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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•].

Table 1

Animal models for SARS-CoV-2 and their application in countermeasures

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	Subunit vaccine (RBD-Fc)	[47]
		Limited availability	PEG-IFN-λ1a	[31*]
		High cost		
hACE2-transduced mouse	Small size, rapid breeding, availability of research tools	Do not develop severe disease in most cases	Subunit vaccine (NVX-CoV2373)	[51]
	Flexible application in commercial mouse strains	individual variations in expression and cellular distribution of hACE2	mAbs (COV2-2196 and COV2-2130)	[42]
	Short time to contruct	Potential inflammation associated with virus-delivery	mAbs (2B04)	[43]
	Low cost		mAbs (1B07)	[33]
			Remdesivir	[32]
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		NDV vectored vaccine (NDV-S)	[99]
	Low cost		mRNA vaccine (mRNA-1273)	[48**]
			Adenovirus vectored vaccine (Ad5-nCoV)	[49]
			mAbs (COV2-2196 and COV2-2130)	[42]
			mAbs (hu-mAbs)	[41]
			Remdesivir	[39]
			PEG-IFN-λ1a	[31*]
hACE2 humanized mouse	Small size, rapid breeding, availability of research tools	Limited availability	mAbs (H014)	[100]
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)	[70]
	Resemble lung pathology with COVID-19 patients		S2E12 and S2M11	[64]
	Active transmission via direct contact and aerosol		Ranitidine bismuth citrate	[62]
			REGN-COV2 (mAbs)	[69]
			BD-368-2 (mAb)	[68]
			Favipiravir	[61]
			Hydroxychloroquine	[61]
			CV07-209 (mAb)	[67]
			IgG1 ab1 (mAb)	[66]
			hACE2 decoys	[63]
			CC12.1 (mAb)	[65]
			hu-mAbs	[41]
Ferret	Asymptomatic or mildly symptomatic model	Low virus loads in the lower respiratory tract	Adenovirus vectored vaccine (Ad5-nCoV)	[49]
	Active transmission via direct or indirect contact	Does not fully represent the severe cases of human infection	MK-4482/EIDD-2801	[81]
			Lopinavir-ritonavir	[80]
			Hydroxychloroquine sulfate	[80]
			Emtricitabine-tenofovir	[80]

Table 1 (_Continued_**)**

Animal model	Strengths	Weaknesses	Application in countermeasures	References
Rhesus macaque	Identical ACE2 sequences in the ACE2-RBD interface to hACE2 and similar binding activity to the RBD with hACE2	Difficult to reach appropriately powered group sizes	mRNA vaccine (mRNA-1273)	[96]
	Pathology and immune responses resemble COVID-19 patients	Ethical concerns	Adenovirus vectored vaccine (Ad5-S-nb2)	[94]
	Recapitulating age related severity in COVID-19 patients	High cost	Adenovirus vectored vaccine (Ad26)	[93]
		Limited availability	Adenovirus vectored vaccine (ChAdOx1 nCoV-19)	[46]
		Complex husbandry	DNA vaccine encoding spike protein	[95]
			Inactivated vaccine (PiCoVacc)	[44]
			Inactivated vaccine (BBIBP-CorV)	[50]
			Remdesivir	[101••]
			Hydroxychloroquine	[60]
			mAbs (REGN-COV2)	[69]
			mAbs (CA1 and CB6)	[90]
			mAbs (COV2-2196 and COV2-2381)	[42]
Cynomolgus macaque	Identical ACE2 sequences in the ACE2-RBD interface to hACE2	Difficult to reach appropriately powered group sizes	Subunit vaccine (NVX-CoV2373)	[97,102]
	Pathology and immune responses resemble COVID-19 patients	Ethical concerns	Hydroxychloroquine	[103]
		High cost		
		Limited availability		
		Complex husbandry		
African green monkey	Identical ACE2 sequences in the ACE2-RBD interface to hACE2	Difficult to reach appropriately powered group sizes		[102]
	Pathology and immune responses resemble COVID-19 patients	Ethical concerns		
	Recapitulating age related severity in COVID-19 patients	High cost		
		Limited availability		
		Complex husbandry		

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

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 *Hfh4-ACE2* transgenic mouse lung [31•]. Passive immunity 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 [8]. 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 $TCID_{50}$ [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 naïve 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_{10} $TCID_{50}$/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/EIDD-2801, developed for influenza virus treatment, showed promise [81]. Oral administration of MK-4482/EIDD-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.

Acknowledgements

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Cucinotta D, Vanelli M: **WHO declares COVID-19 a pandemic**. *Acta Biomed* 2020, **91**:157-160.

