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Review

Thinking Outside the Box: Utilizing Nontraditional Animal Models for COVID-19 Research

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Abstract: The ongoing COVID-19 pandemic continues to affect the lives, wellbeing, and stability of communities worldwide. The race to save human lives is critical, and the development of useful translational animal models to elucidate disease pathogenesis and prevention, and to test therapeutic interventions, is essential to this response. However, significant limitations exist with the currently employed animal models that slow our ability to respond to the pandemic. Non-human primates serve as an excellent animal model for SARS-CoV-2 disease and interventions, but the availability of these animals is scarce, and few facilities are able to house and utilize this model. Adapted murine models are accessible and improving but lack natural hACE-2 receptors and are only moderate representatives of human COVID-19 disease, transmission, and immune responses. On the other hand, there are several animal species that are both naturally and experimentally infected, such as domestic cats, hamsters, ferrets, and mink. Several of these have proven animal-to-animal transmission and evidence of significant clinical and histopathologic disease that mimics acute COVID-19 in humans. Mobilizing these nontraditional animal models could have a crucial role in SARS-CoV-2 research efficiency and impact. This review focuses on what is known about these nontraditional animal models, including their immune responses to SARS-CoV-2 infection, evidence of clinical and histopathologic disease, transmission potential, and the practicality of each model in a research setting. Comparative insight into these animal models for COVID-19 can strengthen the efforts to mitigate this pandemic.

Keywords: COVID-19; SARS-CoV-2; animal models; domestic cats; hamsters; mink; ferrets

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1. Introduction

The ideal animal model for COVID-19 should be susceptible to infection and capable of replicating the varied clinical and histologic disease seen in humans [1]. In order to meet these criteria, infected animals should have comparable receptors with efficient binding of SARS-CoV-2, and ideally, be capable of natural infection as well as transmission to other animals. While there is definite value in optimized in vitro studies, these cannot precisely mimic human pathophysiology. Furthermore, human immune components are exceedingly complex, and also cannot be completely translated in vitro. For these reasons, animal models are the critical bridge to the development and evaluation of prophylactic treatments, specifically drugs, vaccines, and therapeutic agents, and are required to elucidate key mechanisms underlying pathology in vivo. Traditional lab animal species, including mice and nonhuman primates (NHPs), have been used extensively in SARS-CoV-2 research, and their involvement and utility has been thoroughly cataloged [2–13]. This review, however, focuses on the contribution of nontraditional animal models to understanding the pathophysiology and transmission kinetics of SARS-CoV-2 infection, as well as their practicality in a research setting.

There are many well-studied coronaviruses (CoVs) in mammals that offered insight into this virus species even prior to the emergence of SARS-CoV-2 (Figure 1). CoVs are

positive-stranded, encapsulated RNA viruses with genomes ranging in size from 26 to 32 kb [14]. In humans, typical alphacoronaviruses (229E and NL63) and betacoronaviruses (OC43 and HKU1) produce mild and self-limiting respiratory tract infections [15]. In contrast, SARS-CoV-2, the betacoronavirus responsible for the coronavirus disease 2019 (COVID-19) pandemic, causes marked inflammation of the airways and lungs and results in substantial respiratory disease in many infected patients. SARS-CoV-2 attaches to and infects cells through the angiotensin-converting enzyme-II (ACE2) receptor, resulting in subsequent internalization and proliferation of the virus. A robust immune response must be activated for viral clearance, but inflammation from activation of the host immune responses may also result in injury to host tissue [16]. Clinical symptoms of COVID-19 are characterized by fever, lethargy, cough, shortness of breath, and occasional gastrointestinal signs such as diarrhea. Mild disease may progress to severe SARS-CoV-2-induced acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), which is the leading cause of mortality in COVID-19 patients. Hyperinflammatory responses (e.g., cytokine storm syndrome), lymphopenia, and microthrombosis may all contribute to widespread alveolar destruction, significant lung injury, and increased morbidity and mortality [17–20]. Many hospitalized COVID-19 patients also have comorbidities such as diabetes, cardiovascular disease, renal disease, or hypertension [21], and age-related comorbidities have had a tremendous impact on the progression of the disease [22]. The specific mechanisms by which these comorbidities worsen SARS-CoV-2 patient disease remain largely elusive, highlighting the critical need for animal models that can mimic both COVID-19 and these comorbid conditions to help mitigate human disease.

