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Animal models for studying coronavirus infections and developing antiviral agents and vaccines

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ABSTRACT

In addition to severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), SARS-CoV-2 has become the third deadly coronavirus that infects humans and causes the new coronavirus disease (COVID-19). COVID-19 has already caused more than six million deaths worldwide and it is likely the biggest pandemic of this century faced by mankind. Although many studies on SARS-CoV-2 have been conducted, a detailed understanding of SARS-CoV-2 and COVID-19 is still lacking. Animal models are indispensable for studying its pathogenesis and developing vaccines and antivirals. In this review, we analyze animal models of coronavirus infections and explore their applications on antivirals and vaccines.

1. Introduction

Coronaviruses (CoVs) represent a group of enveloped, positive-sense, single-stranded RNA viruses in the family *Coronaviridae*, order Nidovirales (Weiss and Navas-Martin, 2005). CoVs are among the RNA viruses with the largest genome size. Their genome is organized from 5′-methylated cap to 3′-polyadenylated tail into *open-reading frame 1 ab* (*ORF1ab*), *spike* (*S*), *envelope* (*E*), *membrane* (*M*), and *nucleocapsid* (*N*) (Wu et al., 2020a). There are four genera of CoVs, α-, β-, γ-, and δ-CoVs. While CoVs may infect a range of animals including swine, cattle, horses, dogs, cats, rodents, and birds, only α- and β-CoVs can infect humans (Woo et al., 2012).

There are seven known species of human CoVs. HCoV-OC43, HCoV-HKU1, HCoV-229E, and HCoV-NL63 are the four common species continually circulating in humans and cause mild to moderate respiratory infections (Vabret et al., 2003; van der Hoek et al., 2006; Walsh et al., 2013; Woo et al., 2005). However, the other three, severe acute respiratory syndrome CoV (SARS-CoV), Middle East respiratory syndrome CoV (MERS-CoV), and the newly emerged SARS-CoV-2 causes severe acute respiratory diseases and endanger global health. In 2002 and 2003, the outbreaks of SARS-CoV resulted in approximately 800 deaths (Peiris et al., 2003a). Since 2012, there were numerous reports of MERS-CoV infections and deaths, with approximately 2500 laboratory-confirmed cases and 868 associated deaths as of December 2019 (Meo et al., 2020). The novel SARS-CoV-2, first identified in Wuhan, China, in December 2019 (Huang et al., 2020), is causing the ongoing pandemic of coronavirus disease 2019 (COVID-19), and the global death toll is now approximately 6.3 million (2022a, https://covid19.who.int/), highlighting the urgent need for developing preventative and control strategies.

It has been suggested that wild bats are the potential reservoir hosts of the three deadly coronaviruses, SARS-CoV, MERS-CoV and SARS-CoV-2 (Cui et al., 2019; Zhou et al., 2020) and the viruses can be transmitted across species through one or more intermediate hosts (Cui et al., 2019; Wu et al., 2021). Civets (Shi and Hu, 2008) and dromedary camels (Raj et al., 2014a) have been identified as potential intermediate hosts of SARS-CoV and MERS-CoV, respectively. Pangolins might be a potential intermediate host of SARS-CoV-2 as indicated by the study that

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the genome of pangolin-CoV isolated from dead Malayan pangolins is 91% identical to that of SARS-CoV-2 (Zhang et al., 2020b). To date, non-human primates (NHPs) (Koo et al., 2020; Lu et al., 2020), hamsters (Chan et al., 2020) and ferrets (Kim et al., 2020) have been shown to be susceptible to SARS-CoV-2 infection.

Animal models are of great importance to understanding the cause and pathogenesis of many infectious diseases, especially the ongoing COVID-19 pandemic (Genzel et al., 2020). They could also aid the development of vaccines and antivirals for human CoV disease prevention and intervention. In this review, we summarize animal models employed in studies of human CoV infection to date. We specifically address the animal models utilized in SARS-CoV, MERS-CoV and SARS-CoV-2 studies.

2. Lethal human Coronavirus infections, SARS, MERS and COVID-19

The common clinical symptoms of SARS-CoV infections include fever, unproductive cough, muscle soreness, headache, chills and dyspnea (Lee et al., 2003), with the exception of approximately 10% cases developing gastrointestinal symptoms such as diarrhea (Peiris et al., 2003b). The typical laboratory findings include lymphopenia and elevated lactate dehydrogenase (Booth et al., 2003). COVID-19 patients generally manifest fever, cough, muscle pain and fatigue, which are also accompanied by noticeable leukopenia and lymphopenia and increased level of serum aspartate amino transferase (Huang et al., 2020). A small portion of COVID-19 patients might develop severe acute respiratory distress, acute heart injury, liver injury and renal insufficiency (Huang et al., 2020; Yang et al., 2020). These patients usually have higher serum levels of pro-inflammatory cytokines including IL-1β, IL-2, IL-6, IL-7, IL-10, IL-17, GCSF, IP-10, MCP-1, MIP-1α and TNF-α, a result of severe acute immune reaction called “cytokine storms” (Cao, 2020; Huang et al., 2020; Moore and June 2020).

Angiotensin-converting enzyme 2 (ACE2) is a negative regulatory enzyme in the renin-angiotensin-aldosterone system (RAAS), functioning to lower blood pressure and maintain fluid and electrolyte balance (Bourgonje et al., 2020). It is widely expressed in tissues across the body, such as lungs, intestines, heart, eyes, brain, kidneys, and testes (Vabret et al., 2020). It has been demonstrated that SARS-CoV and SARS-CoV-2 both utilize ACE2 as their entry receptor (Kuba et al., 2005; Zhou et al., 2020). Interestingly, however, the binding affinity of SARS-CoV-2 to ACE2 via its S protein receptor-binding domain (RBD) is approximately 10–20 folds higher than that of SARS-CoV (Wrapp et al., 2020). This greatly enhances the transmission of SARS-CoV-2. Meanwhile, the ability of SARS-CoV-2 to cross the species barrier (Dhama et al., 2020) poses a much greater threat to human health. Worse, while the original COVID-19 pandemic is yet to be brought under control, various SARS-CoV-2 variants have boosted COVID-19 transmission (Campbell et al., 2021). They have not only made the COVID-19 pandemic much worse, but also threatened the efficacy of so far largely successful COVID-19 vaccines (de Vries et al., 2021). According to the new nomenclature of the World Health Organization (WHO) (2021a, https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/), clinically relevant variants of concern (VOC) include Alpha (originally termed as B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2) and Omicron (B.1.1.529) variant as well as two other variants of interest (VOI), i.e. Lambda (C.37), and Mu (B.1.621). In particular, over the past year, the SARS-CoV-2 Delta and Omicron emerged successively and became the dominant variant. The SARS-CoV-2 Delta was first identified in India in December 2020 (Kupferschmidt and Wadman, 2021), and Delta variant contains seven S protein mutations, including three mutations (T19R, G142D and R158G) in NTD, two mutations (L452R and T478K) in RBD, two mutations (D614G and P681R) near S1/S2 cleavage site (2021c, https://www.who.int/docs/default-source/coronaviruse/voc_voi_290921.pdf?sfvrsn=61b3acff_5).

The newly emerging SARS-CoV-2 Omicron variant, which was first identified in Botswana and South Africa in November 2021 (Callaway, 2021) and is designated a new VOC variant by the WHO (2021a, https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/), has seriously jeopardized the current prophylaxis and therapeutic strategies. The Omicron variant is particularly frightening since it contains 32 amino acid mutations in the S protein, making it by far the most mutated variant discovered yet. Several of these mutations are also seen in Beta and Delta variants, such as K417N, N501Y, T478K, and D614G (2021c, https://www.who.int/docs/default-source/coronaviruse/voc_voi_290921.pdf?sfvrsn=61b3acff_5). Studies have demonstrated that the SARS-CoV-2 Omicron variant is highly transmissible and induces moderate neutralizing antibody responses (Dejnirattisai et al., 2021; Zhang et al., 2021).

Patients with MERS-CoV infection develop symptoms similar to those of SARS, including early-stage fever, chills, muscle aches, diarrhea, and late-stage acute respiratory and/or renal failure (Assiri et al., 2013; Zaki et al., 2012). Hematological analysis of MERS patients revealed severe lymphopenia and markedly elevated C-reactive protein (Guery et al., 2013). Unlike SARS-CoV and SARS-CoV-2, MERS-CoV uses dipeptidyl peptidase 4 (DPP4) as its entry receptor (Raj et al., 2013). DPP4, also known as adenosine deaminase complexing protein 2 or cluster of differentiation 26 (CD26), is an ectopeptidase ubiquitously expressed on the cell surface of most tissues (Raj et al., 2013; Strollo and Pozzilli, 2020). Interestingly, while its ectopeptidase activity, degrading substrates such as incretin hormones, growth factors, and cytokines, is associated with a variety of metabolic diseases (Nargis and Chakrabarti, 2018), whether such activity is necessary for cell entry of MERS-CoV remains to be determined.

3. Animal models of SARS, MERS and COVID-19

3.1. Non-human primates

Non-human primates closely mimic humans in genetics, physiology and immunology, thereby making them the ideal animal models for human disease studies. Studies examining the susceptibility of New World and Old World monkeys including rhesus macaque, common marmoset and cynomolgus macaque to SARS-CoV, MERS-CoV and SARS-CoV-2 reported that while these species allow the replication of these viruses in their airway and lungs, their symptoms, lung pathology and immune responses vary significantly (Lu et al., 2020; Rockx et al., 2020).

3.1.1. Rhesus macaque

As we currently understand, rhesus macaques (*Macaca mulatta*) are reliable animal models in studying highly pathogenic coronaviruses due to their susceptibility to SARS-CoV, MERS-CoV and SARS-CoV-2 and intrinsic biological similarity related to humans (Pandey et al., 2021). A previous report showed that SARS-CoV could replicate in the respiratory tract of rhesus macaques, whereas the titer of correlated neutralizing antibody induced in the sera were generally low and the animals were found largely asymptomatic (McAuliffe et al., 2004). In contrast, strong inflammatory cytokine responses and severe pulmonary pathology have been observed in the SARS-CoV-2 infected rhesus macaques compared to infected cynomolgus macaques and common marmosets, indicating that rhesus macaques are more susceptible animal model for SARS-CoV-2 study (Lu et al., 2020). Collectively, interstitial pneumonia characterized by thickened alveolar walls, monocyte and lymphocyte infiltration (Koo et al., 2020; Munster et al., 2020; Shan et al., 2020), as well as virus-induced inflammatory cytokine and chemokine production could be observed in most SARS-CoV-2 infected rhesus macaques (Lu et al., 2020; Zheng et al., 2020). Moreover, lymphocytopenia associated with severe infection could also be detected in infected rhesus macaques (Koo et al., 2020; Lu et al., 2020; Zheng et al., 2020), which was similar to those reported in COVID-19 patients (Huang et al., 2020; Wang et al., 2020e; Xu et al., 2020). Importantly, the neutralizing antibodies (NAbs)

induced by the primary SARS-CoV-2 infection could effectively prevent rhesus macaques from secondary infection (Bao et al., 2020; Shan et al., 2020). Rhesus macaques are also susceptible to MERS-CoV infection as reported by de Wit and colleagues. They showed that rhesus macaques allowed widespread dissemination of MERS-CoV in their respiratory tract and developed mild to severe interstitial pneumonia as early as 3 dpi (de Wit et al., 2013b). Therefore, rhesus macaques have so far been identified as suitable animals for modeling human MERS-CoV and SARS-CoV-2 infection.