2. WHO: *COVID-19 Weekly Epidemiological Update*. 2020.

3. Lamb YN: **Remdesivir: first approval**. *Drugs* 2020, **80**:1355-1363.

4. Perrin JM, Kenney GM, Rosenbaum S: **Medicaid and child health equity**. *N Engl J Med* 2020, **383**:2595-2598.

5. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, Diemert D, Spector SA, Rouphael N, Creech CB *et al.*: **Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine**. *N Engl J Med* 2020, **384**:403-416.

6. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL, Perez Marc G, Moreira ED, Zerbini C *et al.*: **Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine**. *N Engl J Med* 2020, **383**:2603-2615.

7. McAuliffe J, Vogel L, Roberts A, Fahle G, Fischer S, Shieh WJ, Butler E, Zaki S, St Claire M, Murphy B *et al.*: **Replication of SARS coronavirus administered into the respiratory tract of African Green, rhesus and cynomolgus monkeys**. *Virology* 2004, **330**:8-15.

8. Roberts A, Vogel L, Guarner J, Hayes N, Murphy B, Zaki S, Subbarao K: **Severe acute respiratory syndrome coronavirus infection of golden Syrian hamsters**. *J Virol* 2005, **79**:503-511.

9. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D:
•• **Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein**. *Cell* 2020, **181**:281-292.e6.
The authors demonstrate that ACE2 is a functional receptor for SARS-CoV-2 and identify the presence of a furin cleavage site at thee S1/S2 boundary of thee SARS-CoV-2 spike protein.

10. Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A *et al.*: **SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor**. *Cell* 2020, **181**:271-280.e8.

11. Imai M, Iwatsuki-Horimoto K, Hatta M, Loeber S, Halfmann PJ, Nakajima N, Watanabe T, Ujie M, Takahashi K, Ito M *et al.*: **Syrian hamsters as a small animal model for SARS-CoV-2 infection and countermeasure development**. *Proc Natl Acad Sci U S A* 2020, **117**:16587-16595.

12. Sia SF, Yan LM, Chin AWH, Fung K, Choy KT, Wong AYL,
• Kaewpreedee P, Perera R, Poon LLM, Nicholls JM *et al.*: **Pathogenesis and transmission of SARS-CoV-2 in golden hamsters**. *Nature* 2020, **583**:834-838.
The authors assess the pathogenicity and transmissibility of SARS-CoV-2 in a Syrian hamster model. This is the first paper reporting transmission of SARS-CoV-2 in hamsters by direct contact, aerosols, and fomite.

13. Bao L, Deng W, Huang B, Gao H, Liu J, Ren L, Wei Q, Yu P, Xu Y,
• Qi F *et al.*: **The pathogenicity of SARS-CoV-2 in hACE2 transgenic mice**. *Nature* 2020, **583**:830-833.
The authors establish hACE transgenic mouse as a model for SARS-CoV-2 infection.

14. Lu S, Zhao Y, Yu W, Yang Y, Gao J, Wang J, Kuang D, Yang M, Yang J, Ma C *et al.*: **Comparison of nonhuman primates identified the suitable model for COVID-19**. *Signal Transduct Target Ther* 2020, **5**:157.

15. Munster VJ, Feldmann F, Williamson BN, van Doremalen N, Perez-
•• Perez L, Schulz J, Meade-White K, Okumura A, Callison J, Brumbaugh B *et al.*: **Respiratory disease in rhesus macaques inoculated with SARS-CoV-2**. *Nature* 2020, **585**:268-272.
The authors establish a rhesus macaque model for SARS-CoV-2 infection.

16. Shan C, Yao YF, Yang XL, Zhou YW, Gao G, Peng Y, Yang L, Hu X, Xiong J, Jiang RD *et al.*: **Infection with novel coronavirus (SARS-CoV-2) causes pneumonia in rhesus macaques**. *Cell Res* 2020, **30**:670-677.

17. Woolsey C, Borisevich V, Prasad AN, Agans KN, Deer DJ, Dobias NS, Heymann JC, Foster SL, Levine CB, Medina L *et al.*: **Establishment of an African green monkey model for COVID-19 and protection against re-infection**. *Nat Immunol* 2020, **22**:86-98.

18. Jiang RD, Liu MQ, Chen Y, Shan C, Zhou YW, Shen XR, Li Q, Zhang L, Zhu Y, Si HR *et al.*: **Pathogenesis of SARS-CoV-2 in transgenic mice expressing human angiotensin-converting enzyme 2**. *Cell* 2020, **182**:50-58.e8.

19. Leist SR, Dinnon KH 3rd, Schafer A, Tse LV, Okuda K, Hou YJ, West A, Edwards CE, Sanders W, Fritch EJ *et al.*: **A mouse-adapted SARS-CoV-2 induces acute lung injury and mortality in standard laboratory mice**. *Cell* 2020, **183**:1070-1085.