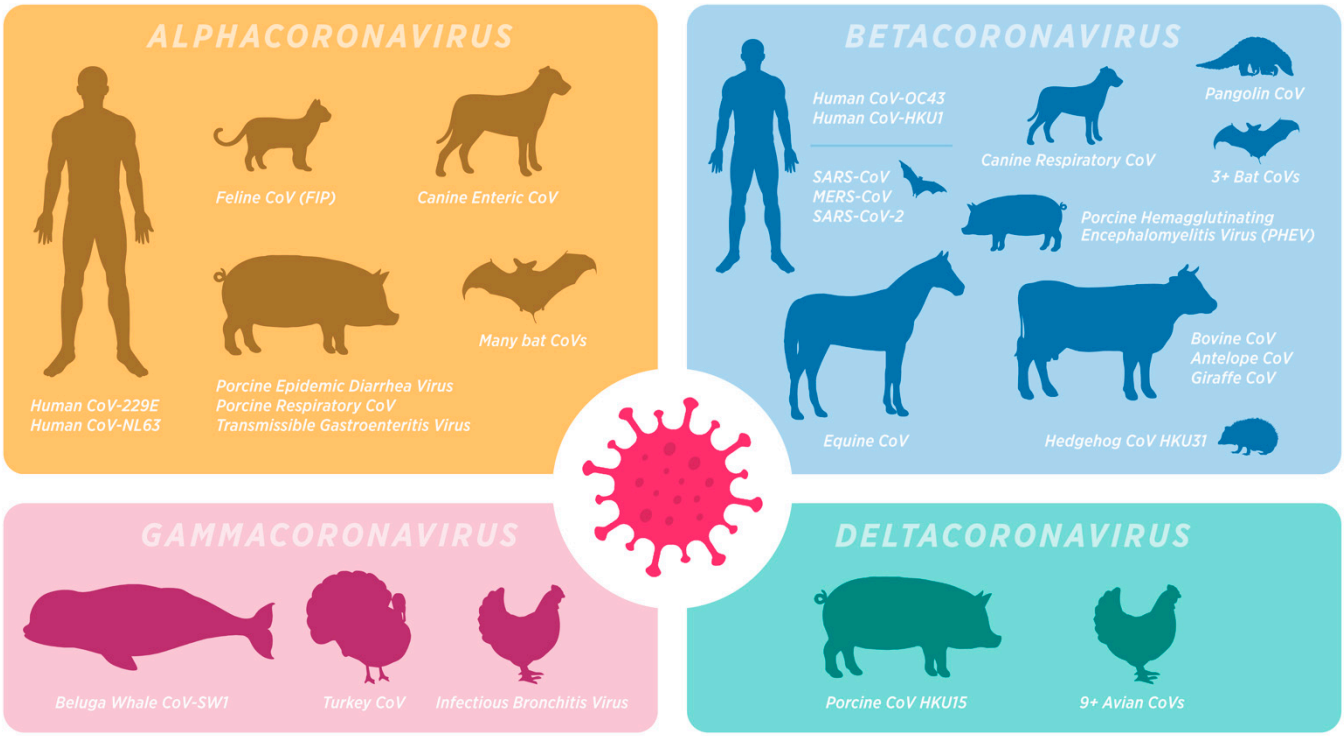

Figure 1. Mammalian coronaviruses. The Coronaviridae family frequently infects and causes disease in a wide variety of mammals. Disease presentations vary based on tissue tropism from mild, self-limiting upper respiratory infections (such as with the alphacoronaviruses CoV-229E and CoV-NL63) to more severe respiratory or systemic diseases such as the SARS-like viruses and enteric diseases of critical veterinary importance, especially those in pigs, cats, dogs, and cattle. Coronaviruses undergo frequent host-shifts between mammals, creating a need to better delineate both origins for non-human mammal coronaviruses that infect humans and mammals that have potential to act as natural reservoirs for human and veterinary diseases.

Since SARS-CoV-2 is best theorized to have zoonotic origins, the human–animal–environment interaction of the COVID-19 pandemic is of enormous scientific, public health, and animal welfare importance. The recognition of animal species that are naturally vulnerable to SARS-CoV-2 infection may aid in the investigation of the virus's possible origin, the identification of potential reservoirs and intermediate hosts, as well as the clarification of mechanisms underlying cross-species transmission back to humans and other species. Such animals that are naturally susceptible for these studies and do not require genetic modification to improve susceptibility or replicate human disease in an experimental setting [23] could provide additional information and assistance in preventing future reverse zoonosis, which might result in the creation of new animal hosts.

2. Nontraditional Animal Models for COVID-19

Murine (*Mus musculus*) and non-human primate (NHP) models for COVID-19 are widely utilized and offer some clear benefits in their use. Rodent models have widely available reagents and can be handled and housed with ease and at less cost than larger animals, allowing greater animal numbers and improved statistical significance in results [1]. Despite these obvious benefits, undeniable limitations to murine models exist. There are inherent biological differences between humans and rodents that specifically affect their susceptibility to SARS-CoV-2 infection, resulting in the need for genetically modified mice or viruses to better mimic human disease. The absence of suitable ACE2 receptors in most mice species is one such key limitation [24]. Other limitations include the lack of infectivity of SARS-CoV-2 clinical isolates in murine species, as well as the lack of persistent infection, immunopathology, severe acute respiratory distress syndrome, and systemic complications that characterize COVID-19 clinically [25,26]. The short lifespan of these animals also makes it difficult to track the disease's long-term effects [9,23,27]. Recently, aged murine models have been utilized to better mimic SARS-CoV-2 in older patients with comorbidities [28,29], but many studies exclusively utilize young and immunologically naïve laboratory animals, posing a construct validity issue [30].

Alternatively, nonhuman primates (NHP) are excellent models for human disease due to the close link in physiological, immunological, and genetic aspects that replicate human disease pathophysiology [31,32]. However, the high cost of these animals and limitations to housing and care are obstacles that are difficult to overcome in many research settings. These limited resources and availability of NHP for COVID-19 studies have been a challenge for many researchers even before the emergence of SARS-CoV-2. Furthermore, most NHPs are outbred animals with a broad range of genetic backgrounds, making it challenging to evaluate study results owing to heterogeneity in outcomes across individual animals [32].

It is more crucial now than ever to explore the use of nontraditional animal models that can fill these gaps. Much has been learned about natural infection, transmission, and disease outcomes in mammals subsequently infected with SARS-CoV-2, offering a great opportunity in their use for COVID-19 studies (Figure 2). While each model has its own set of constraints, having a wider variety of optimal animal models will allow for the investigation of a wider variety of important research problems. Importantly, continuous identification and development of the nontraditional innovative animal models will aid in researching disease pathophysiology, testing therapies, and aiding with vaccine development, providing a very consistent framework. This review aims to summarize what we know about several of these less traditional animal models and encourage further studies to optimize and implement their usage.