3.1.2. Common marmoset

Common marmosets (*Callithrix jacchus*), the smallest NHP in the New World, appear to be the best NHPs for modeling SARS and MERS. Common marmosets infected with SARS-CoV showed mild clinical diarrhea and dyspnea and developed interstitial pneumonitis characterized by pulmonary infiltration of mononuclear cells and multinucleated syncytial cells, edema and bronchiolitis (Greenough et al., 2005b). There was also concomitant hepatitis, mild diffuse colitis and multifocal lymphocytic myocarditis (Greenough et al., 2005b), resembling the extrapulmonary tissue inflammation commonly observed in SARS patients (Ding et al., 2003; Leung et al., 2003; Li et al., 2003). Similarly, common marmosets infected with MERS had a high viral load in their lungs and developed severe respiratory disturbances and extensive bronchial interstitial pneumonia (Falzarano et al., 2014). This is likely due to the nearly identical DPP4 between common marmoset and human, with a 100% identity of the 14 virus-contacting amino acid residues (Falzarano et al., 2014). In contrast, common marmosets are less sensitive to SARS-CoV-2 infection compared to rhesus macaques, as evidenced by lower or barely detectable viral RNA in the swab samples and tissues of infected common marmosets (Lu et al., 2020). Consistently, a study comparing rhesus macaques, baboons, and marmosets in response to acute lung infection with SARS-CoV-2 found that marmosets only showed mild infection with mild recruitment of interstitial lymphocytes and macrophages (Singh et al., 2021). These together confirm that common marmosets are suitable animal models for the pathogenesis study of SARS-CoV and MERS-CoV infection, but not so for SARS-CoV-2.

3.1.3. Cynomolgus macaque

To date, cynomolgus macaques (*Macaca fascicularis*) as an animal model are only used to study SARS-CoV and SARS-CoV-2 infection. SARS-CoV-infected cynomolgus macaques develop mild symptoms as rhesus macaques do. As previously reported, SARS-CoV-infected cynomolgus macaques displayed mild to moderate symptoms, such as reduced appetite and activity, mild cough and sneezing, and mildly labored breathing (Lawler et al., 2006; Rowe et al., 2004). Moreover, the viral RNA levels in nasal and oral swabs were low (Rowe et al., 2004). Aged cynomolgus macaques are more prone to SARS-CoV infection, as evidenced by higher viral RNA load (Rockx et al., 2011) and more severe lung pathology (Smits et al., 2010) relative to those in younger adult macaques. Similarly, interstitial pneumonia with endotheliitis accompanied by elevated inflammatory cytokines and decreased lymphocyte infiltration could be observed in both SARS-CoV-2 infected cynomolgus macaques and rhesus macaques (Koo et al., 2020). Recently, Rockx et al. detected virus replication in the respiratory tract, as well as in the ileum, colon, mesentery and tonsil (Rockx et al., 2020). More importantly, they found higher levels of viral load in the nasal swabs of aged cynomolgus macaques, in line with the clinical observation that the elderly are more susceptible to SARS-CoV-2 infection. Interestingly, however, no overt clinical signs and body weight loss were observed in any of SARS-CoV-2-infected cynomolgus macaques (Rockx et al., 2020; Salguero et al., 2021). This resembles the clinical characteristics of asymptomatic SARS-CoV-2 infections. Together, these studies support cynomolgus macaque as a suitable model for studying the pathogenesis of SARS-CoV and SARS-CoV-2 infections and as an alternative NHP model for testing drugs' and vaccines' efficacy.

3.2. Mice

Syngeneic mice are the most frequently used animals in laboratories, because they are not only cheap and easy to care for but also have identical genetic background, which leads to minimum individual differences and better reproducibility. Over the past decade, various mouse models have been developed for SARS-CoV, MERS-CoV and SARS-CoV-2 studies. Although wild-type mice could be infected by SARS-CoV, no mortality was observed in any SARS-CoV-infected wild-type mouse models, which is not conducive to the development of antiviral drugs and vaccines. Moreover, wild-type mice are not suitable for MERS-CoV or SARS-CoV-2 studies as the viral S proteins do not show sufficient tropism to mDPP4 and mACE2 (Cockrell et al., 2014; Zhou et al., 2020). Therefore, to obtain susceptible mouse models, various strategies such as developing transgenic mice (Jiang et al., 2020; McCray et al., 2007) and receptor-transduced mice (Hassan et al., 2020a; Sun et al., 2020a; Zhao et al., 2014) have been widely applied.

3.2.1. WT mice

The susceptibility of WT mice to SARS-CoV infection is age-associated. For instance, some previous reports showed that while 4- to 6-wk-old young BALB/c mice intranasally infected with SARS-CoV allowed viral replication in the respiratory tract, they did not develop symptoms or lung pathology, and the virus was cleared within a week (Subbarao et al., 2004). However, Roberts et al. showed that intranasal SARS-CoV infection caused significant weight loss, hunching, ruffled fur, slight dehydration and pulmonary inflammation in 12- to 14-month-old BALB/c mice. In addition, the virus was detected in the upper respiratory tract and even in the liver of the old BALB/c mice (Roberts et al., 2005a). Therefore, the susceptibility of WT mice to SARS-CoV infection seems to be positively correlated with age, in accordance with previous findings which demonstrated an age-related viral replication, clinical illness and pneumonia in WT BALB/c mice (Roberts et al., 2005a). This parallels human SARS-CoV infections, to which the elderly are more susceptible.

Both SARS-CoV and SARS-CoV-2 utilize ACE2 as entry receptor, however, the binding affinity of mACE2 to SARS-CoV and SARS-CoV-2 is different. An *in vitro* analysis of viral S protein-receptor binding affinity showed that the binding affinity of SARS-CoV and SAR-CoV-2 S protein to mACE2 was 63.1% and 0.8% of that to hACE2, respectively (Ren et al., 2021). This is probably due to that the sequence identity of receptor binding motif (RBM) in RBD shared by SARS-CoV and SARS-CoV-2 was only 47.8% (Yi et al., 2020). These together may explain why wild-type mice could be infected by SARS-CoV but not SARS-CoV-2 (Cockrell et al., 2014; Zhou et al., 2020). In addition, there are 9 different contact amino acid residues between mACE2 and hACE2 in the ACE2-RBD interface, among which H353 of mACE2 was not conducive to virus binding as K353 in hACE2 is critical for contacting T487 in the S protein's RBM (Li et al., 2005b). Recently, Wan et al. (2020) and Ren et al. (2021) reported that the residues K31 and K353 in hACE2 could interact with Q493 and the carboxyl oxygen of G502 within the S protein RBD of SARS-CoV-2 to form hydrogen bonds, respectively, which could stabilize hACE2 and S protein interaction. Therefore, amino acid substitution at positions 31 and 353 of the hACE2 is not conducive to the receptor binding of the virus. Subsequently, Ren et al. (2021) produced a variety of different ACE2 mutants, such as K353H, Y83F/K353H, F83Y, H353K, and F83Y/H353K. By comparing the binding between these mutants and the SARS-CoV-2 S protein, they revealed that residue H353 in mACE2 affected its binding to SARS-CoV-2 S1. Together, the presence of histidine at position 353 in mACE2 prevents SARS-CoV-2 S protein from binding to mACE2, which further explains why WT mouse model could not effectively simulate COVID-19. Cockrell et al. (2014) found that when amino acids at positions 273 to 340 in mDDP4 were replaced by amino acids at positions 279 to 346 in hDDP4, mDPP4 was endowed with the ability to support MERS infection. Moreover, they mutated five amino acids in this region

of mDPP4 into corresponding amino acids in hDPP4 to produce five mDPP4 mutants including P282 T, A288L, R289I, T330R, and V340I. By introducing A288L and T330R mutants, they demonstrated that mutated mDPP4 could be adapted to support MERS-CoV infection, suggesting that the difference between mDPP4 and hDPP4 at residue A288L and T330R is the reason why mDPP4 does not support MERS-CoV infection.

3.2.2. Mouse-adapted virus strains

One practical approach to overcome weak entry receptor tropism is to use mouse-adapted virus strains. For instance, Gu et al. (2020b) reported that a SARS-CoV-2 mouse-adapted strain specifically named MASCp6 could productively replicate in the lower respiratory tract of WT BALB/c mice, which subsequently developed severe interstitial pneumonia. They further showed that it was Asn501 to Tyr (N501Y) one critical amino acid change that potentially associated with the increased virulence of SARS-CoV-2 MASCp6 in mice (Gu et al., 2020b). Different from the former method of obtaining adapted strain through the continuous nasal passage in 9-month-old BALB/c mice, Wang et al. (2020c) obtained an adapted SARS-CoV-2 strain named HRB26M through 14 passagings in 4–6-week-old young BALB/C mice. HRB26M replicates efficiently in the upper and lower respiratory tracts of BALB/c and C57BL/6J mice and causes severe pathological changes in old BALB/c mice. Whole HRB26M genome sequencing revealed Q498H mutation in the S protein's RBD and A81T mutation in its ORF1ab-non-structural protein 8 (nsp8). These mutations might be associated with the enhanced virus binding and replication (Wang et al., 2020c). Taken together, using mouse-adapted SARS-CoV-2 strains could potentially overcome weak host receptor tropism to yield useful information. Importantly, great caution should be taken to make sure such strains are less virulent than its wild isolate.