20. Hogan RJ, Gao G, Rowe T, Bell P, Flieder D, Paragas J, Kobinger GP, Wivel NA, Crystal RG, Boyer J *et al.*: **Resolution of primary severe acute respiratory syndrome-associated coronavirus infection requires Stat1**. *J Virol* 2004, **78**:11416-11421.

21. Roberts A, Paddock C, Vogel L, Butler E, Zaki S, Subbarao K: **Aged BALB/c mice as a model for increased severity of severe acute respiratory syndrome in elderly humans**. *J Virol* 2005, **79**:5833-5838.

22. Subbarao K, Roberts A: **Is there an ideal animal model for SARS?** *Trends Microbiol* 2006, **14**:299-303.

23. Day CW, Baric R, Cai SX, Frieman M, Kumaki Y, Morrey JD, Smee DF, Barnard DL: **A new mouse-adapted strain of SARS-CoV as a lethal model for evaluating antiviral agents in vitro and in vivo**. *Virology* 2009, **395**:210-222.

24. McCray PB Jr, Pewe L, Wohlford-Lenane C, Hickey M, Manzel L, Shi L, Netland J, Jia HP, Halabi C, Sigmund CD *et al.*: **Lethal infection of K18-hACE2 mice infected with severe acute respiratory syndrome coronavirus**. *J Virol* 2007, **81**:813-821.

25. Roberts A, Deming D, Paddock CD, Cheng A, Yount B, Vogel L, Herman BD, Sheahan T, Heise M, Genrich GL *et al.*: **A mouse-adapted SARS-coronavirus causes disease and mortality in BALB/c mice**. *PLoS Pathog* 2007, **3**:e5.

26. Tseng CT, Huang C, Newman P, Wang N, Narayanan K, Watts DM, Makino S, Packard MM, Zaki SR, Chan TS *et al.*: **Severe acute respiratory syndrome coronavirus infection of mice transgenic for the human Angiotensin-converting enzyme 2 virus receptor**. *J Virol* 2007, **81**:1162-1173.

27. Du L, He Y, Zhou Y, Liu S, Zheng BJ, Jiang S: **The spike protein of SARS-CoV—a target for vaccine and therapeutic development**. *Nat Rev Microbiol* 2009, **7**:226-236.

28. Golden JW, Cline CR, Zeng X, Garrison AR, Carey BD, Mucker EM, White LE, Shamblin JD, Brocato RL, Liu J *et al.*: **Human**

angiotensin-converting enzyme 2 transgenic mice infected with SARS-CoV-2 develop severe and fatal respiratory disease. *JCI Insight* 2020, **5**.

29. Winkler ES, Bailey AL, Kafai NM, Nair S, McCune BT, Yu J, Fox JM, Chen RE, Earnest JT, Keeler SP *et al.*: **SARS-CoV-2 infection of human ACE2-transgenic mice causes severe lung inflammation and impaired function**. *Nat Immunol* 2020, **21**:1327-1335.

30. Rathnasinghe R, Strohmeier S, Amanat F, Gillespie VL, Krammer F, Garcia-Sastre A, Coughlan L, Schotsaert M, Uccellini MB: **Comparison of transgenic and adenovirus hACE2 mouse models for SARS-CoV-2 infection**. *Emerg Microbes Infect* 2020, **9**:2433-2445.

31. Dinnon KH 3rd, Leist SR, Schafer A, Edwards CE, Martinez DR,
•   Montgomery SA, West A, Yount BL Jr, Hou YJ, Adams LE *et al.*: **A mouse-adapted model of SARS-CoV-2 to test COVID-19 countermeasures**. *Nature* 2020, **586**:560-566.
The authors design a mouse-adapted SARS-CoV-2 using reverse genetics. This study enables the use of standard laboratory mice for SARS-CoV-2 infection.

32. Sun J, Zhuang Z, Zheng J, Li K, Wong RL, Liu D, Huang J, He J, Zhu A, Zhao J *et al.*: **Generation of a broadly useful model for COVID-19 pathogenesis, vaccination, and treatment**. *Cell* 2020, **182**:734-743.e5.

33. Hassan AO, Case JB, Winkler ES, Thackray LB, Kafai NM, Bailey AL, McCune BT, Fox JM, Chen RE, Alsoussi WB *et al.*: **A SARS-CoV-2 infection model in mice demonstrates protection by neutralizing antibodies**. *Cell* 2020, **182**:744-753.e4.

34. Israelow B, Song E, Mao T, Lu P, Meir A, Liu F, Alfajaro MM, Wei J, Dong H, Homer RJ *et al.*: **Mouse model of SARS-CoV-2 reveals inflammatory role of type I interferon signaling**. *J Exp Med* 2020, **217**.