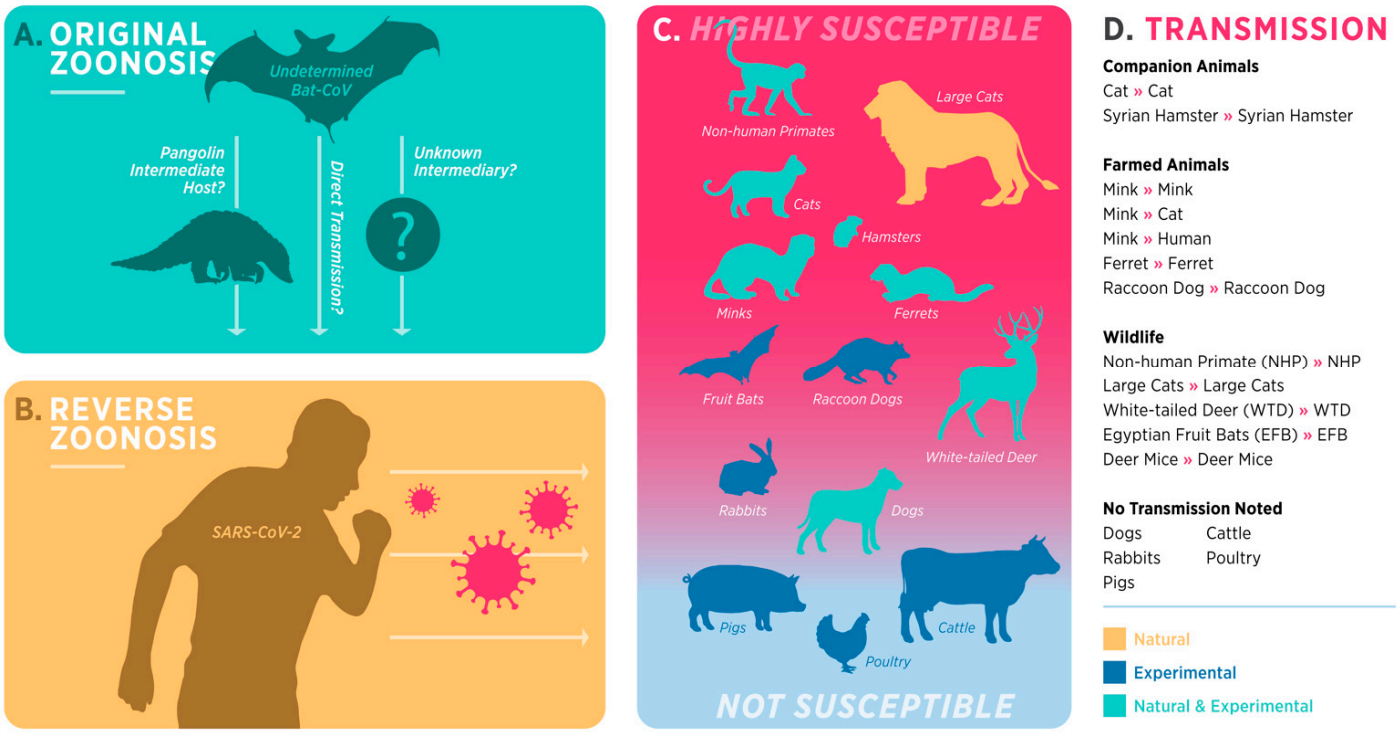

Figure 2. Current summary of SARS-CoV-2 origin, animal susceptibility, and transmission. (**A**) The original zoonosis for the SARS-CoV-2 is yet to be confirmed. It is suspected to be evolved in a selected species of bats. Bats may have shed CoVs and infected humans (solid arrows) via a suspected intermediate host (pangolin), direct transmission, or other intermediate species that remain to be discovered (see references [33,34]). (**B**) SARS-CoV-2 transmission from human to animal (reverse zoonosis events) have been documented in several instances to date (see references [35–40]). (**C**) The susceptibility of animal species for SARS-CoV-2 infection is shown in a descending order, with NHPs and felids being most susceptible to infection while livestock species (cattle, pigs, and poultry) generally being the least susceptible. (**D**) Animals are color coded to represent the mode of infection (natural vs. experimental) and a summary of animal–animal transmission confirmed by relevant methods (viral RNA and sequencing) is shown at the right.

2.1. Domestic Cats

Domestic cats (*Felis catus*) offer an intriguing option as a translational model for several reasons. Cats have been infected with SARS-CoV-2 both experimentally [26,41–44] and naturally [45,46], and human-to-cat as well as cat-to-cat transmission is now well established [35,36,47]. This comes with little surprise as SARS-CoV was identified in wild cats in the early 2000s [48], and felids have the natural expression of ACE2 receptors that act as an efficient binding site for this virus [36,49–51]. Experimentally, intranasal SARS-CoV-2 inoculation results in efficient viral replication in the upper and lower respiratory tracts, peaking at 3 days post-inoculation (dpi) until decreasing below detectable limits around 14 dpi [42,44,52,53]. The virus is detectable in the nasal turbinates, soft palate, tonsils, trachea, lungs, and small intestines, with the live virus in all tissues except the intestines or feces, suggesting low viral shedding via that pathway. The spleen, lymph node, liver, heart, and olfactory bulb also exhibit viral replication. While viral detection and replication were evident, early studies indicated limited to no clinical disease was associated with intranasal experimental inoculation routes [26,42–44], even though mild clinical disease was apparent in natural felid infections [51].

That barrier was later overcome by using an intratracheal inoculation route and higher infective dose of SARS-CoV-2 than had been previously described, resulting in clinical and histopathologic disease in cats consistent with that seen in acutely infected hospitalized patients with COVID-19 [41]. Clinical signs noted in infected cats included

fever, cough, lethargy, and increased respiratory effort [41,42,44,53,54]. These signs mimic the most common clinical symptoms observed in humans with COVID-19 including fever, shortness of breath, dry cough, and lethargy [55]. Similarities between COVID-19 and respiratory disease in SARS-CoV-2-infected felids are also evident histologically. Cats exhibit inflammation in the nasal turbinates and trachea as well as interstitial pneumonia accompanied by marked pulmonary edema, widespread alveolar damage with hyaline membrane formation, and vasculitis [41,53], mirroring the pulmonary and perivascular changes seen in people with acute COVID-19 pneumonia [18,56–60].

Contrary to prior studies that used intranasal delivery of SARS-CoV-2, intratracheal inoculation resulted in lower viral RNA levels in the lungs [41]. However, SARS-CoV-2 virus was readily detectable in the nasal turbinates at 4 and 8 dpi, indicating the mobility of the virus via the mucociliary escalator to establish the upper respiratory infection despite the absence of intranasal inoculation [41]. After the emergence of COVID-19 in Wuhan, China, domestic cats in the region had 14.7% seroprevalence [40]. Viral RNA detection in lung tissue is prolonged in juvenile cats, and while juvenile cats shed more infectious virus, sub-adult cats exhibit greater antibody titers [51]. In cats, the adaptive immune response is initiated early on, with neutralizing antibodies being produced as early as 7 dpi and increasing beyond 28 days, whereas reinfected cats had an even stronger and quicker humoral immune response to the viral infection [43,44].

Concerning the transmission potential of SARS-CoV-2 to domestic cats, several studies support natural transmission from infected humans to domestic cats [54,61–64]. After contact with an infected person, viral RNA was found in oropharyngeal swabs taken from cats, and infections were verified serologically [48]. Several other investigations have confirmed household transmission to cats from infected owners [65], with the infected animals remaining asymptomatic in the majority of instances [62]. In addition to human-to-cat transmission, airborne transmission between cats in adjacent cages was demonstrated under experimental conditions, although infection was limited to one out of every three sentinel animals [26]. Direct contact transmission between cats is even more evident, with infection occurring in all sentinel animals [42,44,47]. Serial transmission of the virus between cats was shown to reduce the effectiveness of transmission from infected to naive cats [53,66], although further transmission from reinfected cats has not yet been established [42]. Transmissibility for the most recent variants of concern (delta and omicron), however, has not been established [67], and as variants continue to emerge, an established feline model is needed to best understand the potential for cat-to-human transmission of SARS-CoV-2.

