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Animal models for SARS-CoV-2
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Since its first detection in December 2019, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has rapidly spread worldwide, resulting in over 79.2 million documented cases in one year. Lack of pre-existing immunity against this newly emerging virus has pushed the urgent development of anti-viral therapeutics and vaccines to reduce the spread of the virus and alleviate disease. Appropriate animal models recapitulating the pathogenesis of and host responses to SARS-CoV-2 infection in humans have and will continue to accelerate this development process. Several animal models including mice, hamsters, ferrets, and non-human primates have been evaluated and actively applied in preclinical studies. However, since each animal model has unique features, it is necessary to weigh the strengths and weaknesses of each according to the goals of the study. Here, we summarize the key features, strengths and weaknesses of animal models for SARS-CoV-2, focusing on their application in anti-viral therapeutic and vaccine development.

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Introduction
Since the first reported outbreak in December 2019, in central China, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has rapidly spread worldwide and become a major global health threat. The syndrome caused by SARS-CoV-2 was termed coronavirus disease 2019 (COVID-19) by WHO and the outbreak was declared to be a pandemic by WHO on March 11, 2020 [1]. As of December 2020, SARS-CoV-2 has led to over 79.2 million recorded cases with over 1.7 million deaths [2]. COVID-19 manifests as a mild respiratory syndrome in most individuals, however, severe cases of COVID-19 implicate the need for better understanding of pathobiology and host immune response. Approximately one year after the start of the outbreak, massive efforts by scientists have contributed to the rapid approval of COVID-19 vaccines and the use of remdesivir as an anti-viral therapeutic [3,4]. However, it is still ambiguous whether the FDA approved vaccines block infection and virus shedding or just symptoms [5,6]. Moreover, the use of remdesivir was advantageous in time to recovery and clinical improvement but failed to demonstrate a survival benefit [4]. Therefore, active studies on the development of anti-viral therapeutics and vaccines are still of importance to reduce the spread of the virus and alleviate severe cases of COVID-19.

Animal models are essential tools in infectious diseases research. The field therefore moved quickly following the emergence of SARS-CoV-2 to identify suitable species. Similar to SARS-CoV, SARS-CoV-2 uses human ACE2 as the main virus entry receptor. Several animals used for SARS-CoV studies, including mice, hamsters, ferrets, and non-human primates (NHPs) have therefore been evaluated as models for SARS-CoV-2 infection [7,8,9,10,11,12,13,14,15,16–19]. These promising animal models have been actively applied not only for elucidating the pathogenesis and host response to infection but also for the evaluation of anti-viral and vaccine candidates. While each system has limitations, together the available models allow pursuit of broad range of critical research questions. The current review summarizes the key features, the strengths and the weaknesses of SARS-CoV-2 animal models, focusing on their application in anti-viral drug and vaccine development (Table 1).

Mouse
Mice have several advantages over other experimental animal models in their small size, low cost, rapid breeding for reaching large group numbers, and availability of research tools. Several inbred mouse species have been evaluated with SARS-CoV but, with the exception of aged or immuno-compromised mice, most do not exhibit severe clinical signs owing to disparity between mouse and human ACE2 [20–22]. Therefore transgenic mice expressing human ACE2 (hACE2) and mouse adapted SARS-CoV were developed for SARS-CoV vaccine and anti-viral research in efforts to recapitulate the severe illness seen with SARS-CoV infection in humans [23–27].