35. Han K, Blair RV, Iwanaga N, Liu F, Russell-Lodrigue KE, Qin Z, Midkiff CC, Golden NA, Doyle-Meyers LA, Kabir ME *et al.*: **Lung expression of human angiotensin-converting enzyme 2 sensitizes the mouse to SARS-CoV-2 infection**. *Am J Respir Cell Mol Biol* 2021, **64**:79-88.

36. Sun SH, Chen Q, Gu HJ, Yang G, Wang YX, Huang XY, Liu SS, Zhang NN, Li XF, Xiong R *et al.*: **A mouse model of SARS-CoV-2 infection and pathogenesis**. *Cell Host Microbe* 2020, **28**:124-133.e4.

37. Gu H, Chen Q, Yang G, He L, Fan H, Deng Y-Q, Wang Y, Teng Y, Zhao Z, Cui Y *et al.*: **Adaptation of SARS-CoV-2 in BALB/c mice for testing vaccine efficacy**. *Science* 2020, **369**:1603-1607.

38. Pruijssers AJ, George AS, Schafer A, Leist SR, Gralinksi LE, Dinnon KH 3rd, Yount BL, Agostini ML, Stevens LJ, Chappell JD *et al.*: **Remdesivir inhibits SARS-CoV-2 in human lung cells and chimeric SARS-CoV expressing the SARS-CoV-2 RNA polymerase in mice**. *Cell Rep* 2020, **32**:107940.

39. Wang J, Shuai L, Wang C, Liu R, He X, Zhang X, Sun Z, Shan D, Ge J, Wang X *et al.*: **Mouse-adapted SARS-CoV-2 replicates efficiently in the upper and lower respiratory tract of BALB/c and C57BL/6J mice**. *Protein Cell* 2020, **11**:776-782.

40. Robbiani DF, Gaebler C, Muecksch F, Lorenzi JCC, Wang Z, Cho A, Agudelo M, Barnes CO, Gazumyan A, Finkin S *et al.*: **Convergent antibody responses to SARS-CoV-2 in convalescent individuals**. *Nature* 2020, **584**:437-442.

41. Schafer A, Muecksch F, Lorenzi JCC, Leist SR, Cipolla M, Bournazos S, Schmidt F, Maison RM, Gazumyan A, Martinez DR *et al.*: **Antibody potency, effector function, and combinations in protection and therapy for SARS-CoV-2 infection in vivo**. *J Exp Med* 2021, **218**.

42. Zost SJ, Gilchuk P, Case JB, Binshtein E, Chen RE, Nkolola JP, Schafer A, Reidy JX, Trivette A, Nargi RS *et al.*: **Potently neutralizing and protective human antibodies against SARS-CoV-2**. *Nature* 2020, **584**:443-449.

43. Alsoussi WB, Turner JS, Case JB, Zhao H, Schmitz AJ, Zhou JQ, Chen RE, Lei T, Rizk AA, McIntire KM *et al.*: **A potently neutralizing antibody protects mice against SARS-CoV-2 infection**. *J Immunol* 2020, **205**:915-922.

44. Gao Q, Bao L, Mao H, Wang L, Xu K, Yang M, Li Y, Zhu L, Wang N, Lv Z *et al.*: **Development of an inactivated vaccine candidate for SARS-CoV-2**. *Science* 2020, **369**:77-81.

45. Silva-Cayetano A, Foster WS, Innocentin S, Belij-Rammerstorfer S, Spencer AJ, Burton OT, Fra-Bidó S, Le Lee J, Thakur N, Conceicao C *et al.*: **A booster dose enhances immunogenicity of the COVID-19 vaccine candidate ChAdOx1 nCoV-19 in aged mice**. *Med* 2020, **2**:243-262.

46. van Doremalen N, Lambe T, Spencer A, Belij-Rammerstorfer S, Purushotham JN, Port JR, Avanzato VA, Bushmaker T, Flaxman A, Ulaszewska M *et al.*: **ChAdOx1 nCoV-19 vaccine prevents SARS-CoV-2 pneumonia in rhesus macaques**. *Nature* 2020, **586**:578-582.

47. Liu Z, Xu W, Xia S, Gu C, Wang X, Wang Q, Zhou J, Wu Y, Cai X, Qu D *et al.*: **RBD-Fc-based COVID-19 vaccine candidate induces highly potent SARS-CoV-2 neutralizing antibody response**. *Signal Transduct Target Ther* 2020, **5**:282.