Hypertension, diabetes, renal disease, and obesity, all of which increase COVID-19 illness, are naturally occurring comorbidities in domestic cats and are easily adapted to feline models [68–73], offering another potential advantage of this model. Limitations do exist, such as required experience with handling cats (in particular within an ABSL-3 environment), and the moderate cost involved compared to mouse studies. In addition, public opinion regarding the use of companion animals in translational research must be taken into account. Additional research on transmission efficiency is required, particularly with regard to cats as intermediary hosts between SARS-CoV-2 and people, as well as on inflammation and how it mimics human illness [74]. Despite these limitations, felids remain a promising option for modeling natural SARS-CoV-2 infection and COVID-19 disease progression for future studies.

2.2. Ferrets

Ferrets (*Mustela putorius furo*) originated from the domestication of the European polecat, and have been a valued model for many viral respiratory diseases including influenza, respiratory syncytial virus (RSV), adenovirus, and SARS-CoV [75–77]. This is in part due to the fact that they have an anatomically comparable respiratory tract to humans, with similar features of glandular density in the bronchial wall, upper and lower respiratory tract proportions, and terminal bronchioles as well as receptor distribution, resulting in similar clinical

courses of disease [76,78–80]. Ferret and human ACE2 receptors vary by only two amino acids and contain the crucial residues required for binding by the SARS-CoV-2 receptor-binding domain [79,81]. The ferret model for COVID-19 has been utilized since early in the COVID-19 pandemic. A sentinel study conducted by Shi et al. revealed that infection with early variants of SARS-CoV-2 (SARS-CoV-2/F13/environment/2020/Wuhan and SARS-CoV-2/CTan/human/2020/Wuhan) resulted in high viral susceptibility in nasal turbinates, soft palates, and tonsils, although low quantities of the virus were identified in the lungs [26]. Clinical signs included elevated body temperature and reduced activity, but fever and appetite loss were observed in just 1 out of 3 ferrets, with the dose and heterogeneity of the isolate affecting the presence of clinical disease [26]. In general, weight reduction has not been a consistent finding in the ferret model [75,82], but clinical disease in CoV-2-infected ferrets was noted in another study in which increased body temperature, lethargy, and coughing were evident at 2 dpi, with all animals recovering by day 8 [75]. In this study, viral loads peaked at 4 dpi in the lungs and nasal turbinates. Viral RNA was detectable in the intestine, saliva, urine, rectal swabs, and feces through 8 dpi, and viral loads were highest in the upper respiratory tract with overall mild disease. Additional studies have reported similar results, with viral loads highest in the nasal turbinates and throat, mild clinical disease, and viral shedding beyond 10 dpi [75,82–86].

Ryan et al. went a step further to try and optimize inoculum dosages for the ferret COVID-19 model [87]. Ferrets were challenged intranasally with 1 mL of Victoria/1/2020 SARS-CoV-2 at three different titers: high (5×10^6 PFU/mL), medium (5×10^4 PFU/mL), and low dose (5×10^2 PFU/mL). While the high and medium doses successfully infected the upper respiratory tract of all the animals, the lower inoculum dose was only successful in 1 of 6. Some in the high dose group developed bronchopneumonia, and viral shedding continued into days 14 to 21 [80]. Age also affects disease pathogenesis and outcome in the ferret model, with infections in older ferrets (>3 years of age) resulting in increased viral loads, prolonged viral replication and shedding, and more severe disease than their younger counterparts [75,88,89].

Ferrets have also been utilized for longitudinal studies of immune responses to SARS-CoV-2 infection through intranasal inoculation with SARS-CoV-2 and repeated assessments of upper respiratory tract gene transcripts from nasal washes. Ferrets infected with SARS-CoV-2 demonstrate unique inflammatory transcriptional responses, as evidenced by low levels of type I and III interferons in contrast to up-regulated IL-6, CCL2, CCL8, and CXCL9 [90]. In depth studies into specific gene signatures and transcripts in infected ferrets have shown that SARS-CoV-2 gene signatures induce more respiratory immune responses than influenza A and SARS-CoV-2 gene signatures are identified in both short-term and longer-term (21 days) infections in ferrets [91]. In both short- and long-term scenarios, metabolic, glucocorticoid, and reactive oxygen species genes were enriched. Activated T cells, macrophages, and type I IFN signaling are all involved in the ferret's immunological responses [92–94], yet all animals survive experimental infection, with a strong adaptive response and neutralizing antibody generation as early as 8 days post-infection [75,90,95,96]. When ferrets are rechallenged with SARS-CoV-2, the generated immune response protects them from harmful disease, decreases viral replication, and no remarkable lesions are noted [26,83,97].

Ferret-to-ferret transmission is also readily achieved. Direct contact transmission appears to be the most efficient method of transmission as all naïve ferrets cohoused with intranasally inoculated ferrets exhibited clinical symptoms (elevated body temperature and reduced activity) 2–6 days after exposure [75,85,97]. Transmission rates in ferrets vary amongst spike glycoprotein mutations seen with different variants, with higher transmissibility of S(614G) over S(614D) glycoprotein structures [98]. Airborne transmission of SARS-CoV-2 was also shown [3,85,96]; however, this transmission appeared less efficient and diminished at distances greater than 1 m [3,99]. Despite multiple studies supporting direct and indirect transmission between ferrets, differences in disease pathogenesis and outcomes are noted between studies. When comparing direct recipient animals to donor

animals, most studies found that infection via either route resulted in comparable durations and levels of virus shedding in direct recipients [85,96]. Kim et al., however, found lower levels of SARS-CoV-2 RNA in nasal washes of indirect recipient ferrets, as well as shorter viral shedding with no infectious virus isolated [75]. Viral RNA was detected in ferret nasal washes 48 h after direct contact with intranasally infected animals, demonstrating that transmission is rapid and can occur before peak disease at 4 dpi. Overall, there is a resemblance between the clinical characteristics of infected naïve ferrets and those of injected ferrets in terms of viral replication, pathology, and immune response [75,82,85,97,100].