3.2.3. hDPP4- and hACE2-transduced mice

Mice transduced to express hDPP4 or hACE2 have been key animal models for studying SARS-CoV, MERS-CoV or SARS-CoV-2 infections. Simply expressing hACE2 or hDPP4 renders mice susceptible to the relevant CoV and the infected mice reproduce the relevant symptoms and pathology observed in the infected patients. For example, C57BL/6 and BALB/c mice transduced by adenovirus encoding hDPP4 became permissive for MERS-CoV infection (Zhao et al., 2014). These mice developed perivascular and peribronchial lymphoid infiltrates in the lungs early after infection and subsequently interstitial pneumonia. Using the same approach, Sun et al. recently generated hACE2-transduced mice to investigate the pathogenesis of SARS-CoV-2 infection (Sun et al., 2020a). As expected, the Ad5-hACE2-transduced mice showed productive viral replication in their lungs and developed severe pulmonary pathology, with a concomitant ruffled fur, hunched back and dyspnea at 2 dpi and approximately 20% weight loss at 4–6 dpi. Further, these studies both demonstrated that knocking out interferon-α/β receptor (IFNAR) and signal transducer and activator of transcription 1 (STAT1) in type-I IFN signaling pathway resulted in more severe disease and pulmonary pathology in these infected hACE2-transduced mice (Sun et al., 2020a; Zhao et al., 2014). Similarly, Hassan et al. observed more severe pathological characteristics in SARS-CoV-2 infected AdV-hACE2 transduced mice with immunosuppression (Hassan et al., 2020a). Taken together, hACE2-transduced mice with immunodeficiency were able to reproduce more severe pathogenesis of SARS-CoV-2, which could be used to study the mechanisms associated with severe pathogenesis in immunodeficient patients.

3.2.4. Transgenic and receptor-engineered mice

To date, various transgenic mice have been developed to study SARS-CoV, MERS-CoV and SARS-CoV-2 pathogenesis and the development of vaccines and specific therapeutics. McCray and the team cloned hDPP4 and hACE2 under cytokeratin-18 gene promoter and generated K18-hDPP4 and K18-hACE2 transgenic mice on a C57BL/6 background, which lead to epithelial expression of the transgenes (Li et al., 2016; McCray et al., 2007). Interestingly, the SARS-CoV-infected K18-hACE2 mice developed severe clinical illness including significant weight loss, lethargy, labored breathing and died by 7 dpi (McCray et al., 2007). Similarly, after intranasal MERS-CoV infection, K18-hDPP4 mice showed significant weight loss, hypothermia and died 6–7 days after infection (Li et al., 2016). Surprisingly, the animals also showed central nervous system damage and kidney damage at the later stage of the infection (Li et al., 2016), the typical clinical manifestations observed in some severely ill patients (Arabi et al., 2015; Zaki et al., 2012). This mouse model was later used in the study of SARS-CoV-2 infection, in which the authors demonstrated that K18-hACE2 mice were highly susceptible to SARS-CoV-2 infection, characterized by a rapid weight loss, high viral load and proinflammatory cytokine levels and massive immune cell infiltration in the lungs (Winkler et al., 2020). Likewise, Menachery et al. cloned hACE2 under a lung ciliated epithelial cell-specific HFH4/FOXJ1 promoter and generated HFH4/FOXJ-HACE2 transgenic mice on a C3H × C57BL/6 background that were susceptible to SARS-CoV and SARS-CoV-2 infections (Jiang et al., 2020; Menachery et al., 2016). Particularly after SARS-CoV-2 infection, the HFH4/FOXJ-HACE2 mice appeared to reproduce interstitial pneumonia and pathology observed in COVID-19 patients, including significant weight loss, lymphocytopenia and higher creatine kinase levels (Jiang et al., 2020). Researchers also made susceptible mice through editing their viral entry receptor gene using the CRISPR/Cas9 system. For example, Cockrell et al. replaced two amino acids of mDPP4 at positions 288 (A→L; exon 10, 5 → 3) and 330 (T→R; exon 11, 5 → 3) from the hDPP4 and the engineered C57BL/6 mice supported effective MERS-CoV infection and replication in the lungs, and more importantly, the infected mice developed severe acute respiratory distress syndrome (ARDS)-like symptoms (Cockrell et al., 2016). Likewise, via replacing mACE2 with hACE2 in WT C57BL/6 mice using CRISPR/Cas9 knock-in technology, Sun et al. generated a stable hACE2-expressing mouse model to investigate SARS-CoV-2 infection. In this study, both infected young and aged hACE2-knock-in mice had high viral load in their trachea, lungs and brains, and the aged mice also developed interstitial pneumonia (Sun et al., 2020b). Taken together, once mice express a hDPP4 or hACE2 or a genetically engineered mDPP4 or mACE2 that supports the relevant CoV entry, they can be very useful models as researchers are able to reproduce most of the clinical outcomes observed in patients.

3.3. Syrian hamster (Mesocricetus auratus)

Unlike mACE2 that has 9 contact amino acid residues different from those of hACE2, there are only 2 different contact residues between hamster ACE2 and hACE2 in the ACE2-RBD interface. More importantly, the amino acid residue at position 353 in hamster ACE2 is a lysine, same as that in hACE2, which might be the major reason why hamsters are more susceptible to SARS-CoV and SARS-CoV-2 than mice (Sutton and Subbarao, 2015). Both SARS-CoV and SARS-CoV-2 could replicate to a high titer in the hamster's respiratory tracts and lungs, whereas the replication of MERS-CoV was not supported (Chan et al., 2020; de Wit et al., 2013a; Roberts et al., 2005b; Sia et al., 2020). Roberts et al. reported that viral titer peaked at 3 dpi in the lungs in SARS-CoV-infected hamsters, and the viruses were continuously detected in the upper and lower respiratory tracts and were not cleared until day 7 (Roberts et al., 2005b). The authors indicated that this represented a more efficient viral replication with longer-duration in comparison with the data they obtained from SARS-CoV-infected WT mice, in which the viral titer was lower by 1.2 log at 3 dpi and the viruses were cleared as early as 5 dpi. Additionally, they found that the serum neutralizing antibodies produced during primary infection were still detectable at 28 dpi and completely protected the hamsters from secondary SARS-CoV challenge. However, in this study the infected hamsters showed no signs of illness (Roberts et al., 2005b). Some studies demonstrated that SARS-CoV-2 could infect and replicate in hamsters and cause clinical

manifestations of weight loss, rapid breathing, ruffled fur, hunched back, lethargy and significant lung tissue damage (Chan et al., 2020; Rosenke et al., 2020; Sia et al., 2020). Similar clinical symptoms were also observed in SARS-CoV-2 Alpha challenged hamsters (Nuñez et al., 2021). In addition, virus transmission from infected to naïve hamsters were demonstrated via both direct contact and indirect aerosol routes. Further, all infected hamsters recovered by 14 days post challenge, with serum neutralizing antibodies developed and maintained at a detectable level (Chan et al., 2020; Rosenke et al., 2020; Sia et al., 2020). Similar findings were reported by Imai and colleagues (Imai et al., 2020). Of note, this study also showed that passive transfer of convalescent serum from infected to naïve hamsters restrained viral replication in the lungs, suggesting inhibitory effects of the serum neutralizing antibodies. Syrian hamsters are one of the most useful animals for studying gender differences in COVID-19. In a study by Dhakal et al., male hamsters showed a higher incidence of SARS-CoV-2 infection, and the infected male hamsters displayed more weight loss and more severe lung damage compared to female hamsters (Dhakal et al., 2021). Yuan and colleagues reported similar results, noting that male hamsters were more susceptible to SARS-CoV-2 than females (Yuan et al., 2021a). These results are significant and should be of concern as there is much clinical evidence that men are more susceptible to COVID-19 than women (Gebhard et al., 2020; Peckham et al., 2020). In recent studies, SARS-CoV-2 Omicron caused less lung infectivity and pathogenicity in hamsters than Delta and B.1.1 did (Suzuki et al., 2022), which is consistent with what has been observed with human patients (Jung et al., 2022). Taken together, most reported studies support hamsters as potential model animals for CoV-, especially SARS-CoV-2-related studies.

3.4. Ferret

The fact that ferret lung is anatomically and physiologically similar to human lung makes ferrets a popular model for studying various respiratory pathogens, including influenza virus, respiratory syncytial virus, adenovirus and coronavirus (Enkirch and von Messling, 2015). Ferrets support the replication of SARS-CoV and SARS-CoV-2 but not MERS-CoV (Raj et al., 2014b; Shi et al., 2020a; van den Brand et al., 2008), likely due to the 9 amino acid variations in the S protein interaction region of the ferret DPP4 compared to hDPP4 (van Doremalen et al., 2014). Following SARS-CoV infection, viruses were detected in the lungs of the ferrets, accompanied by obvious lung tissue damage, and the animals were lethargic. However, no other clinical symptoms, such as weight loss, were observed (van den Brand et al., 2008). Similarly, weight loss and death were not observed in SARS-CoV-2 infected ferrets (Kim et al., 2020; Kutter et al., 2021; Marsh et al., 2021b; Monchatre-Leroy et al., 2021). Nevertheless, ferret models are still of great interest for studying SARS-CoV-2 as it can be transmitted via both direct contact and aerosol in these infected hosts, which mimics COVID-19 in humans (Kim et al., 2020; Kutter et al., 2021; Richard et al., 2020). For example, whether infected by high dose of SARS-CoV-2 UCN19 (Monchatre-Leroy et al., 2021) or low doses of SARS-CoV-2 CoV/Munich/BavPat/2020 (Kutter et al., 2021), no obvious clinical symptoms could be observed in the infected ferrets. Interestingly, ferrets in the direct contact group were infected 1–3 days post-exposure after being contacted with the inoculated donor group while those in the indirect contact group, placed in adjacent cages, only became infected between 3 and 7 days post-exposure. In addition, the pattern of virus shedding, and the level of SARS-CoV-2 RNA were similar among the groups, which further confirmed that SARS-CoV-2 could be transmitted through direct contact and aerosol in ferrets (Richard et al., 2020). Bear in mind, animals in their direct contact group could also potentially be infected through aerosol. Taken together, ferrets are more suitable for simulating the rapid spread of SARS-CoV and SARS-CoV-2 in humans than for pathogenesis in severe patients (Johansen et al., 2020).

In summary, wild bat might be the potential natural host, while NHP, mouse, hamster, civet, pangolin, ferret and camel could all potentially serve as the intermediate hosts as shown in Fig. 1. The use of these animals as experimental models may support the study of SARS-CoV, MERS-CoV and SARS-CoV-2 pathogenesis and the development of vaccines and specific therapeutics.

4. The application of animal models in therapeutic and vaccine evaluation

Animal models are primarily used to investigate disease pathogenesis and evaluate therapeutic and vaccine effectiveness. Here, we show natural and intermediate hosts of SARS-CoV, MERS-CoV, and SARS-CoV-2 in Fig. 1. Importantly, animal models used for therapeutic and vaccine evaluation should ideally reveal the different therapeutic outcomes, antibody levels and protective effects against disease challenge between treated and untreated groups (Gretebeck and Subbarao, 2015).