48. Corbett KS, Edwards DK, Leist SR, Abiona OM, Boyoglu-
••   Barnum S, Gillespie RA, Himansu S, Schafer A, Ziwawo CT, DiPiazza AT *et al.*: **SARS-CoV-2 mRNA vaccine design enabled by prototype pathogen preparedness**. *Nature* 2020, **586**:567-571.
The authors demonstrate that a mRNA vaccine, mRNA-1273, induced robust neutralizing responses and rapid protection from SARS-CoV-2 infection in non-human primate model.

49. Wu S, Zhong G, Zhang J, Shuai L, Zhang Z, Wen Z, Wang B, Zhao Z, Song X, Chen Y *et al.*: **A single dose of an adenovirus-vectored vaccine provides protection against SARS-CoV-2 challenge**. *Nat Commun* 2020, **11**:4081.

50. Wang H, Zhang Y, Huang B, Deng W, Quan Y, Wang W, Xu W, Zhao Y, Li N, Zhang J *et al.*: **Development of an inactivated vaccine candidate, BBIBP-CorV, with potent protection against SARS-CoV-2**. *Cell* 2020, **182**:713-721.e9.

51. Tian JH, Patel N, Haupt R, Zhou H, Weston S, Hammond H, Logue J, Portnoff AD, Norton J, Guebre-Xabier M *et al.*: **SARS-CoV-2 spike glycoprotein vaccine candidate NVX-CoV2373 immunogenicity in baboons and protection in mice**. *Nat Commun* 2021, **12**:372.

52. Sun W, McCroskery S, Liu WC, Leist SR, Liu Y, Albrecht RA, Slamanig S, Oliva J, Amanat F, Schafer A *et al.*: **A Newcastle Disease Virus (NDV) expressing a membrane-anchored spike as a cost-effective inactivated SARS-CoV-2 vaccine**. *Vaccines (Basel)* 2020, **8**.

53. Miao J, Chard LS, Wang Z, Wang Y: **Syrian hamster as an animal model for the study on infectious diseases**. *Front Immunol* 2019, **10**:2329.

54. Chan JF, Zhang AJ, Yuan S, Poon VK, Chan CC, Lee AC,
••   Chan WM, Fan Z, Tsoi HW, Wen L *et al.*: **Simulation of the clinical and pathological manifestations of Coronavirus Disease 2019 (COVID-19) in golden Syrian hamster model: implications for disease pathogenesis and transmissibility**. *Clin Infect Dis* 2020, **71**:2428-2446.
The authors establish a golden Syrian hamster model for COVID-19, demonstrating pathogenesis and transmissibility of SARS-CoV-2 in golden Syrian hamsters.

55. Rosenke K, Meade-White K, Letko M, Clancy C, Hansen F, Liu Y, Okumura A, Tang-Huau TL, Li R, Saturday G *et al.*: **Defining the Syrian hamster as a highly susceptible preclinical model for SARS-CoV-2 infection**. *Emerg Microbes Infect* 2020, **9**:2673-2684.

56. Zhang AJ, Lee AC, Chu H, Chan JF, Fan Z, Li C, Liu F, Chen Y, Yuan S, Poon VK *et al.*: **SARS-CoV-2 infects and damages the mature and immature olfactory sensory neurons of hamsters**. *Clin Infect Dis* 2020 http://dx.doi.org/10.1093/cid/ciaa995.

57. Hornuss D, Lange B, Schroter N, Rieg S, Kern WV, Wagner D: **Anosmia in COVID-19 patients**. *Clin Microbiol Infect* 2020, **26**:1426-1427.

58. Klopfenstein T, Kadiane-Oussou NJ, Toko L, Royer PY, Lepiller Q, Gendrin V, Zayet S: **Features of anosmia in COVID-19**. *Med Mal Infect* 2020, **50**:436-439.

59. Hou YJ, Chiba S, Halfmann P, Ehre C, Kuroda M, Dinnon KH,
•   Leist SR, Schäfer A, Nakajima N, Takahashi K et al.: **SARS-CoV-2
    D614G variant exhibits efficient replication ex vivo and
    transmission in vivo**. *Science* 2020, **370**:1464-1468.
The authors demonstrate experimentally that spike D614G substitution
enhances SARS-CoV-2 infectivity, competitive fitness, and transmission
in primary human cells and animal models.

60. Rosenke K, Jarvis MA, Feldmann F, Schwarz B, Okumura A,
    Lovaglio J, Saturday G, Hanley PW, Meade-White K,
    Williamson BN et al.: **Hydroxychloroquine prophylaxis and
    treatment is ineffective in macaque and hamster SARS-CoV-2
    disease models**. *JCI Insight* 2020, **5**.

61. Kaptein SJF, Jacobs S, Langendries L, Seldeslachts L, Ter
    Horst S, Liesenborghs L, Hens B, Vergote V, Heylen E,
    Barthelemy K et al.: **Favipiravir at high doses has potent
    antiviral activity in SARS-CoV-2-infected hamsters, whereas
    hydroxychloroquine lacks activity**. *Proc Natl Acad Sci U S A*
    2020, **117**:26955-26965.