The ferret model for COVID-19 is also well utilized in evaluating antiviral and other treatment effects. The use of repurposed medications (hydroxychloroquine sulfate, lopinavir-ritonavir, and emtricitabine-tenofovir) in the treatment of infected ferrets was shown to provide no substantial advantage over standard therapy [95]. In fact, emtricitabine, tenofovir, lopinavir-ritonavir, and hydroxychloroquine sulfate markedly enhanced clinical symptoms in ferrets infected with SARS-CoV-2 and did not significantly lower viral titers [95]. Those who received 18-azathioprine had a longer duration of clinical illness, higher viral titers in the nasal turbinates, delayed virus clearance, and lower serum-neutralizing antibody titers compared to those who did not receive the drug [95]. In contrast, MK-4482/EIDD-2801, a ribonucleoside analog inhibitor developed for influenza virus therapy, demonstrated promise as a SARS-CoV-2 therapy as evidenced by reduced viral load and prevention of transmission to untreated contact ferrets [101]. Using this model, newly developed lipoprotein fusion inhibitors were shown to successfully suppress S protein conformational changes and prevent virus–host cell membrane fusion by integrating into host cell membranes, also decreasing SARS-CoV-2 transmission between ferrets [98,102]. Recent studies also demonstrate that intranasal treatment with the TLR2/6 agonist INNA-051 can effectively reduce viral levels in ferrets infected with SARS-CoV-2 [103].

Although the application of ferrets in vaccine evaluation is limited due to dose-dependent responses to SARS-CoV-2 infection [87], several studies have utilized this animal model in the process of vaccine development. Immunization of ferrets with Ad5-nCoV, an adenovirus-vectored vaccine, suppressed viral multiplication in the upper respiratory tract (URT) through both mucosal and intramuscular routes, with mucosal vaccination completely protecting from infection [104]. Furthermore, according to Dong et al., intranasal immunization with CVXGA1 inhibited viral infection in ferrets and prevented contact transmission, additionally suppressing SARS-CoV-2 replication in the URT and limiting disease progression to the lower respiratory tract [105].

Given their susceptibility to SARS-CoV-2, histopathological changes, detectable viral loads, and shedding from the respiratory tract during infection, ferrets continue to be a highly regarded model for asymptomatic or mild COVID-19 [3,79]. Unfortunately, the lack of pulmonary viral replication and edema or the development of ARDS in ferrets suggest a major limitation for the study of lung pathology with COVID-19 [106]. Ferrets are larger than mice or hamsters and, thus, add some housing and handling limitations; furthermore, as with most nontraditional models, they have costlier and less available optimized reagents. However, ferrets live a long time, and have the potential for researching aging and long-term effects of SARS-CoV-2, only adding to their value as a useful model to research SARS-CoV-2 pathogenesis and therapeutic targets [26].

2.3. Mink

Similar to ferrets, mink (*Neovison vison*) belong to the *Mustelidae* family and are naturally prone to SARS-CoV-2 infection. In fact, mink represents an exceptional animal model to study SARS-CoV-2 since they show efficient interspecies transmission and clinical features of SARS-CoV-2 infection comparable to humans [37,107]. Recent SARS CoV-2 outbreaks on mink farms in the Netherlands and Spain resulted in the culling of thousands of animals. In these cases, though the initial infection was likely to be transmitted from infected farm laborers, studies suggest human reinfection can occur from

infected minks [108,109]. Inter-species transmission is supported through an analysis of mutations in the spike protein of SARS-CoV-2 virus, with specific mutations (L452M, Y453F, F486L, and N501T) identified in both mink and workers closely in contact with animals on those farms [110]. Two of these mutations (Y435F and N501T) adapt the spike protein of SARS CoV-2 to improve transmission to both mink and ferrets. These mutations arose independently in mink and seem to have minimal effect on human airway epithelial cells in vitro. However, studies suggest that these mutations carry minimal effects on human disease and are tolerated by the available vaccines against SARS-CoV-2 [111].

In mink, SARS-CoV-2 infection produces vigorous virus replication in the upper and lower respiratory tracts, including the nasal turbinates, tonsils, soft palate, trachea, and lung tissue, peaking at 2 dpi and continuing until 8 dpi before falling below measurable limits at 14 dpi [112]. SARS-CoV-2 also replicates in the gastrointestinal tract of mink, limiting feed intake and exhibiting mild to severe symptoms including up to 20% body-weight loss [112]. Neutrophil infiltration, epithelial degeneration, and necrosis are found in the inflamed nasal turbinates of SARS-CoV-2-infected minks [112–114]. Mink intranasally infected with 10^6 PFU of WA1 isolate resulted in a productive viral replication in the upper and lower respiratory tract, and viral replication was detected in the left cranial lung and nasal turbinates, but not from nasal washes of 3–5 dpi [115]. Infection results in severe, diffuse interstitial pneumonia with swelling and degeneration of bronchial epithelial cells, thickening of alveolar septa, collagen deposition, hemorrhage, and marked pulmonary edema [112–114]. Mink also exhibit pneumocyte proliferation and pulmonary consolidation with diffuse alveolar damage during SARS-CoV-2 infection, as well as infiltration of macrophages, monocytes, and neutrophils throughout the lungs in addition to perivascular lymphocyte accumulations [112–114]. The virus can cause lethal disease in mink; additionally, naïve mink infected experimentally exhibit enhanced clinical features [112,113].

Mink not only offer potential as an animal model for human COVID-19, but should be evaluated as a possible farmed animal reservoir for SARS-CoV-2 and for their role, through mutants, on viral fitness, contagiousness, re-infection, immunotherapy, and vaccine efficacy. Limitations related to the use of minks as an animal model include animal behavior, the scarcity of reagents and resources, and difficulty in housing and handling mink under laboratory conditions [108,109,113,114].