4.1. Therapeutic and vaccine for SARS and MERS

To date, various animal models have been applied to evaluate therapeutics and vaccines against SARS and MERS (Tables 1 and 2). To cope with the threat of SARS, several vaccines including adenovirus vector vaccines (Gao et al., 2003; Kobinger et al., 2007) (targeting SARS-CoV S protein's S1 subunit), inactivated vaccines (the whole SARS-CoV) (Qin et al., 2006), recombinant MAV vector vaccine (S protein) (Bisht et al., 2004; Chen et al., 2005; Weingartl et al., 2004), subunit vaccine (N-terminal segment of the S protein) (Bisht et al., 2005), DNA vaccine (S protein) (Yang et al., 2004) and recombinant BHPIV3/SARS vector vaccine (S protein) (Buchholz et al., 2004) were developed using animal models such as rhesus macaques, cynomolgus macaques, mice, ferrets and hamsters. Animal models such as rhesus macaques, mice, ferrets and hamsters were also used to verify the effects of siRNA inhibitors (Li et al., 2005a), stinging nettle lectin (Kumaki et al., 2011), interferon-α (Barnard et al., 2006) and two monoclonal antibodies (MAb201 (Greenough et al., 2005a; Roberts et al., 2006) and CR3014 (ter Meulen et al., 2004)), confirming their inhibitory effects against SARS-CoV infection.

Unlike SARS-CoV, MERS-CoV cannot infect small animals such as WT mice, ferrets and hamsters. Currently, the main animal models used for MERS vaccine development and evaluation include transgenic mice, and NHPs. Accordingly, transgenic mouse models have been used to assess vaccines such as recombinant Measles Virus vector vaccine (targeting MERS-CoV S protein) (Malczyk et al., 2015), DNA vaccine (S protein) (Muthumani et al., 2015), recombinant MVA-MERS-S vaccine (S protein) (Volz et al., 2015), recombinant bivalent (MERS-CoV and Rabies Virus) vaccine (S protein S1 subunit) (Kato et al., 2019) and subunit vaccine (composed of 212-amino-acid fragment spanning residues 377–588 of the S protein) (Du et al., 2013). Other vaccines including recombinant VSV vector vaccines (S protein) (Liu et al., 2018), recombinant S protein RBD vaccines (composed of 240-amino-acid fragment spanning residues 367–606) (Lan et al., 2015) and ChAdOx1 MERS vaccines (S protein) (van Doremalen et al., 2020a) were developed using rhesus macaques, among which DNA vaccines have been proven protective (Muthumani et al., 2015). Using rhesus macaques, researchers demonstrated the therapeutic effects of a combination treatment of IFN-α2b and ribavirin, inhibiting viral replication and improving clinical outcomes (Falzarano et al., 2013). Monoclonal antibodies (MCA1 (Chen et al., 2017), hMS-1 (Qiu et al., 2016) and 4C2h (Li et al., 2015) and polyclonal antibody (SAB-301 (Luke et al., 2016)) specific for the S protein were evaluated and shown effective in common marmoset, CAG-hDPP4 transgenic mouse model and Ad5-hDPP4-transduced mouse model. In marmosets, lopinavir/ritonavir or interferon-β1b alone or in combination was demonstrated to effectively reduce virus titer and limit infection-induced pathology (Chan et al., 2015). In Ces1c$^{-/-}$ hDPP4 transgenic mice, remdesivir was evaluated and shown to significantly reduce MERS titer and lung pathology (Sheahan et al., 2020).

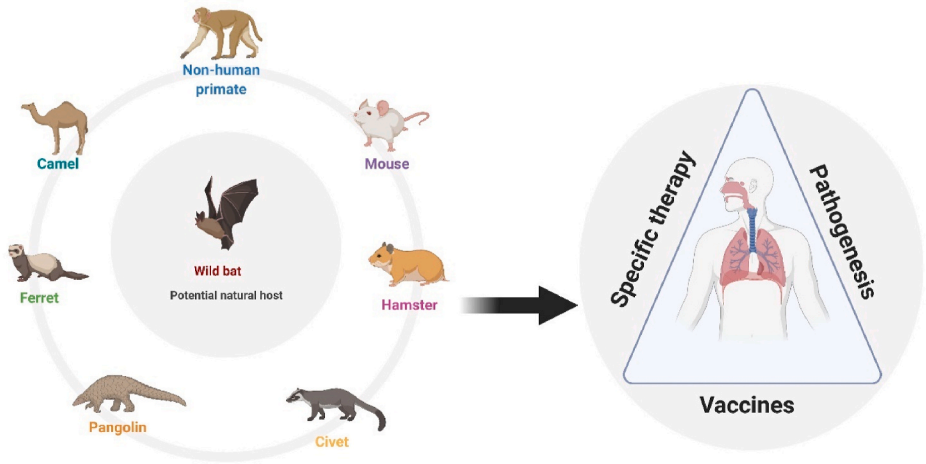

Fig. 1. The potential natural and intermediate hosts of SARS-CoV, MERS-CoV and SARS-CoV-2. The inner and outer circles on the left outline the potential natural and intermediate hosts of SARS-CoV, MERS-CoV, and SARS-CoV-2.

Table 1
Animal models used in SARS-specific therapy and vaccine evaluation.

Animal models						
SARS-CoV Intervention	Non-human primates			Mouse	Ferret	Hamster
	Rhesus macaque	Common marmoset	Cynomolgus macaque			
Neutralizing antibody	ND	ND	ND	Monoclonal antibody 201 (Greenough et al., 2005a)	CR3014 monoclonal antibody (ter Meulen et al., 2004)	Monoclonal antibody 201 (Roberts et al., 2006)
Medicine	siRNA Inhibitor (Li et al., 2005a)	ND	ND	IFN-α (Barnard et al., 2006); Stinging nettle lectin (Kumaki et al., 2011);	ND	ND
Vaccine	Adenovirus vector vaccine (targeting SARS-CoV S protein S1 subunit) (Gao et al., 2003); Inactivated vaccine (targeting the whole SARS-CoV) (Qin et al., 2006); ADS-MAV vector vaccine[a] (Chen et al., 2005)	ND	Inactivated vaccine (targeting SARS-CoV S protein S1 subunit) (Qin et al., 2006)	MVA/S vector vaccine[a] (Bisht et al., 2004); DNA vaccine[a] (Yang et al., 2004); Subunit vaccine (targeting N-terminal segment of the SARS-CoV S protein) (Bisht et al., 2005)	MAV/S vector vaccine[a] (Weingartl et al., 2004); Adenovirus vector vaccine (targeting SARS-CoV S protein S1 subunit) (Kobinger et al., 2007)	Recombinant BHPIV3/ SARS vector vaccine[a] (Buchholz et al., 2004)

ND: Not Determined.
[a] Targeting SARS-CoV S protein.

4.2. Therapeutic and vaccine for COVID-19

SARS and MERS outbreaks and their relevant studies provided lessons that enable us to respond promptly and effectively to the new pandemic COVID-19. In Fig. 2, we summarize the order in which several animal models have been developed and used for drug and vaccine evaluation since the outbreak of COVID-19, based on the times of online literature reports. Furthermore, we have collected studies utilizing animal models in the evaluation of most relevant medicines, monoclonal antibodies, and vaccinations. Of note, multiple animals such as rhesus macaques, cynomolgus macaques, mice, ferrets, and hamsters have been utilized in these studies (Table 3). To date, totally 559 vaccine studies and 2011 therapy studies including 1916 drug and 95 monoclonal antibody studies for combating COVID-19 were listed on the *ClinicalTrials.gov* site. Among these, 131 vaccines, 648 drugs, and 21 monoclonal antibodies have entered phase III clinical trials (2021b, https://clinicaltrials.gov/ct2/covid_view). Nowadays, there are currently 10 COVID-19 vaccines on WHO's emergency use list (2022b, https://extranet.who.int/pqweb/vaccines/vaccinescovid-19-vaccine-eul-issued), as well as four medications and five monoclonal antibodies licensed by the Food and Drug Administration (FDA) for emergency use authorizations (2022c, https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs), but not all vaccines and therapies have been studied in animal models (Table 4). Here, we focus on describing some representative vaccines and specific therapy studies based on animal models.

4.2.1. Therapeutic medicine

Therapeutic medications are vital in epidemic prevention and control as well as in treating patients. To date, paxlovid, molnupiravir, remdesivir, and baracitinib have been licensed by the FDA to treat COVID-19 patients (2022c, https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs). Viruses invade host cells and cause diseases, which is essentially a race between viruses and the

Table 2
Animal models used in MERS-specific therapy and vaccine evaluation.

MERS-CoV Intervention	Animal models					
	Non-human primates			Mouse	Ferret	Hamster
	Rhesus macaque	Common marmoset	Cynomolgus macaque			
Neutralizing antibody	ND	MCA1 monoclonal antibody (Chen et al., 2017)	ND	hMS-1 monoclonal antibody (Qiu et al., 2016); 4C2h monoclonal antibody (Li et al., 2015); SAB-301 polyclonal antibody (Luke et al., 2016)	ND	ND
Medicine	Combination of IFN-α2b and ribavirin (Falzarano et al., 2013)	Lopinavir/Ritonavir and interferon-β1b (Chan et al., 2015)	ND	Remdesivir (Sheahan et al., 2020)	ND	ND
Vaccine	Recombinant VSV vector vaccine[a] (Liu et al., 2018); DNA vaccine[a] (Muthumani et al., 2015); Recombinant RBD vaccine (composed of 240-amino-acid fragment spanning residues 367–606) (Lan et al., 2015); ChAdOx1 MERS vaccine[a] (van Doremalen et al., 2020a)	ND	ND	Recombinant MV vector vaccine[a] (Malczyk et al., 2015); DNA vaccine[a] (Muthumani et al., 2015); MVA-MERS-S vector vaccine[a] (Volz et al., 2015); Recombinant bivalent vaccine (Kato et al., 2019) (targeting S protein S1 subunit); Subunit vaccine (Du et al., 2013) (composed of 212-amino-acid fragment spanning residues 377-58)	ND	ND

ND: Not Determined.
[a] Targeting MERS-CoV S protein.

infected host. From this perspective, antiviral drug development strategies can be roughly divided into two types, targeting viruses themselves and targeting host cell factors.

