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Review

Animal models for SARS-Cov2/Covid19 research-A commentary

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ABSTRACT

Introduction: There is an urgent need for new animal models of SARS CoV-2 infection to improve research and drug development. This brief commentary examines the deficits of current models and proposes several improved alternates. The existing single transgene mouse models poorly mimic the clinical features of COVID-19; those strains get a milder disease than human COVID-19 disease. Many of the current transgenic models utilize random integration of several copies of single ACE2 transgenes, resulting in unnatural gene expression and exhibit rapid lethality. We suggest preparing precision knock-in of selected human mini genes at the mouse initiation codon and knock-out of the mouse homolog as a better option. Three genes critical for infection are suggested targets, ACE2 (the viral cellular receptor), its co-infection protease TMRPSS2, and the primary antibody clearance receptor FcγRT. To offer the best platform for COVID 19 research, preparation of single, double, and triple humanized combinations offers the researcher the opportunity to better understand the contributions of these receptors, coreceptors to therapeutic efficacy. In addition, we propose to create the humanized strains in the C57BL/6J and BALB/c backgrounds. These two backgrounds are Th1 responders and Th2 responders, respectively, and allow modeling of the variability seen in human pathology including lung pathology and late sequelae of COVID-19 disease (BALB/c). We suggest the need to do a thorough characterization of both the short-term and long-term effects of SAR-CoV-2 infection at the clinical, virologic, histopathologic, hematologic, and immunologic levels. We expect the multiply humanized strains will be superior to the single-gene and multiple-gene-copy transgenic models available to date. These mouse models will represent state-of-the-art tools for investigating mechanisms of COVID-19 pathogenesis and immunity and developing vaccines and drugs.

This communication focuses on animal models of COVID-19, the pandemic disease caused by SARS-CoV-2. There is widespread acknowledgment that additional mouse models that permit human like infection by SARS-CoV-2 will be highly valuable [1,2]. The current worldwide pandemic is now in its third wave, and worldwide efforts to produce therapeutic solutions are making progress. However, that progress is hampered by the currently available animal models. We share the view that a better set of animal models in well-studied mouse settings will prove valuable for developing new and better therapeutics. We suggest that a better approach would be multigene humanized mice, in both the C57BL/6J and BALB/c backgrounds, carrying the human ACE2 (hACE2), the human transmembrane protease serine 2 (hTMPRSS2), and the human FcγRT (hFcγRT) antibody clearance receptor (Fig. 1). It is our hypothesis that these strains, in several combinations, would make a better research platform for discovering and analyzing new therapeutics.

The Coronaviridaeβ genus, αβ-CoV, are positive-strand RNA viruses and are pathogenic to humans and a few other species. The genus includes those that cause relatively mild colds (OC43, NL63, 229E, and HKU1) and viruses such as SARS CoV-1, MERS-CoV, and SARS-CoV-2 that cause severe and sometimes fatal diseases [3]. SARS-CoV-2 contains at least four structural proteins, the Spike (S) protein, the envelope protein (E), the membrane protein (M), and the nucleocapsid (N) protein. The S protein binds to target cells via the ACE2 receptor and is activated by the host TMPRSS2 protease and coreceptor. These two proteins and the activated spike protein induce fusion of the virus lipid coat with the cell membrane. The S protein determines the host range of the virus [4]. Those infected with SARS-CoV-2 develop a disease syndrome, COVID-19. Individuals with COVID-19 manifest a wide range of symptoms, ranging from mild disease to fatal illness. Mild COVID-19 with fever, headache, muscle pain, sore throat, or cough may progress to life-threatening illness with dyspnea and cyanosis. Many patients

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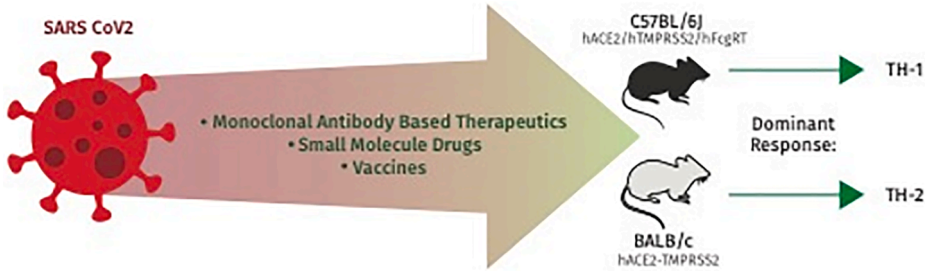