2.4. Hamsters

Syrian hamsters (*Mesocricetus auratus*) are widely used in viral respiratory disease research, being valuable models for influenza virus, adenovirus, and most recently, SARS-CoV-2 [116]. With these viral infections, hamsters show productive viral replication, pathological signs and successful disease pathogenesis in the lung [117]. Hamsters are naturally infected with SARS-CoV-2 virus, in part due to a high degree of homology with the human ACE2 receptor domain and successful interaction with SARS-CoV-2 spike glycoprotein [118]. Experimentally infected hamsters show significant weight loss [119–121], respiratory distress, lethargy, ruffled fur, and hunched posture with recovery around 7 dpi [121]. In a study conducted to determine if age differences appear to influence disease outcomes, it was found that weight loss was faster and more consistent in older hamsters developing severe SARS-CoV-2 symptoms, while juvenile hamsters resisted severe disease with a stronger and earlier immune cell influx than adult hamsters. Only young hamsters showed fast lung recovery on day 14 following infection [119].

In a comparative study including several variants, namely 1.617.2, B.1.617.3, and B.1.351, a similar degree of viral shedding was shown regardless of the variant, although the delta variant (1.617.2) resulted in the least body-weight gain and the most severe lung disease, affecting 40% of infected animals [122]. Infected hamsters produced neutralizing antibodies, but the neutralizing response was lower with B.1.351 variant infection. This study supports that 1.617.2 infection (delta variant) induces a stronger neutralizing antibody response and that B.1.351 infection in hamsters is more immune evasive than the other variants studied [122].

Histopathological features of SARS-CoV-2 infection in Syrian hamsters include necrosuppurative bronchitis, intra-alveolar and intrabronchial infiltration of macrophages and neutrophils, pulmonary edema, and severe alveolar hemorrhage in infected lungs [119,120,123,124]. SARS-CoV-2 viral replication was observed in both the upper and lower respiratory tracts, with peak viral titer at 3 dpi progressing to viral clearance at 7 to 10 dpi [118]. The innate immune response exhibited by hamsters involves rapid augmentation of local antiviral responses [125] facilitated by the production of pro-inflammatory cytokines, namely IFN and IL-6, which peak at 2 to 4 dpi and resolve by 14 dpi [118]. The immune response also incorporates significant production of chemokines and the recruitment of a potent type 1 T cell response [125]. The macrophage response to intracellular viral RNA is driven by CCL2 and CXCL10, and the expression profile of pro-inflammatory cytokines in monocytic macrophages favored effector T cell recruitment chemokines targeting CXCR3 and CCR5 [125]. Emergence of IgM-neutralizing antibodies was shown to precede viral clearance at day 5 post infection [125]. Hamsters also show significant potential in studies involving intraspecies viral transmission. Sia et. al. [121] showed that SARS-CoV-2 is transmitted between hamsters through both close contact and non-contact routes such as aerosols and fomites. Naive hamsters were successfully infected within one day of direct contact with intranasally infected hamsters, highlighting the potential to evaluate the transmission risk of continually evolving variants and to study the mutation rates of SARS-CoV-2 [121].

Apart from transmission studies, Syrian hamsters have been utilized to study prophylactic modalities against SARS-CoV-2 infection. According to Rosenke et al., oral administration of the nucleoside analog MK-4482 suppressed SARS-CoV-2 replication, and led to decreased lung pathology [124]. The aforementioned outcomes were also observed in a study that was conducted using ranitidine bismuth citrate [126]. Notably, viral shedding was reduced by the administration of therapeutic neutralizing antibodies that targeted the receptor-binding domain (RBD) of the virus [5,102,120,127,128].

Syrian hamsters have also been widely utilized as an animal model for preliminary vaccine studies. According to Tostanoski et al., Ad26.COV2.S vaccination reduces humoral immune responses in hamsters and protects against severe disease [129]. In addition, pre-clinical trials conducted using the Newcastle disease virus (NDV-S) vaccine showed substantial immunogenicity, generating spike-protein-specific neutralizing antibodies and lower lung viral titers with less body-weight loss [130]. Other pre-clinical vaccine trials, such as that of the PTX-COVID19-B mRNA vaccine, exhibited significant humoral and cellular immune responses and protected the upper respiratory tract from SARS-CoV-2 infection in hamsters [131]. A single dosage of another approved adeno virus-based vaccine, ChAdOx1 nCoV-19 (AZD1222), protected hamsters against SARS-CoV-2 illness and pneumonia [132]. In this study, vaccinated hamster sera for B.1.351 had a 9.5-fold lower viral neutralizing antibody titer than B.1.1.7, and the lungs of vaccinated animals exhibited no gross lesions in comparison to control animals [132]. Hamsters intranasally inoculated with another vaccine candidate (COVI-VAC) showed lower tissue virus loads, milder lung pathology, and less weight loss compared to wild type hamsters, and this was followed by the development of spike IgG antibody levels and plaque-reduction-neutralization titers [133]. Moreover, inoculation of a number of live attenuated vaccine candidates generated by the recoding of the SARS-CoV-2 genome resulted in two-fold immunogenicity, while two of the candidates elicited substantial protective immunity [134]. The attenuated viruses caused minor pulmonary histopathology in the upper—but not the lower—airways, and after challenge, the hamsters developed no signs of disease and virus could not be recovered from the lungs of the infected animals [134]. Drawbacks to the Syrian hamster model for COVID-19 include limited disease severity and fatality, which may be explained by the presence of asparagine at position 82 in the sequence of the ACE2 receptor instead of lysine in human ACE2, thus limiting their potential as a model for moderate-to-severe COVID-19 [118]. Additionally, reagents and bioinformatic resources are more limited for hamsters when compared to several other models [118,121].

The susceptibility of Chinese hamsters to SARS-CoV-2 infection was recently demonstrated by the presence of viral replication in the upper and lower respiratory tract, accompanied by the development of pneumonia and bronchitis [74]. In this model, intranasal infection results in transient but significant body-weight loss and a slight reduction in body temperature. Lung lesions are less severe but are associated with diffuse alveolar damage and the persistence of viral RNA in tissues may still be found up to 14 dpi [74]. In fact, this animal model may prove advantageous to the Syrian hamster model due to prolonged and more prominent clinical symptoms, smaller size, a well-characterized genome (supported by transcriptome and translatome data), and the availability of molecular tools specific to the species [74]. However, while most commercial breeders of laboratory animals only provide a single line of Syrian hamsters, Chinese hamsters that meet laboratory criteria such as uniform genetics and specific-pathogen-free (SPF) status are far less available.