The viral proteases of SARS-CoV-2, including 3C-like protease (3CLpro), RNA-dependent RNA polymerase (RdRp), and papain-like protease (PLpro), play crucial roles in viral replication and have been proven to be important targets for the development of drugs against SARS-CoV-2 (Báez-Santos et al., 2015; Ullrich and Nitsche, 2020; Zhu et al., 2020). Some drugs targeting SARS-CoV-2 virus proteases have shown good clinical effects. Molnupiravir (MK-4482/EIDD-2801) targeting SARS-CoV-2 RdRp was shown to reduce the risk of hospitalization or death in non-hospitalized adult patients by approximately 50% (Mahase, 2021a). Paxlovid targeting SARS-CoV-2 3CLpro significantly reduced hospitalizations and mortality in severe COVID-19 patients, with an 89% reduction in mortality compared to that of the placebo (Mahase, 2021b). Remdesivir targeting SARS-CoV-2 RdRp significantly reduced the time to recovery relative to control (Beigel et al., 2020). Here, we primarily focus on the effectiveness of these three drugs on SARS-CoV-2 in animal models. Cox et al. showed that molnupiravir could significantly lower viral load in the upper respiratory tract of SARS-CoV-2-infected ferrets and completely blocked viral transmission to the untreated animals (Cox et al., 2021b). Additionally, molnupiravir significantly reduced viral RNA load and titer in the lung of hamsters infected with the SARS-CoV-2 B.1-G, Alpha, and Beta variants (Abdelnabi et al., 2021a). Paxlovid is a combination of PF-07321332 (nirmatrelvir) and ritonavir. The former is an inhibitor of SARS-CoV-2 3CLpro, while the latter is an inhibitor of CYP3A4 isoenzyme, which contributes to the enhancement of PF-07321332 (Heskin et al., 2022). PF-07321332 was effective in reducing pulmonary lesions and viral load in mouse models using the adaptive SARS-CoV-2 MA10 strain (Owen et al., 2021). A recent study showed that PF-07321332 could effectively inhibit SARS-CoV-2 variant replication including Alpha, Beta, B.1.1.28.1, and Delta, with EC_{50} values ranging from 70 to 280 nM. Furthermore, oral administration of PF-07321332 (250 mg·kg−1·d−1) twice daily protected Syrian hamsters against SARS-CoV-2 Delta and Beta variants and blocked transmission of Delta variant to untreated hamsters (Abdelnabi et al., 2022). Unlike molnupiravir and paxlovid, remdesivir is administered intravenously and was the first drug to be approved for the treatment of COVID-19 patients. Remdesivir might play an important role in early viral replication to reduce disease progression (Lin et al., 2021). As reported, rhesus macaques were used to evaluate the efficacy of remdesivir and the results showed that treatment with remdesivir early after SARS-CoV-2 infection was associated with reduced virus replication and immune infiltration in the lungs (Williamson et al., 2020). Although remdesivir had shown promising therapeutic effects *in vitro* and in animal studies, its effectiveness in clinical studies remains controversial. A randomized, double-blind clinical study indicated that remdesivir did not effectively reduce mortality in severe COVID-19 patients (Wang et al., 2020f). Sun et al. showed that remdesivir had low tissue distribution and permeability in vivo, so the concentration of remdesivir necessary to kill SARS-CoV-2 virus in the lung tissue could not be reached via intravenous injection, therefore, a combination of intravenous and pulmonary administration was recommended to improve its efficacy (Sun, 2020). Remdesivir cannot be administered orally because it is hydrolyzed in the gastrointestinal tract to nucleoside monophosphate, which cannot easily cross cell membranes due to its negatively charge (Sun, 2020). Notably, oral administration of remdesivir parent GS-441524 was demonstrated to inhibit SARS-CoV-2 replication and its spread in ferrets (Cox et al., 2021a). Furthermore, GS-441524 effectively inhibited SARS-CoV-2 replication and reduced lung inflammation and injury in AAV-hACE2 mice when administrated intraperitoneally (Li et al., 2022b).

Viruses are intracellular obligate parasites, and their replication relied on a variety of host proteins. Due to the high variability of SARS-CoV-2, drugs targeting the virus itself might fail when crucial variation occurs at the target site. Another important strategy for developing drugs against SARS-CoV-2 infection is to target host factors that, often possess broad-spectrum antiviral activity, which breaks free from the variability of SARS-CoV-2 (Kausar et al., 2021). SARS-CoV-2 requires host-derived Transmembrane protease serine 2 (TMPRSS2) for membrane fusion with host cells. Hence, drugs that inhibit TMPRSS2, such as camostat mesylate, can effectively block the entry of SARS-CoV-2 and its replication in the lung cells (Hoffmann et al., 2020). Further, it was used to treat severe COVID-19 patients (Sakr et al., 2021). Li et al. show that another TMPRSS2 protease inhibitor, nafamostat, effectively inhibited the replication of SARS-CoV-2 in Calu-3 and primary human airway

Table 3
Animal models used in COVID-19 therapeutic and vaccine evaluation.

SARS-CoV-2 Intervention	Animal models					
	Non-human primates			Mouse	Ferret	Hamster
	Rhesus macaque	Common marmoset	Cynomolgus macaque			
Neutralizing antibody	CB6 (Shi et al., 2020b); CT-P59 (Kim et al., 2021); MW05/LALA (Wang et al., 2020d); REGN-COV2 (Baum et al., 2020); LY-CoV555 (bamlanivimab) (Jones et al., 2021); COV2-2196-COV2-2130 (Zost et al., 2020); C135-LS and C144-LS (Van Rompay et al., 2021)	ND	COVA1-18 (Maisonnasse et al., 2021)	BD-368-2 (Cao et al., 2020); ab1 (Li et al., 2020a); CA521^{FALA} (Song et al., 2021); STE90-C11 (Bertoglio et al., 2021); nCoVmab1 (Zhao et al., 2021); h11B11 (Du et al., 2021); SARS2-38 (VanBlargan et al., 2021); 58G6 and 510A5 (Li et al., 2021c); 2B11 (Pan et al., 2021); 3E8 (Chen et al., 2021); COVA1-18 (Maisonnasse et al., 2021); XAV-19 (Vanhove et al., 2021)	CT-P59 (Ryu et al., 2021)	VH -Fc ab8 (Li et al., 2020b); BD-368-2 (Du et al., 2020); CV07-209 (Kreye et al., 2020); hu-mAbs (Schäfer et al., 2021); HuNAb (Zhou et al., 2021); STE90-C11 (Bertoglio et al., 2021); COVA1-18 (Maisonnasse et al., 2021); REGN-COV2 (Baum et al., 2020)
Medicine	Remdesivir (Williamson et al., 2020); n(CAT) (Qin et al., 2020); SSK1 (Lu et al., 2021b); Baricitinib (Hoang et al., 2021)	ND	ND	GS441524 + GC376 (Shi et al., 2021); Dalbavancin (Wang et al., 2021a); Paquinimod (Guo et al., 2021); 25-Hydroxycholestero (Zu et al., 2020); Protoporphyrin IX and verteporfin (Gu et al., 2020a); Remdesivir (Sun et al., 2020a)	TLR2/6 agonist (Proud et al., 2021); Molnupiravir (Cox et al., 2021b)	Combinational methylprednisolone and remdesivir (Ye et al., 2021); Cas13a (Blanchard et al., 2021); Ranitidine bismuth citrate (Yuan et al., 2020); Favipiravir (Kaptein et al., 2020); PBI-06150 (Plante et al., 2021); Clofazimine (Yuan et al., 2021c); ALG-097111 (Vandyck et al., 2021); TOP1 (Ho et al., 2021); Molnupiravir (Abdelnabi et al., 2021a, 2021b; Rosenke et al., 2021)
Vaccine	Adenovirus vector vaccine: ChAdOx1 nCoV-19/AZD1222 (Lambe et al., 2021; van Doremalen et al., 2020b, 2021); Ad26.COV2.S (He et al., 2021; Mercado et al., 2020; Roozendaal et al., 2021; Solforosi et al., 2021; Yu et al., 2021); Ad5-S-nb2 (Feng et al., 2020)	ND	ND	Adenovirus vector vaccine: ChAd-SARS-CoV-2-S (Hassan et al., 2020b); Ad5-nCoV (Wu et al., 2020b)	Adenovirus vector vaccine: Ad5-nCoV (Wu et al., 2020b); ChAdOx1 nCoV-19/AZD1222 (Lambe et al., 2021; Marsh et al., 2021a)	Adenovirus vector vaccine: Ad26.COV2.S (Tostanoski et al., 2020, 2021; van der Lubbe et al., 2021); ChAdOx1 nCoV-19/AZD1222 (Fischer et al., 2021b; van Doremalen et al., 2021)
	Inactivated vaccine: BBIBP-CorV (Wang et al., 2020b); BBV152 (Yadav et al., 2021); PiCoVacc (Gao et al., 2020);	ND	ND	Inactivated vaccine: PiCoVacc (Bao et al., 2021)	ND	Inactivated vaccine: BBV152A (Mohandas et al., 2021); NRC-VACC-01 (Kandeil et al., 2021)
	mRNA vaccine: mRNA-1273 (Corbett et al., 2020, 2021a, 2021b, 2021c); BNT162b (Vogel et al., 2021)	ND	mRNA vaccine: ARCoV (Zhang et al., 2020a)	mRNA vaccine: ARCoV (Zhang et al., 2020a); BNT162b (Ji et al., 2021); mRNA-1273 (DiPiazza et al., 2021)	ND	mRNA vaccine: mRNA-1273 (Meyer et al., 2021)
	DNA vaccine (Li et al., 2021d; Yu et al., 2020)	ND	ND	ND	ND	DNA vaccine: nCoV-S(JET) (Brocato et al., 2021)
	Virus vector vaccine:MVA/S (Routhu et al., 2021)	ND	Virus vector vaccine: YF-SO (Sanchez-Felipe et al., 2021)	Virus vector vaccine: MVA (Liu et al., 2021); VSV-eGFP (Case et al., 2020); NDV-S (Sun et al., 2020c)	ND	Virus vector vaccine: VSV-G-S protein (Yahalom-Ronen et al., 2020); rMeV-preS (Lu et al., 2021a); CORAVAX (Kurup et al., 2021);
	Subunit vaccine (Liang et al., 2021)	ND	Subunit vaccine: NVX-CoV2373 (Guebre-Xabier et al., 2020)	Subunit vaccine: NVX-CoV2373 (Tian et al., 2021)	ND	ND
	Nanoparticle vaccine (Ma et al., 2020)	ND	Nanoparticle vaccine: SARS-CoV-2 S–I53–50NP (Brouwer et al., 2021)	ND	ND	ND

ND: Not Determined.

