions

S. A., T. D. S., Y. S. Z. and A. O. L. designed the structure of the review and wrote the initial draft. All the authors contributed to the writing, discussion and correction of the review and giving approval to the final manuscript.

Declaration of competing interest

The authors declare no conflicts of interests.

Acknowledgments

A.O.L. and F.R.M. would like to thank the financial support from the National Council for Scientific and Technological (CNPq, grant #310883/2020-2 to A.O.L. and grant #311531/2020-2 to F.R.M.). T.S. would like to thank the research funding agency CAPES for financial support. Y.S.Z. would like to acknowledge the support by the Brigham Research Institute.

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