SARS-CoV-2 infection in Roborovski dwarf hamsters leads to the rapid and robust development of severe clinical illness due to early destructive and lethal lung pathology, as well as signs of systemic SARS-CoV-2 infection, recapitulating human COVID-19 symptoms such as coughing, snuffling, dyspnea, labored breathing, and gradual weight loss [135,136]. Roborovski dwarf hamsters may represent an important addition to current animal models given the advantage of a small animal model and faster and more consistent development of clinical symptoms following infection [135,136]. It is also less prone to aggressive behavior than other hamster species, making it easier to handle and house in greater groups [135,136]. Roborovski dwarf hamsters are commercially accessible and farmed in large quantities for the pet industry, and the species reaches sexual maturity at 4 weeks of age and reproduces easily in a laboratory setting. However, unrecognized co-infections with other pathogens, different individual infection histories, and changeable, uncontrolled microbiomes may substantially influence their responses to experimental infections with specific pathogens [137].

In addition to Chinese hamsters and Roborovski dwarf hamsters, a recent study indicated that cardiomyopathic J2N-k hamsters display characteristics comparable to those associated with severe COVID-19 complications. Male J2N-k hamsters of 7 weeks of age were infected with 10^6 PFU SARS-CoV-2 and demonstrated high viral titers in the lung with a weight loss of 25.7% at 3 dpi. Mortality was reported in all infected J2N-k hamsters at 9 dpi and pathological characteristics were consistent with SARS-CoV-2-associated lung damage [138].

Overall, the beneficial impacts of the hamster model for SARS-CoV-2 infection are vast and include easy handling for ABSL-3 and well-documented natural susceptibility to SARS-CoV-2 virus with disease pathogenesis and severity comparable to mild COVID-19 in humans. Recently, significant progress has been achieved in spatial proteomics and transcriptomics in these species, allowing the determination of the individual expression levels of almost all proteins and mRNA molecules with single-cell-type precision [137]. Although the use of hamsters in biomedical research is somewhat limited by the absence of suitable inbred strains and species bred under standardized, controlled circumstances, these species offer an intriguing alternative to current SARS-CoV-2 animal models.

2.5. Other Species

Current research indicates that the origins of SARS-like coronaviruses stem from bats, with these coronaviruses having the capability of docking and entrance via different orthologues of human ACE2 according to research prior to the emergence of SARS-CoV-2 [139,140]. As bats are natural reservoirs for several coronaviruses, including SARS-CoV and SARS-CoV-2, recent studies highlight the need for continued coronavirus surveillance in bats [141,142]. While ongoing research into coronavirus origins and maintenance in bats is clearly indicated, questions remain as to the usefulness of the bat as an animal model for human COVID-19. Studies have shown that intranasal inoculation of SARS-CoV-2 in fruit bats (*Rousettus aegyptiacus*) results in viral replication in the upper respiratory tract and seroconversion in 7/9 animals, and infection occurred in only 1 out of

every 3 animals during direct contact [96]. However, clinical signs were lacking apart from mild rhinitis [96]. In contrast, another study demonstrated that a coronavirus related to SARS did not grow in fruit bats after an experimental infection [143,144]. While Rousettus bats are not the major reservoir species for SARS-CoV-2, these findings suggest further studies are needed to evaluate if experimental infection in fruit bats might help simulate the physiopathology of the virus in its host [145–149].

Another emerging reservoir of interest for SARS-CoV-2 are white-tailed deer (*Odocoileus virginianus*). In a recent study, rRT-PCR detected SARS-CoV-2 in 129 out of 360 (35.8%) free-ranging white-tailed deer from northeast Ohio (USA) sampled between January and March 2021 [150]. At least three lineages of SARS-CoV-2 were identified in six different locations (B.1.2, B.1.596, and B.1.582), and deer of the B.1.2 lineage, which were prevalent in Ohio at the time, likely spread to deer populations in several different locales over different timepoints [150]. It was further concluded that deer-to-deer transmission likely occurred in at least three different sites [150]. Based on this study and others, white-tailed deer may serve as a natural reservoir for SARS-CoV-2, which could lead to distinct evolutionary trajectories and potential spillover to people, confounding long-term COVID-19 control attempts [150,151]. Another study of 624 pre- and post-pandemic blood samples collected from wild deer in four different states in the United States identified antibodies to SARS-CoV-2 in 152 of 200 (40%) via surrogate virus neutralization testing [152]. These findings and others underscore the need for further evaluation of white-tailed deer as a natural reservoir and potential animal mode for COVID-19 [153].

Deer mice and bushy-tailed woodrats are also susceptible to SARS-CoV-2 infection [154–156]. In a recent study, busy-tailed woodrats were observed to shed virus orally for <5 dpi, and virus was also isolated from the nasal turbinates, trachea, and lung of study animals at 3 dpi [154]. In another study by Fagre et al., young adult female deer mice (6 months old) were intranasally challenged with 2×10^4 $TCID_{50}$ SARS-CoV-2 and viral replication was detected in lungs, upper respiratory tract, and intestines, and this persisted for up to 21 days in oral swabs and 14 days in lungs [155]. IFNα, Cxcl10, Oas2, Tbk1, and Pycard were upregulated in the lungs, demonstrating an activated innate immune response, as well as the expression of Tbx21, IFNγ, and IL-21, indicating a type I inflammatory immune response [155]. Griffin et al. showed that intranasal SARS-CoV-2 infection with a human isolate (hCoV-19/Canada/ON-VIDO-01/2020) resulted in viral replication in the upper and lower respiratory tracts of deer mice with little or no illness [156]. Viral RNA was also detected in nasal washes, oropharyngeal, and rectal swabs, and could also be detected in feces and, in rare cases, urine [156]. Several studies have also demonstrated that contact transmission may occur between naïve and infected deer mice [155,156]. Overall, SARS-CoV-2-infected deer mice exhibited few clinical signs with no age-related changes observed, and no animals died of illness or lost weight at any time post-infection [155,156].

3. Conclusion: A Call for Improved Development of Nontraditional Animal Models

Validated animal models for COVID-19 are critical to uncovering pathogenic mechanisms, immune responses, and therapeutic effects that can be subsequently translated to human patients. The present knowledge of these animal models is summarized in Table 1. In large-scale clinical studies, a variety of potential preventative and treatment techniques are presently being evaluated in humans [157]. These clinical-efficacy trials will give a once-in-a-lifetime opportunity to back-validate and enhance these animal models. Continued refining and enhancement of COVID-19 animal models will aid in the investigation of key features of viral infection, including pathology, transmission, and host responses to SARS-CoV-2, as well as impending issues of vaccination effectiveness, the efficacy of novel therapeutics, possible adverse effects, and long-term repercussions of SARS-CoV-2 infection in recovered patients, in addition to the development of other countermeasures [2,158,159].