Fig. 1. Proposed humanized mouse models for COVID-19 research. The two strains offer the possibility of examining different aspects of SARS-CoV2 infection that may involve either TH-1 or TH-2 dominant responses.

with severe COVID-19 also exhibit signs of lung, liver, heart, and kidney damage, diarrhea, conjunctivitis, stroke, seizure, and encephalitis [5–8]. There is critical need for well-defined, genetically tractable small animal models for SARS-CoV-2 infection that captures a broad spectrum of illnesses ranging from mild to lethal COVID-19 disease. It should be noted that proper models of viral infection focusing on the binding of the virus to host tissues, should still be useful regardless of the mutations that occur in the virus spike protein [9].

Suitable animal models are essential for understanding aspects of disease pathogenesis and for evaluating the safety and efficacy of vaccine candidates, antibody candidates, or antiviral compounds. A comprehensive review was recently published by Ehaideb et al., [10,24,25] that surveyed publications that reported data on SARS CoV-2 infections in a variety of animals. These included hamsters, non-human primates (macaques), mice, rats, ferrets, rabbits, and cats. All supported viral replication in the lung with mild disease ensuing as assessed by tissue pathology. No animals developed the severe symptoms seen in humans although a transient inflammation was observed inconsistently in non-human primates, hamsters and mice (see below). No cytokine storms, coagulopathy, hypoxemic respiratory failure, multiple organ failure or death were reported. It is our hypothesis that due to the lack of widespread availability of many of these models along with the need for specialized facilities for growth and maintenance that the best choice for routine and widespread use is the laboratory mouse. It is by far the preferred choice of study by immunologists and infectious disease researchers [11] due to the extensive research data and reagents that are available, the relative ease of colony growth and maintenance and a wide number of strains, many with specific pathologies of interest (e.g. SCID, diabetes). For these reasons we focused our attention on mice.

Mice are not easily infectable with SARS-CoV-2 due to differences between the human and murine ACE2 [2] and TMPRSS2. Other infectable species, such as primates, are not commonly available, are expensive, and lack the diagnostic and research tools available for mice. A few transgenic mouse models expressing the human ACE2 gene are available, [5–7]) but most except for the K18-hACE2 transgenic mouse, (in which hACE2 expression is under the control of the epithelial cell cytokeratin-18 promoter) show limited infectability by SARS-CoV-2 and develop mild symptoms upon infection [7] see below). The K18-hACE2 transgenic mice do develop many features of severe COVID-19 [5] but they are available on only one genetic background and do not express human FcγRT. Humanized FcγRT allows for better modeling of human antibody clearance in mice and thus aids antibody drug development. The weaknesses of the current humanized models have been highlighted in the scientific literature and suggest the need for new models that reproduce key features of the human disease [9,10].

The majority of existing mouse models including the K18-hACE2 transgenic mice, were created using first-generation transgenic approaches and have significant limitations. First, these mice still express the mouse ACE2 receptor, which can confound studies using small molecule inhibitors or antibodies that disrupt the binding of ACE2 to the virus. Second, they do not express the human ACE2 gene in the same cellular pattern as the endogenous protein [10], and due to multipule ACE2 integrations, express more hACE2 than seen naturally. Several tissue types in humans express high levels of ACE2 and are susceptible to infection with SARS-CoV-2 and contribute to severe disease [3,8,10]. Infectable cells include pneumocytes, cardiomyocytes, cardiac fibroblasts, and coronary endothelial cells. Also, the humanization of a single receptor is not sufficient to achieve full infectivity in mice or exhibit long-term consequences, as shown by the mild lung pathology in the majority of existing humanized models; thus, the human TMPRSS2 may be needed for both efficient infection by SARS-CoV-2 and resolution of the infection by the host immune system [4]. Lastly, many of the existing single humanized models have been constructed in the Th1-dominant mouse strain C57BL/6J; this strain exhibits mild symptoms upon other viral and bacterial infections [1,5–7,9,10] and is generally considered a poor strain for respiratory investigations. Thus, the mechanisms of disease pathogenesis and immunity in C57BL/6 may be different as compared to a Th2 predominant strain like BALB/c.