62. Yuan S, Wang R, Chan JF, Zhang AJ, Cheng T, Chik KK, Ye ZW,
    Wang S, Lee AC, Jin L et al.: **Metallodrug ranitidine bismuth
    citrate suppresses SARS-CoV-2 replication and relieves virus-
    associated pneumonia in Syrian hamsters**. *Nat Microbiol* 2020,
    5:1439-1448.

63. Linsky TW, Vergara R, Codina N, Nelson JW, Walker MJ, Su W,
    Barnes CO, Hsiang T-Y, Esser-Nobis K, Yu K et al.: **De novo
    design of potent and resilient hACE2 decoys to neutralize
    SARS-CoV-2**. *Science* 2020, **370**:1208-1214.

64. Tortorici MA, Beltramello M, Lempp FA, Pinto D, Dang HV,
    Rosen LE, McCallum M, Bowen J, Minola A, Jaconi S et al.:
    **Ultrapotent human antibodies protect against SARS-CoV-
    2 challenge via multiple mechanisms**. *Science* 2020,
    370:950-957.

65. Rogers TF, Zhao F, Huang D, Beutler N, Burns A, W-t He, Limbo O,
    Smith C, Song G, Woehl J et al.: **Isolation of potent SARS-CoV-2
    neutralizing antibodies and protection from disease in a small
    animal model**. *Science* 2020, **369**:956-963.

66. Li W, Chen C, Drelich A, Martinez DR, Gralinski LE, Sun Z,
    Schafer A, Kulkarni SS, Liu X, Leist SR et al.: **Rapid identification
    of a human antibody with high prophylactic and therapeutic
    efficacy in three animal models of SARS-CoV-2 infection**. *Proc
    Natl Acad Sci U S A* 2020, **117**:29832-29838.

67. Kreye J, Reincke SM, Kornau HC, Sanchez-Sendin E, Corman VM,
    Liu H, Yuan M, Wu NC, Zhu X, Lee CD et al.: **A therapeutic non-
    self-reactive SARS-CoV-2 antibody protects from lung
    pathology in a COVID-19 hamster model**. *Cell* 2020, **183**:1058-
    1069.

68. Du S, Cao Y, Zhu Q, Yu P, Qi F, Wang G, Du X, Bao L, Deng W,
    Zhu H et al.: **Structurally resolved SARS-CoV-2 antibody shows
    high efficacy in severely infected hamsters and provides a
    potent cocktail pairing strategy**. *Cell* 2020, **183**:1013-1023.e3.

69. Baum A, Ajithdoss D, Copin R, Zhou A, Lanza K, Negron N, Ni M,
    Wei Y, Mohammadi K, Musser B et al.: **REGN-COV2 antibodies
    prevent and treat SARS-CoV-2 infection in rhesus macaques
    and hamsters**. *Science* 2020, **370**:1110-1115.

70. Tostanoski LH, Wegmann F, Martinot AJ, Loos C, McMahan K,
    Mercado NB, Yu J, Chan CN, Bondoc S, Starke CE et al.: **Ad26
    vaccine protects against SARS-CoV-2 severe clinical disease
    in hamsters**. *Nat Med* 2020, **26**:1694-1700.

71. van Riel D, Munster VJ, de Wit E, Rimmelzwaan GF, Fouchier RA,
    Osterhaus AD, Kuiken T: **Human and avian influenza viruses
    target different cells in the lower respiratory tract of humans
    and other mammals**. *Am J Pathol* 2007, **171**:1215-1223.

72. Bouvier NM, Lowen AC: **Animal models for influenza virus
    pathogenesis and transmission**. *Viruses* 2010, **2**:1530-1563.

73. Chu YK, Ali GD, Jia F, Li Q, Kelvin D, Couch RC, Harrod KS,
    Hutt JA, Cameron C, Weiss SR et al.: **The SARS-CoV ferret model
    in an infection-challenge study**. *Virology* 2008, **374**:151-163.

74. Martina BEE, Haagmans BL, Kuiken T, Fouchier RAM,
    Rimmelzwaan GF, van Amerongen G, Peiris JSM, Lim W,
    Osterhaus ADME: **SARS virus infection of cats and ferrets**.
    Nature 2003, **425**:915.

75. Wan Y, Shang J, Graham R, Baric RS, Li F: **Receptor recognition
    by the novel coronavirus from Wuhan: an analysis based on
    decade-long structural studies of SARS coronavirus**. *J Virol*
    2020, **94**.