Table 1. Summary of current SARS-CoV-2 animal models.

	Hamsters	**Mink**	**Ferrets**	**Cats**	**Mice**	**NHP**
Naturally susceptible?	Yes	Yes	Yes	Yes	Not all variants	Yes
Experimental inoculation dose	10^3–$10^{5.3}$ PFU; 10^5–10^7 $TCID_{50}$ (I.N.)	Not reported	10^5–$10^{5.5}$ PFU (I.N.)	10^5 PFU (I.N.); 1.2×10^6 TCID50 (I.T.)	4×10^5–10^5 PFU 3×10^4–$10^5$$TCID_{50}$	$(2.4–4.75) \times 10^6$ TCID50
Lung pathology	Inflammatory cell infiltration, pulmonary edema, and alveolar hemorrhage Apoptosis of the cells in upper and lower respiratory tract Increased IL-6 and IL-10 in lungs	Diffuse alveolar damage and interstitial pneumonia with hyaline membrane formation Histopathological lesions exhibit ARDS and mimic human COVID-19	Bronchopneumonia Infiltration of inflammatory cells to the lung Thickening of alveolar septa	Alveolar flooding Diffuse alveolar damage with hyaline membrane formation Vasculitis Pulmonary edema Histopathological lesions exhibit ARDS and mimic human COVID-19	Interstitial pneumonia and lymphocyte infiltration in transgenic mice; some severe disease with alveolar necrosis Diffuse alveolar damage, exudation, and hemorrhage in mouse-adapted virus	Pulmonary edema Alveolar flooding Hyaline membranes Histopathological lesions exhibit ARDS and mimic human COVID-19
Clinical signs and/or Systemic effects	Weight loss, respiratory distress, lethargy, ruffled fur and hunched posture Younger hamsters more resistant to severe disease than more aged hamsters Increase in IL-6, IL-1β, TNF-α	Labored breathing and watery to mucoid nasal exudates, anorexia Natural infection can progress to death	Lymphopenia Pyrexia (Fever) Mild clinical signs (fever, lethargy, coughing)	Increased respiratory effort Cough Pyrexia (Fever) Lethargy	Weight loss Nasal congestion and dyspnea Increase in IL-6, IL-1β, TNF-α, MCP-1, G-CSF and GM-SCF in BALB/c mice	Neutropenia, anemia (CBC) Inflammatory cytokine boost (IL-1Ra, IL-1β, IFNγ, TNF-α, IL-6, IL-2, IL-4, IL-5, RANTES, G-CSF, GM-CSF, CCL-2) Increased respiratory rate
Advantages	Small size and rapid breeding High susceptibility to SARS-CoV-2 Useful for immunological studies for vaccine Lung pathology similar to COVID-19 Active transmission via direct contact and aerosol development	Naturally infected Mimic human lung pathology (ARDS) and other clinical features Can produce severe disease as in COVID-19	Active transmission via direct or indirect contact Similar distribution of ACE2 receptors in respiratory tract; high similarity to hACE2 Suitable for longitudinal studies of immune responses and treatment efficacy during SARS-CoV-2 infection	Naturally infected Mimic human lung pathology (ARDS) and clinical features of COVID-19 Can be used for transmission studies COVID-19 comorbidities (hypertension, diabetes, obesity, renal disease) occur naturally in cats	Useful for pathogenesis studies and testing of antiviral therapeutics Small size Rapid breeding Widespread availability of research reagents	Useful for pathogenesis, vaccine, and therapeutic studies Mimic human lung pathology (ARDS) and clinical features of COVID-19

Table 1. *Cont.*

	Hamsters	Mink	Ferrets	Cats	Mice	NHP
Disadvantages	Do not mimic all clinical signs of COVID-19 Mortality is not observed Viral clearance is rapid; cannot be used for long-term pathogenesis Fail to develop diffuse alveolar disease and acute respiratory distress found in COVID-19	Difficultly in handling Limited available resources and reagents Specific pathogen free animals not yet available for longitudinal studies	Do not mimic all clinical signs of COVID-19 Mortality is not observed. Low viral titer in the lungs Do not fully represent the severe cases of human infection	Requires species-specific training to handle animals Moderate cost involved Intratracheal inoculation needed to induce severe respiratory disease	Short supply and high cost of hACE2 transgenic mice Mild inflammatory responses and lung damage Cannot be used directly; needs a transgenic animal or mouse-adapted virus to cause infection Fatal encephalitis in transgenic mice	Requires species-specific training to handle animals Not all macaques can be infected Clinical signs are mild/moderate Small sample size and availability High costs for housing facilities and animal care
References	[118,121,160,161]	[109,112–114]	[75,76,78–81,83,90]	[18,26,41,47,62]	[24,25,158,160,162–165]	[31,32,166–170]

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; IN, intranasal; IT, intratracheal; TCID50, 50% Median Tissue Culture Infectious Dose; PFU, plaque-forming units; dpi, days post infection.

Many questions concerning the SARS-CoV-2 transmission route remain unresolved [157,171,172]. The dynamic differences in outcomes following infection encourage the identification of different animals for different disease outcomes in order to better elucidate the pathophysiology and underlying circumstances that may trigger increased susceptibility to disease, as well as host genetics that may contribute to these varied outcomes [173,174]. There are numerous unanswered questions regarding SARS-CoV-2 comorbidities, coinfections, and their long-term effects, many of which can be successfully mirrored in naturally infected animals—such as diabetes, obesity, and hypertension in the cat [175–178]. Varied models also offer unique opportunities to test the effectiveness of repurposed therapies for COVID-19 [179–181].

Due to fundamental variations in the biology and physiology of different animal species, no single animal model will be able to address all human translational concerns. The emergence of new variants may also lead to increased or decreased potential utilization for specific animal models of COVID-19. While some offer more value for studying transmission, other may have greater benefit for studying severe disease, new therapies, vaccines, or other preventions. By thinking outside of the box with our choices in translational animal models, we add significant potential to select experimental designs that will best address specific research questions. As available animal resources and limitations continue to evolve, it is important to have a strong knowledge base supporting a more varied approach to animal models for diseases such as COVID-19.

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