Given the resemblance of SARS-CoV-2 to SARS-CoV in its use of ACE2 as an entry receptor, several research teams have evaluated transgenic mice expressing of hACE2 under the control of HFH1/FOXJ1, HFH4, K18, and mouse ACE2 promoters [13,18,28–30,31].
| Animal model                        | Strengths                                                                 | Weaknesses                                                                                   | Application in countermeasures                                                                 | References |
|------------------------------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|------------|
| Transgenic mouse expressing hACE2  | Small size, rapid breeding, availability of research tools               | Neuroinvasion and viral replication in brain, Limited availability, High cost               | Subunit vaccine (RBD-Fc)                                                                                   | [47]       |
| hACE2-transduced mouse             | Small size, rapid breeding, availability of research tools               | Do not develop severe disease in most cases, individual variations in expression and cellular distribution of hACE2 | Subunit vaccine (NVX-CoV2373), mAbs (COV2-2196 and COV2-2130)                                           | [51]       |
| Mouse adapted SARS-CoV-2 strain    | Small size, rapid breeding, availability of research tools               | Mouse adapted mutations may attenuate the efficacy of some human mAbs or vaccine candidates | Subunit vaccine (RBD-Fc vaccine)                                                              | [37]       |
|                                   |                                                                           | Reproduces lung damage and inflammatory responses seen in COVID-19 patients, Low cost       | NDV vectored vaccine (NDV-S)                                                                                   | [99]       |
| hACE2 humanized mouse             | Small size, rapid breeding, availability of research tools               | Limited availability                                                                       | mRNA vaccine (mRNA-1273), Adenovirus vectored vaccine (Ad5-nCoV), mAbs (COV2-2196 and COV2-2130), mAbs (hu-mAbs), Remdesivir, PEG-IFN-λ1a | [48**] [49] [42] [41] [39] [31*] |
| Hamster                           | Small size and rapid breeding                                            | Fail to develop diffuse disease and acute respiratory distress found in severe human cases | NDV vectored vaccine (NDV-S)                                                                                   | [52]       |
|                                   | High susceptibility to SARS-CoV-2                                       | Adenovirus vectored vaccine (Ad26), S2E12 and S2M11                                        |                                                                                                              | [70]       |
|                                   | Resemble lung pathology with COVID-19 patients                           | Ranitidine bismuth citrate                                                                 |                                                                                                              | [62]       |
|                                   | Active transmission via direct contact and aerosol                       | REGN-CO2 (mAbs), BD-368-2 (mAb), Favipiravir, Hydroxychloroquine, CV07-209 (mAb), IgG1 ab1 (mAb), hACE2 decoys, CC12.1 (mAb), hu-mAbs |                                                                                                              | [69] [68] [61] [61] [67] [66] [69] [65] [41] |
| Ferret                            | Asymptomatic or mildly symptomatic model                                | Low virus loads in the lower respiratory tract, Does not fully represent the severe cases of human infection | Adenovirus vectored vaccine (Ad5-nCoV), MK-4482/EIDD-2801, Lopinavir-ritonavir, Hydroxychloroquine sulfate, Emtricitabine-tenofovir | [49] [81] [80] [80] |
|                                   | Active transmission via direct or indirect contact                       |                                                                                              |                                                                                                              |            |
The transgenic mouse models are susceptible to SARS-CoV-2 but vary in disease severity, which is likely associated with the tissue distribution and expression level of the hACE2 transgene. In particular, SARS-CoV-2 infection in some transgenic mouse models led to neuro-invasion with high viral replication in brain, which may be related to high lethality [18,28,30]. Mice transduced with adeno-associated virus or adenovirus encoding hACE2 have also been used for understanding of pathogenesis and host response of SARS-CoV-2 infection [30,32–35]. The exogenous delivery of hACE2 resulted in productive viral replication in mouse lung with mild to moderate clinical symptoms. While its flexible application and shorter time to construct than the transgenic mice are favorable, viral delivery may trigger individual variations in expression and cellular distribution of hACE2 [31*,33]. Gene editing technology by CRISPR/Cas9 was also applied in the development of a hACE2 knock-in mouse (hACE2 humanized mouse) which developed interstitial pneumonia with mild clinical signs [36]. As an alternative approach, mouse adapted SARS-CoV-2 variants have also been developed by serial passage of SARS-CoV-2 or reverse genetics of SARS-CoV-2 with structure-based remodeling of spike protein to allow recognition of murine ACE2 [19,31*,37]. The important residues for mouse adaptation are located in the receptor binding domain (RBD) of SARS-CoV-2 and changes in those residues facilitated viral replication in the airways of standard BALB/c mice [31*,37].

The mouse model has been the first option for in vivo evaluation of anti-viral therapeutics and vaccine candidates for SARS-CoV-2. Remdesivir, an anti-viral approved for emergency use to treat COVID-19, reduced the lung viral load of mice infected with chimeric SARS-CoV encoding the SARS-CoV-2 RNA-dependent RNA polymerase [38], which was also seen in adenovirus-transduced mice infected with SARS-CoV-2 [32] and BALB/c mice infected with mouse-adapted SARS-CoV-2 [39]. Administration of PEG-IFN-λ1a, which is