In an early 2020 report, Bao et al. [15] described their experiments comparing wildtype ICR mice with transgenic huACE2 ICR mice in which the huACE2 protein was expressed mainly in the lung, heart, kidney, and intestine. Intranasally infected SARS-CoV-2 mice (viral strain HB-01) observed on days 1, 3, 5, and 7 post-infection showed no disease pathology until day three when lung damage and co-localization of S protein in alveolar epithelial cells was seen. The pathology occurred only in hACE2 transgenic mice, not wildtype mice. The disease was mild compared to that seen with human SARS-CoV-2, where extensive organ damage outside the lung (brain, kidney, intestine, heart, and liver) is noted. The hACE2 mice also produced SARS-CoV-2 antibodies. These findings show that existing humanized mouse strains poorly model the wide range of disease severity observed in humans and thus are not optimal for COVID-19 research. There have been several solutions offered to solve this problem, including using mouse strains that contain human immune cells [19] or alternatively a genetically modified SARS-CoV-2 that infects mice [20,22]. These approaches will certainly contribute to the study of the virus but will likely not be the whole solution. Improved humanized mouse models offer a better approach to the development of a more broadly useful model. What follows is a suggested pathway to the development of suitable mouse model(s) for SARS-CoV-2 that could be applied to the development of vaccines, monoclonal antibodies and other drugs as appropriate by all interested research groups. As well, it should be useful for the study of the SARS-CoV-2 variants that are now appearing [9,12–14,18–23].

To make these strains highly useful they must be fully characterized. Characterization is a critical task and is crucial to understanding new strains' utility and best application for drug development. It is also important that such strains be made widely available. For instance, one might assemble a consortium to validate such strains during live infections and ex vivo tissue tests. The comments below indicate what might be done with such strains.

Genomic characterization: Genomic characterization of each strain is necessary in order to show the accurate insertion of the human gene in the target locus. This should be done in a way that inactivates the expression of the endogenous gene and that shows the lack of off-target

integrations. mRNA level tests should be conducted to establish tissue-level expression patterns and to compare the humanized expression pattern to the unmodified mouse expression pattern. Tissue samples should be analyzed by flow cytometry and immunohistochemical staining using human-specific antibodies to hACE2, hTMPRSS2, or hFcγRT to define protein expression patterns.

Clinical signs and symptoms characterization: For clinical monitoring and survival studies, mice could be infected with SARS-CoV-2 including both lab-adapted strains and natural isolates with several pathogenic potentials. For virologic, histopathologic, and immunologic studies, mice would be observed to see whether they are manifesting overt clinical signs as scored by severity scores: weight loss, ruffling of fur, ataxia, inability to eat/drink, lethargy, signs of distress such as dyspnea, rales, tachypnea, and dehydration. Diabetes, obesity, and hypertension are major risk factors for the development of severe COVID-19. It is to be hoped that the improved mouse models could be used look at the effects such diseases have on infection and disease development and progression under the appropriate experimental conditions. Also, many patients with severe disease exhibit extrapulmonary symptoms such as liver damage, kidney injury, diarrhea, cardiac injury, and encephalopathy. It remains to be seen if these mouse models of severe COVID-19 show clinical signs related to extrapulmonary organ damage, such as diarrhea, hematuria, and paresis/paralysis. Histological analysis will be a key tool to characterize these pathologies.

Virologic characterization: Virologic analysis must focus on the kinetics of SARS-CoV-2 infection in tissues and infectious viral load analyzed at various time points after infection in respiratory and non-respiratory organs, using qPCR and viral plaque assays. Particular attention should be paid to organs with high ACE2 expression, including digestive, cardiovascular, and neuronal tissues. Levels of viral RNA and the infectious virus should be measured by qRT-PCR and plaque assay, and immunohistochemistry. An important aspect of severe COVID-19 disease in humans is the cytokine storm syndrome as well as the antibody and T cell responses. Studies may implicate a role for Th2-driven pathology or antibody-dependent enhancement (ADE) of pathogenesis in SARS-CoV-2-infected patients [20–26]. Thus, one could develop ADE-mediated COVID-19-like disease models by injecting humanized mice with SARS-CoV-2-specific or coronavirus-cross-reactive antibodies before the viral challenge.

Cytokine characterization: Mice with mild disease may have elevated levels of several cytokines after infection, depending on the nature of the inflammatory response in each mouse strain. Levels of these key cytokines should be measured in the serum and bronchoalveolar lavage fluid from SARS-CoV-2-infected mice. One would expect to observe a cytokine storm (i.e., high levels of cytokines and chemokines associated with severe COVID-19) in mice with severe COVID-19-like disease, especially at late time points just before death.