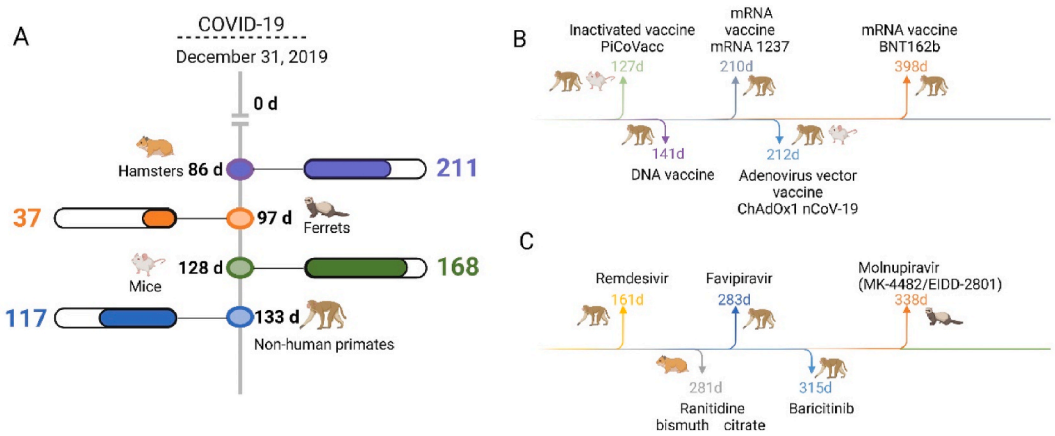

Fig. 2. A schematic summary of the timeline in which several animal models were developed and used for drug and vaccine evaluation since the outbreak of COVID-19, based on the online times published in literatures. As shown in (A), since the outbreak of COVID-19 on December 31, 2019, research based on hamster model appeared 86 days after the outbreak. To date, there are 211 reports using the hamster model to study the pathogenesis and evaluate therapeutics and vaccines against COVID-19. Similarly, we summarize the development timeline and application progress in ferrets, mice, and NHPs. (B) We summarize the timeline and reports for various vaccines in animal models, including inactivated vaccines, DNA vaccines, mRNA vaccines and adenovirus vector-based vaccines. (C) Similarly, the timeline and reports for various drugs evaluated in animal models, including remdesivir, ranitidine bismuth citrate, favipiravir, baricitinib and molnupiravir (MK-4482/EIDD-2801).

epithelial cells, and was more effective than camostat mesylate. Furthermore, in Ad5-hACE2-transduced mouse and K18-hACE2 mouse, they demonstrated that prophylactic administration of nafamostat significantly reduced weight loss and pulmonary viral titers induced by SARS-CoV-2 (Li et al., 2021b). The excessive inflammatory cytokine storm caused by SARS-CoV-2 infection is one of the important factors causing death in severe COVID-19 patients (Ye et al., 2020), therefore, reducing inflammation seems to be one of the effective ways to treat COVID-19-induced pneumonia. Both the β-galactosidase (β-gal)-activated prodrug SSK1 (Lu et al., 2021b) and JAK1/JAK2 inhibitor baricitinib (Hoang et al., 2021), were reported to dampen inflammation response and showed protective effects in SARS-CoV-2 infection rhesus macaques.

Compared to monotherapy, drug combinations improve therapeutic effects, reduce drug's adverse reactions, and minimize drug resistance (van Hasselt and Iyengar, 2019; White et al., 2021). White et al. proposed drug combinations as the first line of defense against pandemics (White et al., 2021). Although numerous drug combinations are currently in the clinical trial, extensive preclinical studies are lacking (Bobrowski et al., 2021). Only some drug combinations have been validated in animal models. For instance, Yuan et al. showed that the anti-leprosy drug clofazimine inhibited SARS-CoV-2 by interfering with S protein-mediated membrane fusion and viral helicase activity. In addition, clofazimine and remdesivir showed synergistic antiviral effects in hamster (Yuan et al., 2021b). As a result, remdesivir dosage was reduced 10-fold and clofazimine dosage was reduced 1.6-fold. Furthermore, the drug combinations effectively inhibited viral shedding in the nasal wash, which could not be achieved with remdesivir or clofazimine alone (Yuan et al., 2021b). Combining anti-inflammatory methylprednisolone with remdesivir was more effective in inhibiting viral replication, reducing inflammation and tissue damage in SARS-CoV-2-infected hamsters compared with single administration (Ye et al., 2021). Combining drugs targeting different viral proteases, such as molnupiravir and PF-07321332, was shown to be synergistic in inhibiting SARS-CoV-2 Omicron variant infection in Calu-3 cells (Li et al., 2022a; White et al., 2021); however, the effectiveness of this combination needs to be further investigated in animal models and clinical trials.

4.2.2. *Monoclonal antibody*

Monoclonal antibodies have become an important tool in the fight against COVID-19 due to their high specificity (Hwang et al., 2022). Both pre- and post-treatment with a monoclonal antibody, named as CB6, isolated from a convalescing COVID-19 patient were shown to effectively inhibit SARS-CoV-2 infection in rhesus macaques. In *vitro* experiments further demonstrated that CB6 acted by interfering virus-ACE2 interactions (Shi et al., 2020b). More interestingly, Li and the team built VEEV-VRP-CB6, a vehicle for delivering CB6 monoclonal antibody to the lung, and demonstrated that it could effectively prevent BALB/c mice infected with mouse-adapted SARS-CoV-2 strain (MP7) body weight loss and reduce viral titer in the lung and nasal turbinate (Li et al., 2021a). Such evidence supports the use of monoclonal antibody against COVID-19. In Ad5-hACE2-transduced mouse model, pre-treatment with an anti-SARS-CoV-2 mAb 1B07, which recognizes SARS-CoV-2 S protein RBD, was shown to effectively block SARS-CoV-2 infection, prevent body weight loss, and inhibit the production of several pro-inflammatory cytokines and chemokines (Hassan et al., 2020a). Similarly, another monoclonal antibody against S protein RBD, COVA1-18, was demonstrated recently to significantly reduce SARS-CoV-2 infections in three animal models, including hamsters, Ad5-hACE2 transduced mice, and cynomolgus macaques (Maisonnasse et al., 2021).

When compared to single monoclonal antibody therapy, therapeutic cocktail antibodies, a combination of many monoclonal antibodies with different fine specificities, showed increased efficacy against SARS-CoV-2 variants (Ning et al., 2021). So far, FDA has approved several therapeutic cocktail antibodies, including REGEN-COV (Casirivimab and Imdevimab), Evusheld/AZD7442 (tixagevimab co-packaged with cilgavimab) and a combination of bamlanivimab (LY-CoV555) and etesevimab (LY-CoV016) for emergency use (2022c, https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs). To be specific, both pre- and post-treatment with REGEN-COV were shown to effectively reduce viral load in the lower and upper airways and protect rhesus macaques and hamsters from losing body weight (Baum et al., 2020). Jones et al. demonstrated that intravenously injecting LY-CoV555 monoclonal antibodies 24 h before SARS-CoV-2 infection could effectively reduce virus replication and load in the lower and upper airways of rhesus macaques (Jones et al., 2021). However, studies on Evusheld/AZD7442 in animal models are still to be conducted. Moreover, an *in vitro* study demonstrated that COVA1-18 in a cocktail with COVA1-16 could effectively neutralize SARS-CoV-2 variant D614G, Alpha and Beta (Maisonnasse et al., 2021). Taken

Table 4
Animal models used in COVID-19 vaccines on the emergency use listing of WHO and medicines or monoclonal antibodies approved for emergency use authorizations by the FDA.

Number	Ten COVID-19 vaccines on the emergency use listing of WHO and four medicines and five monoclonal antibodies approved for emergency use authorizations by the FDA.	Vaccine/ Medicine/ Monoclonal antibody	Animal model	Mode of administration	SARS-CoV-2 strain	Routes of virus inoculation	Virus dose
1	COMIRNATY® (BNT162b2)	Vaccine	Rhesus macaque (Vogel et al., 2021)	Intramuscular injection	SARS-CoV-2/human/USA/WA-CDC-02982586-001/2020; (GenBank accession no. MN985325.1)	Intranasal and intratracheal routes	1.05×10^6 PFUs
			Transgenic mouse (Ji et al., 2021)	Intramuscular injection	SARS-CoV-2/human/CHN/WH-09/2020; (GenBank accession no. MT093631.2)	Intranasal route	10^5 $TCID_{50}$
2	SPIKEVAX (mRNA-1273)	Vaccine	Rhesus macaque (Corbett et al., 2020)	Intramuscular injection	SARS-CoV-2/USA-WA1/2020; (BEI Resources: NR-52281)	Intranasal and intratracheal routes	7.6×10^5 PFUs
			BALB/c mouse (DiPiazza et al., 2021)	Intramuscular injection	Adapted SARS-CoV-2 MA10 strain	Intranasal route	1.0×10^4 PFUs or 1.0×10^5 PFUs
			Rhesus macaque (Corbett et al., 2021b)	Intramuscular injection	SARS-CoV-2/USA-WA1/2020; (BEI Resources: NR-70038893)	Intranasal and intratracheal routes	8×10^5 PFUs
			Rhesus macaque (Corbett et al., 2021a)	Intramuscular injection	SARS-CoV-2 JHU B.1.351 P2	Intranasal and intratracheal routes	2×10^5 PFUs
			Rhesus macaque (Corbett et al., 2021c)	Intramuscular injection	SARS-CoV-2 JHU B.1.351 P2	Intranasal and intratracheal routes	5×10^5 PFUs
			Hamster (Meyer et al., 2021)	Intramuscular injection	SARS-CoV-2/human/USA/WA-CDC-02982586-001/2020; (GenBank accession no. MN985325.1)	Intranasal route	1.0×10^5 PFUs
3	VAXZEVRIA (ChAdOx1 nCoV-19/AZD1222)	Vaccine	Rhesus macaque and ferret (Lambe et al., 2021)	Intramuscular injection	SARS-CoV-2 (VERO/hSLAM cell passage 3 (Victoria/1/2020))	Intratracheal and intranasal routes in rhesus macaques, intranasal routes in ferrets	5×10^6 PFUs
			Rhesus macaque and hamster (van Doremalen et al., 2021)	Intranasal inoculation	SARS-CoV-2/human/USA/RML-7/2020; (GenBank accession no. MW127503.1)	Intratracheal and intranasal routes in rhesus macaques, intranasal routes in hamsters	1.0×10^4 $TCID_{50}$
			Ferret (Marsh et al., 2021a)	Intramuscular or Intranasal inoculation	hCoV-19/Australia/VIC01/2020	Intranasal route	3×10^4 $TCID_{50}$
			Hamster (Fischer et al., 2021b)	Intramuscular or Intranasal inoculation	SARS-CoV-2 variant B.1.351-1 (hCoV-19/South African/KRISP-K005325/2020, GISAID: EPI_ISL_678615); SARS-CoV-2 variant B.1.351–2 (USA/MD-HP01542/2021, GISAID: EPI_ISL_890360); SARS-CoV-2 variant B.1.1.7 (hCoV-19/England/204820464/2020, GISAID: EPI_ISL_683466)	Intranasal route	1.0×10^4 $TCID_{50}$
4	Ad26.COV2.S	Vaccine	Rhesus macaque (He et al., 2021)	Intramuscular injection	SARS-CoV-2/USA-WA1/2020; (BEI Resources: NR-52281)	Intranasal and intratracheal routes	1.1×10^4 PFUs
			Rhesus macaque (Yu et al., 2021)	Intramuscular injection	SARS-CoV-2/USA-WA1/2020 (BEI Resources: NR-5228) or SARS-CoV-2 variant B.1.351 (South Africa/KRISP-K005325/2020; BEI Resources: NR-54974)	Intranasal and intratracheal routes	5×10^5 $TCID_{50}$
			Rhesus macaque (Solforosi et al., 2021)	Intramuscular injection	SARS-CoV-2/human/NLD/Leiden-0008/2020; (GenBank accession no.MT705206.1)	Intranasal and intratracheal routes Intranasal route	1.0×10^5 $TCID_{50}$