| Table 1 (Continued) |          |          |          | References |
|----------------------|----------|----------|----------|------------|
| **Rhesus macaque**   | Identical ACE2 sequences in the ACE2-RBD interface to hACE2 and similar binding activity to the RBD with hACE2 | Pathology and immune responses resemble COVID-19 patients | Recapitulating age related severity in COVID-19 patients | mRNA vaccine (mRNA-1273) [96] |
|                      |          | Ethical concerns |          | Adenovirus vectored vaccine (Ad5-S-nb2) [94] |
|                      |          | Difficult to reach appropriately powered group sizes |          | Adenovirus vectored vaccine (Ad26) [93] |
|                      |          | High cost |          | Adenovirus vectored vaccine (ChAdOx1 nCoV-19) [46] |
|                      |          | Limited availability |          | DNA vaccine encoding spike protein [95] |
|                      |          | Complex husbandry |          | Inactivated vaccine (PGoVacc) [44] |
|                      |          |          | Inactivated vaccine (BBIBP-CorV) Remdesivir Hydroxychloroquine mAbs (REGN-COV2) mAbs (CA1 and CB6) mAbs (COV2-2196 and COV2-2381) [50] |
| **Cynomolgus macaque** | Identical ACE2 sequences in the ACE2-RBD interface to hACE2 | Pathology and immune responses resemble COVID-19 patients |          | Subunit vaccine (NVX-CoV2373) Hydroxychloroquine [97,102] |
|                      |          | Ethical concerns |          |          |
|                      |          | Difficult to reach appropriately powered group sizes |          |          |
|                      |          | High cost |          |          |
|                      |          | Limited availability |          |          |
|                      |          | Complex husbandry |          |          |
| **African green monkey** | Identical ACE2 sequences in the ACE2-RBD interface to hACE2 | Pathology and immune responses resemble COVID-19 patients | Recapitulating age related severity in COVID-19 patients |          |
|                      |          | Ethical concerns |          |          |
|                      |          | Difficult to reach appropriately powered group sizes |          |          |
|                      |          | High cost |          |          |
|                      |          | Limited availability |          |          |
|                      |          | Complex husbandry |          |          |
a phase-3-ready treatment for hepatitis delta virus, diminished mouse-adapted SARS-CoV-2 replication in mouse lung and SARS-CoV-2 replication in H/84-ACE2 transgenic mouse lung [31*]. Passive immunity was induced through administration of monoclonal antibodies (mAbs) is a promising tool for combating emerging viral infections. Neutralizing human mAbs obtained from individuals who recovered from COVID-19 reduced viral loads of mouse-adapted SARS-CoV-2 in aged BALB/c mice [40,41] or prevented severe SARS-CoV-2 induced weight loss and lowered viral loads in two mouse models [42]. Neutralizing mAbs generated from mice immunized with recombinant SARS-CoV-2 RBD and S proteins were also effective in reduced viral shedding and clinical signs in hACE2-transduced mice [33,43]. Vaccine candidates using diverse platforms have been tested in mice, including mRNA vaccine (mRNA-1273), adenoviral vectored vaccines (ChAdOx1 nCoV-19 and Ad5-nCoV), Newcastle disease virus vectored vaccine (NDV-S), recombinant subunit vaccines (RBD-Fc-based COVID-19 and NVX-CoV2373), and purified inactivated vaccines (PiCoVacc and BBIBP-CorV). These candidates induced protective immune responses in inbred mice [44–47,48**,49–52], and protected against SARS-CoV-2 infection [47,48**,49,51,52]. While genetically engineered mice and mouse-adapted SARS-CoV-2 may not fully reflect pathogenesis and host responses of SARS-CoV-2 in humans, they can be valuable tools for initial evaluations and large group studies of anti-viral therapeutics and vaccine candidates.