76. Kim YI, Kim SG, Kim SM, Kim EH, Park SJ, Yu KM, Chang JH,
•   Kim EJ, Lee S, Casel MAB et al.: **Infection and rapid
    transmission of SARS-CoV-2 in ferrets**. *Cell Host Microbe* 2020,
    27:704-709.e2.
The authors demonstrate that ferrets are susceptible to SARS-CoV-2
infection and effectively transmit the virus by direct or indirect contact.

77. Schlottau K, Rissmann M, Graaf A, Schön J, Sehl J, Wylezich C, Höper D,
    Mettenleiter TC, Balkema-Buschmann A, Harder T et al.: **SARS-CoV-2
    in fruit bats, ferrets, pigs, and chickens: an experimental
    transmission study**. *Lancet Microbe* 2020, **1**:e218-e225.

78. Ryan KA, Bewley KR, Fotheringham SA, Slack GS, Brown P,
    Hall Y, Wand NI, Marriott AC, Cavell BE, Tree JA et al.: **Dose-
    dependent response to infection with SARS-CoV-2 in the
    ferret model and evidence of protective immunity**. *Nat
    Commun* 2021, **12**:81.

79. Patel DR, Field CJ, Septer KM, Sim DG, Jones MJ, Heinly TA,
    Vanderford TH, McGraw EA, Sutton TC: **Transmission and
    protection against re-infection in the ferret model with the
    SARS-CoV-2 USA-WA1/ reference isolate**. *J Virol* 2021.

80. Park SJ, Yu KM, Kim YI, Kim SM, Kim EH, Kim SG, Kim EJ,
    Casel MAB, Rollon R, Jang SG et al.: **Antiviral efficacies of FDA-
    approved drugs against SARS-CoV-2 infection in ferrets**. *mBio*
    2020, **11**.

81. Cox RM, Wolf JD, Plemper RK: **Therapeutically administered
    ribonucleoside analogue MK-4482/EIDD-2801 blocks SARS-
    CoV-2 transmission in ferrets**. *Nat Microbiol* 2020, **6**:11-18.

82. Safronetz D, Geisbert TW, Feldmann H: **Animal models for highly
    pathogenic emerging viruses**. *Curr Opin Virol* 2013, **3**:205-209.

83. Zhao X, Chen D, Szabla R, Zheng M, Li G, Du P, Zheng S, Li X,
    Song C, Li R et al.: **Broad and differential animal angiotensin-
    converting enzyme 2 receptor usage by SARS-CoV-2**. *J Virol*
    2020, **94**:e00940-00920.

84. Chandrashekar A, Liu J, Martinot AJ, McMahan K, Mercado NB,
    Peter L, Tostanoski LH, Yu J, Maliga Z, Nekorchuk M et al.: **SARS-
    CoV-2 infection protects against rechallenge in rhesus
    macaques**. *Science* 2020, **369**:812-817.

85. Rockx B, Kuiken T, Herfst S, Bestebroer T, Lamers MM, Oude
    Munnink BB, de Meulder D, van Amerongen G, van den Brand J,
    Okba NMA et al.: **Comparative pathogenesis of COVID-19,
    MERS, and SARS in a nonhuman primate model**. *Science* 2020,
    368:1012-1015.

86. Cross RW, Agans KN, Prasad AN, Borisevich V, Woolsey C,
    Deer DJ, Dobias NS, Geisbert JB, Fenton KA, Geisbert TW:
    **Intranasal exposure of African green monkeys to SARS-CoV-2
    results in acute phase pneumonia with shedding and lung
    injury still present in the early convalescence phase**. *Virol J*
    2020, **17**:125.

87. Hartman AL, Nambulli S, McMillen CM, White AG, Tilston-
    Lunel NL, Albe JR, Cottle E, Dunn MD, Frye LJ, Gilliland TH et al.:
    **SARS-CoV-2 infection of African green monkeys results in
    mild respiratory disease discernible by PET/CT imaging and
    shedding of infectious virus from both respiratory and
    gastrointestinal tracts**. *PLoS Pathog* 2020, **16**:e1008903.

88. Blair RV, Vaccari M, Doyle-Meyers LA, Roy CJ, Russell-
    Lodrigue K, Fahlberg M, Monjure CJ, Beddingfield B, Plante KS,
    Plante JA et al.: **Acute respiratory distress in aged, SARS-CoV-
    2-infected African green monkeys but not rhesus macaques**.
    Am J Pathol 2020, **191**:274-282.

89. Yu P, Qi F, Xu Y, Li F, Liu P, Liu J, Bao L, Deng W, Gao H, Xiang Z
•   et al.: **Age-related rhesus macaque models of COVID-19**. *Anim
    Model Exp Med* 2020, **3**:93-97.
The authors demonstrate age-related disease severity of SARS-CoV-2
infection in a rhesus macaque model. This is the first study to assess age-
related disease severity of SARS-CoV-2 infection in an animal model.