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Table 4 (*continued*)

Number	Ten COVID-19 vaccines on the emergency use listing of WHO and four medicines and five monoclonal antibodies approved for emergency use authorizations by the FDA.	Vaccine/ Medicine/ Monoclonal antibody	Animal model	Mode of administration	SARS-CoV-2 strain	Routes of virus inoculation	Virus dose
			Hamster (Tostanoski et al., 2021)	Intramuscular injection	SARS-CoV-2/USA-WA1/2020 (BEI Resources: NR-5228) or SARS-CoV-2 variant B.1.351 (South Africa/KRISP-K005325/ 2020; BEI Resources: NR-54974)		5×10^4 $TCID_{50}$
			Hamster (van der Lubbe et al., 2021)	Intramuscular injection	SARS-CoV-2/Beta CoV/Munich/ BavPat1/2020	Intranasal route	1.0×10^2 $TCID_{50}$
			Rhesus macaque (Roozendaal et al., 2021)	Intramuscular injection	SARS-CoV-2/USA-WA1/2020	Intranasal and intratracheal routes	1.0×10^5 $TCID_{50}$
5	COVOVAX™	Vaccine	ND				
6	COVISHIELD™	Vaccine	ND				
7	NUVAXOVID™ (NVX-CoV2373)	Vaccine	Cynomolgus macaque (Guebre-Xabier et al., 2020)	Intramuscular injection	SARS-CoV-2/USA-WA1/2020; (BEI Resources: NR-52281)	Intranasal and intratracheal routes	1.1×10^4 PFUs
			Virus-transduced mouse (Tian et al., 2021)	Intramuscular injection	SARS-CoV-2 (WA-1) isolated	Intranasal route	1.5×10^5 PFUs
8	CoronaVac (PiCoVacc)	Vaccine	Rhesus macaque (Gao et al., 2020)	Intramuscular injection	SARS-CoV-2/human/CHN/ CN1/2020; (GenBank accession no.MT407649)	Intratracheal route	1.0×10^6 $TCID_{50}$
			Transgenic mouse (Bao et al., 2021)	Intraperitoneal injection	SARS-CoV-2/WH-09/human/ 2020/CHN; (GenBank accession no.MT093631.2)	Intranasal route	1.0×10^2 $TCID_{50}$
9	COVAXIN® (BBV152)	Vaccine	Hamster (Mohandas et al., 2021)	Intramuscular injection	hCoV19/India/2020770/2020 (GISAID: EPI_ISL_420546)	Intranasal route	$1.0 \times 10^{5.5}$ $TCID_{50}$
			Rhesus macaque (Yadav et al., 2021)	Intramuscular injection	hCoV19/India/2020770/2020 (GISAID: EPI_ISL_420546)	Intranasal and intratracheal routes	$1.0 \times 10^{6.5}$ $TCID_{50}$
10	Sinopharm (BBIBP-CorV)	Vaccine	Rhesus macaque (Wang et al., 2020b, a)	Intramuscular injection	SARS-CoV-2/WH-09/human/ 2020/CHN; (GenBank accession no.MT093631.2)	Intratracheal route	1.0×10^6 $TCID_{50}$
11	Molnupiravir (MK-4482/ EIDD-2801)	Medicine	Hamster (Abdelnabi et al., 2021a)	Oral administration	SARS-CoV-2 variant B.1-G (BetaCov/Belgium/GHB-03021/ 2020; GISAID: EPI_ISL_109 407976), B.1.1.7 (hCoV-19/ Belgium/rega-12211513/2020; GISAID: EPI_ISL_791333) and B.1.351(hCoV-19/Belgium/ rega-1920/2021; GISAID: EPI_ISL_896474)	Intranasal route	1.0×10^5 $TCID_{50}$
			Hamster (Abdelnabi et al., 2021b)	Oral administration	BetaCov/Belgium/GHB-03021/ 2020; (GISAID: EPI_ISL_109407976)	Intranasal route	2×10^6 $TCID_{50}$
			Ferret (Cox et al., 2021b)	Oral administration	2019-nCoV/USA-WA1/2020	Intranasal route	1.0×10^4 or 1.0×10^5 PFUs
			Hamster (Rosenke et al., 2021)	Oral administration	SARS-CoV-2/human/USA/WA-CDC-02982586-001/2020; (GenBank accession no. MN985325.1)	Intranasal route	5×10^2 $TCID_{50}$

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Table 4 (*continued*)

Number	Ten COVID-19 vaccines on the emergency use listing of WHO and four medicines and five monoclonal antibodies approved for emergency use authorizations by the FDA.	Vaccine/ Medicine/ Monoclonal antibody	Animal model	Mode of administration	SARS-CoV-2 strain	Routes of virus inoculation	Virus dose
12	Baricitinib (Olumiant)	Medicine	Rhesus macaque (Hoang et al., 2021)	Oral administration	SARS-CoV-2/USA-WA1/2020; (BEI Resources: NR-52281)	Intranasal and intratracheal routes	1.1×10^6 PFUs
13	Remdesivir	Medicine	Rhesus macaque (Williamson et al., 2020)	Intravenous injection	SARS-CoV-2/human/USA/WA-CDC-02982586-001/2020; (GenBank accession no. MN985325.1)	Intranasal, oral, ocular and intratracheal routes	2.6×10^6 $TCID_{50}$
			Hamster (Ye et al., 2021)	Intraperitoneal injection	SARS-CoV-2/human/HKG/ HKU-001a/2020; (GenBank accession no.MT230904.1)	Intranasal route	1.0×10^5 PFUs
			Virus-transduced mouse (Sun et al., 2020a)	Subcutaneous injection	SARS-CoV-2/human/CHN/ IQTC01/2020; (GenBank accession no.MT123290.1) and SARS-CoV-2/human/USA/WA-CDC-02982586-001/2020; (GenBank accession no. MN985325.1)	Intranasal route	1.0×10^5 PFUs
14	Paxlovid (nirmatrelvir tablets and ritonavir tablets)	Medicine	ND				
15	Bamlanivimab and Etesevimab (LY-CoV555 and LY-CoV016)	Monoclonal antibody	Rhesus macaque (Jones et al., 2021)	Intravenous injection	SARS-CoV-2/USA-WA1/2020; (BEI Resources: NR-52281)	Intratracheal and intranasal routes	1.1×10^5 PFUs
16	REGEN-COV (Casirivimab and Imdevimab)	Monoclonal antibody	Rhesus macaque and hamster (Baum et al., 2020)	Intravenous injection	SARS-CoV-2/USA-WA1/2020; (BEI Resources: NR-52281)	Intranasal and intratracheal routes in rhesus macaques and intranasal routes in hamsters	1×10^5 PFUs in rhesus macaques and 2.3×10^4 PFUs in hamsters
17	Evusheld/AZD7442 (tixagevimab co-packaged with cilgavimab)	Monoclonal antibody	ND				
18	Actemra (Tocilizumab)	Monoclonal antibody	ND				
19	Sotrovimab	Monoclonal antibody	ND				

ND: Not Determined.

together, monoclonal, especially cocktail monoclonal antibodies hold great promise for future COVID-19 treatment, especially for those who have preclinical conditions including compromised immunity and old age, as these could be ever ready and mixed with great flexibility to take into account of variant specificities.

4.2.3. Vaccine

Animal models especially NHPs, transgenic mice and receptor-transduced mice are of great importance in evaluating the effectiveness of vaccine candidates against SARS-CoV-2. Rhesus macaques have been the best animal model among NHPs and they have been extensively used to evaluate vaccines against SARS-CoV-2 infection (Lu et al., 2020), ranging from inactivated virus vaccines (Gao et al., 2020; Wang et al., 2020b; Yadav et al., 2021), DNA vaccines (Li et al., 2021d; Yu et al., 2020), mRNA vaccines (Corbett et al., 2020; Vogel et al., 2021), subunit vaccines (Liang et al., 2021), nanoparticle vaccines (Ma et al., 2020) to several adenovirus vector-based vaccines (Feng et al., 2020; Mercado et al., 2020; van Doremalen et al., 2020b). Van Doremalen and Munster teams developed an adenovirus-vector-based vaccine ChAdOx1 nCoV-19 encoding the full-length SARS-CoV-2 S protein and evaluated its immunogenicity and efficacy in rhesus macaques (van Doremalen et al., 2020b). They showed that ChAdOx1 nCoV-19 could elicit a robust humoral response and a predominantly type-1 T helper cell-mediated cellular response. More importantly, ChAdOx1 nCoV-19-vaccinated rhesus macaques were protected from secondary SARS-CoV-2 challenge. Recently, Fischer et al. demonstrated that ChAdOx1 nCoV-19