**Hamster**

Golden Syrian hamster models have been widely used for studies on many different viral infections [53]. SARS-CoV replicates to high titer in the respiratory tract of Syrian hamsters accompanied with lung pathology [5]. Recent studies have found that Syrian hamster ACE2 is highly homologous to human ACE2 in the predicted ACE2-RBD interface and it binds efficiently to SARS-CoV-2 RBD [54**,55]. In SARS-CoV-2 challenge experiments, inoculated hamsters showed progressive weight loss with lethargy, ruffled fur, hunched back posture, and rapid breathing, with recovery by 14 days after inoculation [54**]. The virus replicates to high titer in the upper and lower respiratory tracts (URT and LRT), and the 50% infectious dose in Syrian hamsters is only five TCID50 [11,55]. SARS-CoV-2 causes pathological lung lesions including pulmonary edema and consolidation with evidence of interstitial pneumonia [11,55]. However, Syrian hamsters failed to develop diffuse alveolar disease and acute respiratory distress found in severe human cases [55]. Of note, SARS-CoV-2 can replicate in the brain or olfactory bulb of Syrian hamsters and damage olfactory sensory neurons [11,56]. Given almost half of COVID-19 patients have experienced loss of olfactory function (anosmia) and neuroinvasion by SARS-CoV-2 through olfactory sensory neurons has been discussed, Syrian hamsters can be a valuable tool for studying neurological impacts caused by SARS-CoV-2 [57,58]. Collectively, Syrian hamsters are a highly susceptible model for SARS-CoV-2 infection with mild to moderate disease.

In addition to pathogenesis, the Syrian hamster model is useful to evaluate the transmissibility of SARS-CoV-2. Both direct contact and aerosol exposures enable efficient SARS-CoV-2 transmission from inoculated to naive hamsters [12*]. This feature of the model is valuable for assessing the risks posed by newly emerging variant viruses. For example, the phenotypic impact of the D614G substitution in the spike protein that became prevalent globally was evaluated in Syrian hamster model [59*]. The D614G mutation did not alter viral loads in the URT or LRT but allowed faster transmission and increased competitive fitness compared to wild-type virus in hamsters.

High susceptibility to SARS-CoV-2, similarity to human pathology, small size, and fast reproductive rate have led to use of the Syrian hamster model for several preclinical efficacy studies for repurposed or novel drugs. Standard or high dose of hydroxychloroquine did not show clinical benefits nor reduce viral shedding in a Syrian hamster model [60,61]. A broad-spectrum anti-viral drug, favipiravir, decreased viral shedding and transmission in SARS-CoV-2 infected hamsters, but only at high dose [61]. Metallodrug ranitidine bitmuth citrate, which has been used for the treatment of Helicobacter pylori infection, suppressed SARS-CoV-2 viral replication in the respiratory tract of Syrian hamsters with significant amelioration of lung damage [62]. Preclinical study of a de novo hACE2 decoy (CTC-445.2d) was performed in the Syrian hamster model and a single prophylactic administration of the drug enhanced clinical signs [63]. Therapeutic or prophylactic administration of neutralizing antibodies targeting the RBD effectively reduced viral shedding in the Syrian hamster model [41,64–69]. Syrian hamsters have also been highly valuable for evaluation of SARS-CoV-2 vaccines. An adenovirus serotype 26 vector-based vaccine expressing a stabilized SARS-CoV-2 spike protein elicited RBD targeted neutralizing antibodies and protected immunized hamsters against severe clinical disease after high-dose SARS-CoV-2 challenge [70]. Similarly, an NDV vectored vaccine expressing a membrane-anchored spike of SARS-CoV-2 (NDV-S) induced spike-specific antibodies in immunized hamsters and reduced lung viral titers with attenuated body weight loss after SARS-CoV-2 challenge [52].

**Ferret**

Ferrets are commonly used in studies of influenza virus pathogenesis and transmission because of similarities to humans in receptor distribution and clinical course of disease [71,72]. Ferrets are also susceptible to SARS-CoV infection, developing mild disease including increased
body temperature and sneezing [73,74]. In early 2020, Wan et al. found that ferrets and humans share critical virus-binding residues in their ACE2 sequences and suggested that ferrets may serve as an animal model for SARS-CoV-2 [75]. In the first reported ferret challenge experiment, SARS-CoV-2 infected ferrets showed mild clinical signs including elevated body temperature and reduced activity but no detectable body weight loss [76*]. Viral shedding was mainly observed in the URT but infectious viral titers were low (1.83–2.88 log\textsubscript{10} TCID\textsubscript{50}/mL) [76*]. Similar mild clinical signs and upper respiratory tract tropism were subsequently observed in different laboratories using distinct SARS-CoV-2 isolates [77,78]. In transmission studies, SARS-CoV-2 was efficiently transmitted from infected to naïve ferrets via direct contact [76*,79]. Transmission between ferrets separated by perforated dividers was also observed but was not as efficient as direct contact transmission [76*,79]. Taken together, ferrets can be a suitable model for asymptomatic or mildly symptomatic SARS-CoV-2 spread in the human population.