90. Shi R, Shan C, Duan X, Chen Z, Liu P, Song J, Song T, Bi X, Han C,
    Wu L et al.: **A human neutralizing antibody targets the receptor-
    binding site of SARS-CoV-2**. *Nature* 2020, **584**:120-124.

91. Zheng H, Li H, Guo L, Liang Y, Li J, Wang X, Hu Y, Wang L, Liao Y, Yang F *et al.*: **Virulence and pathogenesis of SARS-CoV-2 infection in rhesus macaques: a nonhuman primate model of COVID-19 progression**. *PLoS Pathog* 2020, **16**:e1008949.

92. Fahlberg MD, Blair RV, Doyle-Meyers LA, Midkiff CC, Zenere G, Russell-Lodrigue KE, Monjure CJ, Haupt EH, Penney TP, Lehmicke G *et al.*: **Cellular events of acute, resolving or progressive COVID-19 in SARS-CoV-2 infected non-human primates**. *Nat Commun* 2020, **11**:6078.

93. Mercado NB, Zahn R, Wegmann F, Loos C, Chandrashekar A, Yu J, Liu J, Peter L, McMahan K, Tostanoski LH *et al.*: **Single-shot Ad26 vaccine protects against SARS-CoV-2 in rhesus macaques**. *Nature* 2020, **586**:583-588.

94. Feng L, Wang Q, Shan C, Yang C, Feng Y, Wu J, Liu X, Zhou Y, Jiang R, Hu P *et al.*: **An adenovirus-vectored COVID-19 vaccine confers protection from SARS-COV-2 challenge in rhesus macaques**. *Nat Commun* 2020, **11**:4207.

95. Yu J, Tostanoski LH, Peter L, Mercado NB, McMahan K, Mahrokhian SH, Nkolola JP, Liu J, Li Z, Chandrashekar A *et al.*: **DNA vaccine protection against SARS-CoV-2 in rhesus macaques**. *Science* 2020, **369**:806-811.

96. Corbett KS, Flynn B, Foulds KE, Francica JR, Boyoglu-Barnum S, Werner AP, Flach B, O'Connell S, Bock KW, Minai M *et al.*: **Evaluation of the mRNA-1273 vaccine against SARS-CoV-2 in nonhuman primates**. *N Engl J Med* 2020, **383**:1544-1555.

97. Guebre-Xabier M, Patel N, Tian JH, Zhou B, Maciejewski S, Lam K, Portnoff AD, Massare MJ, Frieman MB, Piedra PA *et al.*: **NVX-CoV2373 vaccine protects cynomolgus macaque upper and lower airways against SARS-CoV-2 challenge**. *Vaccine* 2020, **38**:7892-7896.

98. Osterrieder N, Bertzbach LD, Dietert K, Abdelgawad A, Vladimirova D, Kunec D, Hoffmann D, Beer M, Gruber AD, Trimpert J: **Age-dependent progression of SARS-CoV-2 infection in Syrian hamsters**. *Viruses* 2020, **12**.

99. Sun W, Leist SR, McCroskery S, Liu Y, Slamanig S, Oliva J, Amanat F, Schafer A, Dinnon KH 3rd, Garcia-Sastre A *et al.*: **Newcastle disease virus (NDV) expressing the spike protein of SARS-CoV-2 as a live virus vaccine candidate**. *EBioMedicine* 2020, **62**:103132.

100. Lv Z, Deng Y-Q, Ye Q, Cao L, Sun C-Y, Fan C, Huang W, Sun S, Sun Y, Zhu L *et al.*: **Structural basis for neutralization of SARS-CoV-2 and SARS-CoV by a potent therapeutic antibody**. *Science* 2020, **369**:1505-1509.

101. Williamson BN, Feldmann F, Schwarz B, Meade-White K, Porter DP,
•• Schulz J, van Doremalen N, Leighton I, Yinda CK, Perez-Perez L *et al.*: **Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2**. *Nature* 2020, **585**:273-276.
The authors demonstrate that treatment with remdesivir has a clinical benefit in rhesus macaques infected with SARS-CoV-2.

102. Melin AD, Janiak MC, Marrone F 3rd, Arora PS, Higham JP: **Comparative ACE2 variation and primate COVID-19 risk**. *Commun Biol* 2020, **3**:641.

103. Maisonnasse P, Guedj J, Contreras V, Behillil S, Solas C, Marlin R, Naninck T, Pizzorno A, Lemaitre J, Goncalves A *et al.*: **Hydroxychloroquine use against SARS-CoV-2 infection in non-human primates**. *Nature* 2020, **585**:584-587.