$CD4^+$ and $CD8^+$ cellular response characterization: To monitor SARS-CoV-2-elicited $CD4^+$ and $CD8^+$ T cell responses in the lungs and lung draining lymph nodes, it is suggested to perform flow cytometric analysis and activation marker analysis. Tests for the expression of intracellular cytokines and transcription factors that define Th subsets such as Th1 (IFNγ, TNF, IL-2, T-bet) and Th2 (IL-10, IL-4, IL-5, GATA3) should be planned. It is to be expected that humanized mice in the C57BL/6 and BALB/c genetic background, respectively, will mount a Th1-and Th2-dominant CD4+ T cell response. The ex-vivo lymphocyte production of IFNγ, TNF, and IL-2 by epitope-specific CD8+ T cells should be restimulated with peptide epitopes restricted by H-2b and H-2d CD8+ T cells in vitro assays. CD8+ T cells play a role in mediating protective immunity; thus, the features of the anti-SARS-CoV-2 CD8+ T cell response in Th1-biased C57BL/6J vs. Th2-biased BALB/c mice may be correlated with the clinical and pathologic phenotype of the mice.

Based on our working hypothesis, humanized mice in the BALB/c background should model more severe COVID-19 disease [14–17]. In contrast, the humanized C57BL/6 mice are likely to serve as models of asymptomatic or mild COVID-19. Mouse models that reproduce a spectrum of SARS-CoV-2-induced illnesses will be critical tools for deciphering mechanisms of SARS-CoV-2 pathogenesis and immunity and for developing and testing vaccines and other therapies for COVID-19. One might expect, for example, to observe no difference in SARS-CoV-2 infection and pathogenesis in double hACE2/hTMPRSS2 vs. triple hACE2/hTMPRSS2/hFCγRT mice. However, for investigation of antibody-based therapies, one would predict that a triple hACE2/hTMPRSS2/hFCγRT mouse model will be better suited for study due to its more human-like antibody clearance. Results obtained from studies with single hACE2 vs. single hTMPRSS2 vs. double hACE2/hTMPRSS2 mice may better inform the precise role of ACE2 and TMPRSS2 in SARS-CoV-2 in vivo infection. The nine different proposed humanized mouse strains, along with control wildtype BALB/c and C57BL/6 mice, would be the best models for analyzing the mechanism of pathology and for therapeutic discovery (see Table 1). Finally, having the various strains available to the entire research community also allows for the study of ex vivo cells from the double and triple humanized mouse strains compared to cells derived from normal volunteers and patients. Such studies could be used to compare the cellular processing of SARS-CoV-2 and help discover new antiviral medicines. Moreover, sufficient production of such mouse strains would also allow the testing of the role of co-morbitities such as age, obesity and type II diabetes.

Table 1
Proposed Mouse Strains for COVID 19 Research.

	Strain Background	Strain Name
1	C57BL/6J	C57BL/6J-hACE2/hFCγR
2	C57BL/6J	C57BL/6J-hTMPRSS2/hFCγRT
3	C57BL/6J	C57BL/6J-hACE2
4	C57BL/6J	C57BL/6J-hTMPRSS2
5	C57BL/6J	C57BL/6J-hACE2/hTMPRSS2
6	C57BL/6J	C57BL/6J/hACE2/hTMPRSS2/hFCγRT
7	BALB/c	BALB/c-hACE2
8	BALB/c	BALB/c-hTMPRSS2
9	BALB/c	BALB/c-hACE2/hTMPRSS2

Even with vaccines for SARS-CoV-2, it is expected that the disease will remain a public health problem for some time [27,28]. Like influenza, new vaccines and therapeutics will likely be needed as the virus evolves and the scientific community better understands the long-term consequences of SARS-CoV-2 infection and as new close relatives to SARS-CoV-2 arise and circulate in the human population [24,25]. Thus, the need for widely available, new and better animal models of infectious diseases will continue as long as the risk of new pandemics remains. As this is the case, our group has already begun the long process of building versions of the strains outlined here.

Financial Interests

KJ, OA and DRW are all employees of Synbal, Inc. a private biotechnology company and own shares of the company; SJ has no financial interests to declare.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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