High susceptibility to SARS-CoV-2 has led to use of the ferret model in evaluating the efficacy of anti-viral therapeutics. Anti-viral efficacies of repurposed drugs were evaluated and three (lopinavir-ritonavir, hydroxychloroquine sulfate, and emtricitabine-tenofovir) had no clear benefit in the treatment of infected ferrets [80]. In contrast, a ribonucleoside analogue inhibitor, MK-4482/EIFDD-2801, developed for influenza virus treatment, showed promise [81]. Oral administration of MK-4482/EIFDD-2801 after SARS-CoV-2 infection to ferrets reduced viral loads in the URT and inhibited close contact transmission [81]. Finally, mucosal or intramuscular vaccination of ferrets with Ad5-nCoV, an adenovirus vectored vaccine, suppressed viral replication in the URT after challenge with SARS-CoV-2, with mucosal vaccination resulting in sterilizing protection [49].

**Non-human primates**

Non-human primates (NHPs) are often considered the gold standard model for study of emerging viruses because of their physiological and phylogenetic similarities to humans [82]. Rhesus macaque ACE2 shares 23 critical residues with hACE2 in the region of the protein that makes close contact with the RBD of the SARS-CoV-2 spike and has the highest receptor activity among 14 mammalian species [83]. Three Old World monkey species including rhesus and cynomolgus macaques and African green monkey (AGM) have been evaluated as SARS-CoV-2 infection models. Rhesus macaques generally developed mild clinical signs with pulmonary infiltration after SARS-CoV-2 infection, but disease severity appeared to vary with age, inoculation route, SARS-CoV-2 isolate, and inoculation dose [14,15*,16,84]. Viral loads were observed in the URT and LRT and interstitial pneumonia was diagnosed upon histopathologic examination. Cynomolgus macaque and AGM models shared similar clinical manifestations, virus shedding, and histopathology with a rhesus macaque model after SARS-CoV-2 infection [14,17,85–87]. A valuable feature of NHP models is the potential for age-dependent disease progression to represent severe cases of COVID-19 in elderly individuals. Aged AGMs manifested severe respiratory distress with severe lung consolidation and edema [88]. Similarly, 15 year old rhesus macaques developed severe interstitial pneumonia with higher viral loads than three to five year old rhesus macaques [89*]. In a cynomolgus macaque model, however, increased age was not correlated with disease severity, but prolonged viral shedding in the URT [85].

While remdesivir reduced SARS-CoV-2-induced lung damage and decreased viral shedding in a rhesus macaque model, hydroxychloroquine did not show prophylactic or therapeutic benefits in rhesus or cynomolgus macaque models, as was observed in human clinical trials [60]. The administration of neutralizing antibodies targeting spike protein was prophylactically and therapeutically effective in NHP models [69,90]. NHP models have an important advantage in preclinical studies in that immune responses following SARS-CoV-2 infection recapitulate crucial aspects of COVID-19 in humans [91,92]. For this reason, researchers evaluating different vaccine platforms including adenovirus vectored [46,93,94], DNA [95], mRNA [96], inactivated [44], and subunit vaccines [97] have applied NHP models for assessing the immunogenicity and protective efficacy.

**Conclusions**

Animal models that replicate key features of human infection are essential tools for the development of SARS-CoV-2 countermeasures. Since no animal model fully reproduces every aspect of COVID-19, it is necessary to weigh the strengths and weaknesses of each according to the goals of the study. Mouse models have the important advantage that they are amenable to large-scale studies, despite some limitations. Hamsters offer many strengths including tractability, mild to moderate lung pathology as seen in COVID-19 patients, and efficient transmission. On the other hand, whether age-dependent or sex-dependent outcomes of SARS-CoV-2 infection found in human cases are recapitulated in hamsters is still under debate [11,55,98]. Ferrets, although typically asymptomatic or mildly symptomatic, are a useful model for evaluation of SARS-CoV-2 transmission. NHP models closely recapitulate clinical symptoms and immune responses of COVID-19 patients, but they are not appropriate for large scale studies because of their high cost and limited availability.
Preclinical studies using animal models are prerequisites of clinical trials owing to their utility in identifying promising countermeasures. Fit-for-purpose use of animal models accelerates this process. Thus, continual refinement and development of animal models for COVID-19 will help advance understanding of the pathobiology of and host immune response to SARS-CoV-2 infection and ultimately win the fight against the COVID-19 pandemic.

Conflict of interest statement
Nothing declared.

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