vaccination prevented Syrian hamsters from being infected by SARS-CoV-2 Alpha or Beta variant as they showed no weight loss or lower respiratory tract infection (Fischer et al., 2021a, b). Similarly, Hassan et al. (2020b) developed a chimpanzee adenovirus-vectored vaccine candidate ChAd-SARS-CoV-2-S encoding the full-length SARS-CoV-2 S protein. They demonstrated that a single intramuscular immunization of ChAd-SARS-CoV-2-S induced robust humoral and cellular responses and blocked subsequent SARS-CoV-2 infection in the upper and lower respiratory tract in the highly susceptible K18-hACE2 transgenic mice. Gao et al. (2020) assessed the efficacy of a purified and inactivated SARS-CoV-2 vaccine PiCoVacc and showed that it could induce SARS-CoV-2 specific neutralizing antibodies in mice, rats and rhesus macaques. When being intramuscularly administrated three times at a dose of 6 μg each time per rhesus macaque, PiCoVacc effectively stimulated the production of neutralizing antibodies which subsequently protected the rhesus macaques from SARS-CoV-2 infection. No viral load was detected in the pharynx, crissum and lung in the PiCoVacc vaccinated rhesus macaques at 7 dpi, while severe interstitial pneumonia had developed in the control group. Similarly, another inactivated SARS-CoV-2 vaccine BBIBP-CorV (Wang et al., 2020b) was shown to induce high levels of neutralizing antibody in mice, rats, guinea pigs, rabbits and NHPs (cynomolgus macaques and rhesus macaques). More importantly, two-dose immunizations with BBIBP-CorV at 2 μg each time protected rhesus macaques from intratracheal SARS-CoV-2 infection as no virus was detected in the lungs of all vaccinated rhesus macaques. Likewise, using rhesus macaques, researchers demonstrated that a single dose of the adenovirus serotype 26 (Ad26) vector-based vaccine Ad26.COV2.S encoding the full-length SARS-CoV-2 S protein could induce robust neutralizing antibody responses (Mercado et al., 2020) and specific $CD8^+$ and $CD4^+$ T cell responses, and protected rhesus macaques from SARS-CoV-2 Alpha and Beta variant (Yu et al., 2021) challenges. Additionally, in hamsters, a single immunization of Ad26.COV2.S, termed as Ad26-S.PP in the report (Tostanoski et al., 2020) could prevent pneumonia and mortality caused by high-dose SARS-CoV-2 infection. Similar outcome was observed in a study using BALB/c mice challenged with mouse-adapted SARS-CoV-2 HRB26M and ferrets vaccinated with a replication-defective human adenovirus type 5-based COVID-19 vaccine candidate (Ad5-nCoV) encoding the full-length SARS-CoV-2 S protein (Wu et al., 2020b). A single vaccination of Ad5-nCoV protected BALB/c mice from mouse-adapted SARS-CoV-2 HRB26M infection in the upper and lower respiratory tracts and protected ferrets against SARS-CoV-2 infection in the upper respiratory tract. Likewise, data from rhesus macaques and mice showed that a recombinant serotype 5 adenovirus vaccine candidate Ad5-S-nb2 carrying a codon-optimized gene encoding SARS-CoV-2 S protein was immunogenic and protective as it elicited both spike-specific humoral and cellular immune responses (Feng et al., 2020).

The messenger RNA (mRNA) vaccines have played and are still playing an important role in the fight against COVID-19. Corbett and colleagues (Corbett et al., 2020) synthesized an mRNA vaccine named mRNA-1273 encoding the full-length prefusion SARS-CoV-2 S protein that was stabilized in its prefusion conformation by two proline substitutions and showed that inoculated rhesus macaques produced higher titer neutralizing antibodies than those found in convalescent-phase human sera. Moreover, mRNA-1273 vaccine induced Th1 and interleukin-21-producing Tfh responses, a critical Th response required for efficient antibody response, and effectively protected the infection of upper and lower respiratory tract in rhesus macaques. Two recent studies showed that boosting mRNA-1273 vaccine could limit the replication of SARS-CoV-2 Beta variant in rhesus macaques (Corbett et al., 2021a, 2021c). Similar outcomes including high neutralizing antibodies and Th1 response could be observed in the mRNA vaccine BNT162b-inoculated mice and rhesus macaques; and BNT162b provided effectively protection on rhesus macaques from 1.05×10^6 PFU SARS-CoV-2 challenge (Vogel et al., 2021). Subsequent clinical trial data showed that two-dose regimen of BNT162b2 provided up to 95% protection against SARS-CoV-2 infection (Polack et al., 2020). However, several *in vitro* studies demonstrated that the neutralizing capacity of the BTN162b2 vaccinated human sera against SARS-CoV-2 variants was reduced. Specifically, compared with the original wild SARS-CoV-2 strain, the neutralizing capacity of these human sera against the five SARS-CoV-2 variants Alpha, Beta, Gamma, Delta and Omicron decreased by 2.6 (Wall et al., 2021), 4.9–14 (Planas et al., 2021; Wall et al., 2021), 3.8 (Wang et al., 2021b), 5.8 (Wall et al., 2021) and 14.9 (Nemet et al., 2021) folds, respectively. According to a recent study, three doses of the BNT162b2 vaccine effectively neutralized SARS-CoV-2 Omicron and was 100-fold more effective than antibodies induced by two doses, suggesting that promoting the third booster dose of vaccination might be an effective way to prevent and control future epidemics (Nemet et al., 2021).

5. Advantages and limitations of animal models used in the study of SARS, MERS and COVID-19

An ideal animal model should mimic human SARS, MERS and COVID-19 in aspects such as viral receptor expression and distribution, infection route, correlation between virus titer and disease severity, pathogenesis as well as morbidity and mortality (Gretebeck and Subbarao, 2015). Here, we review the ability of six animal models to recapitulate the COVID-19 characteristics in Fig. 3. However, it is difficult, if not impossible, to develop an animal model that could perfectly recapitulate all the characteristics of human SARS, MERS and COVID-19. Therefore, it is important to understand both the advantages and limitations of the above reviewed animal models (Table 5).

Although NHPs are considered as the most reliable animal models for vaccine and antiviral evaluation, as large animals, NHPs require larger experimental space and more cost compared with small animals, which limits large-scale animal experiments (Pandey et al., 2021). Besides, all the species have limited susceptibility, and are only suitable for studying one or two of the three viruses. For instance, rhesus macaques are

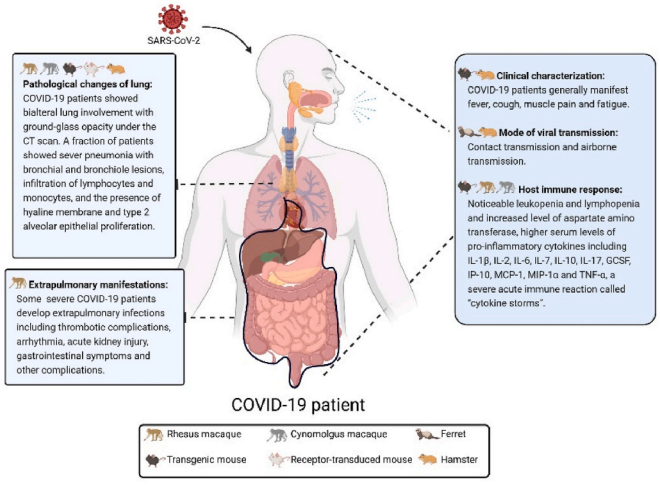

Fig. 3. The application of six animal models to recapitulate the COVID-19 characteristics. Indeed, six animal models including rhesus macaques, cynomolgus macaques, receptor-transduced mice, transgenic mice, ferrets, and hamsters could reproduce mild to moderate pneumonia of COVID-19 patients, but only hamsters and some transgenic mice could reproduce some of the more obvious clinical manifestations. Rhesus macaques can be used to study COVID-19 patients with extrapulmonary pathology such as endovascular dermatitis. Ferrets and hamsters are more suitable to studying viral transmission modes. Additionally, transgenic mice, rhesus macaques and cynomolgus macaques have been reported to exhibit host immune responses like those observed in COVID-19 patients, such as marked lymphocytopenia and increased cytokine expression.

Table 5
The advantages and disadvantages of animal models used in studying SARS, MERS and COVID-19.

Disease	Advantages/ Disadvantages	Animal models					
		Non-human primates			Mouse	Ferret	Hamster
		Rhesus macaque	Common Marmoset	Cynomolgus macaque			
SARS	Advantages	Support replication (McAuliffe et al., 2004)	Multifocal interstitial mononuclear pneumonia with extrapulmonary inflammation (Greenough et al., 2005b)	Old cynomolgus macaque are more susceptible to infection (Lawler et al., 2006; Rockx et al., 2011; Rowe et al., 2004)	Old mice supported viral replication (Roberts et al., 2005a; Subbarao et al., 2004)	Diffuse alveolar injury, multiple focal lesions. Similar lung anatomy to that of humans. (van den Brand et al., 2008)	Higher viral titers and longer course of disease than mice (Roberts et al., 2005b)
	Disadvantages	No symptoms (McAuliffe et al., 2004)	Mild clinical symptoms (Greenough et al., 2005b)	No obvious pneumonia and low viral replication level (Lawler et al., 2006; Rockx et al., 2011; Rowe et al., 2004)	Low replication efficiency (Roberts et al., 2005a; Subbarao et al., 2004)	No obvious clinical symptom (van den Brand et al., 2008)	No obvious symptoms (Roberts et al., 2005b)
COVID-19	Advantages	Used for vaccine evaluation (Lu et al., 2020)	ND	Higher levels of the virus replication in the aged (Koo et al., 2020; Rockx et al., 2020; Salguero et al., 2021)	Both hACE2 transduction mice and transgenic mice can be used for the pathogenetic study and evaluation of drugs and vaccines (Sun et al., 2020a; Winkler et al., 2020; Zhou et al., 2020)	Viruses shed and spread in a similar way to those in humans (Richard et al., 2020)	Viruses replicate in both respiratory and digestive tracts (Chan et al., 2020; Rosenke et al., 2020; Sia et al., 2020)
	Disadvantages	No severe pneumonia or death (Lu et al., 2020)	Not sensitive (Lu et al., 2020; Singh et al., 2021)	No obvious clinical symptoms (Koo et al., 2020; Rockx et al., 2020; Salguero et al., 2021)	WT mice do not support replication; No death in infected transduction mice; Need long acquisition time to gain transgenic mice (Sun et al., 2020a; Winkler et al., 2020; Zhou et al., 2020)	No severe pneumonia or death (Richard et al., 2020)	No severe pneumonia or death (Chan et al., 2020; Rosenke et al., 2020; Sia et al., 2020)
MERS	Advantages	Support replication (de Wit et al., 2013b)	Obvious clinical symptoms, higher viral titer and longer course of disease (Falzarano et al., 2014)	ND	Transgenic mice showed severe clinical symptoms and high mortality (Cockrell et al., 2014; Li et al., 2016; Zhao et al., 2014)	ND	ND
	Disadvantages	Histological lesions were limited to the lungs (de Wit et al., 2013b)	No renal injury (Falzarano et al., 2014)	ND	No death; Need long acquisition time to gain transgenic mice (Cockrell et al., 2014; Li et al., 2016; Zhao et al., 2014)	ND	ND

ND: Not Determined.

suitable for SARS-CoV-2 and MERS-CoV studies but not for SARS-CoV. Lu et al. demonstrated that rhesus macaques are the best model for SARS-CoV-2 infection (Lu et al., 2020). Hence, antivirals such as remdesivir and vaccines against SARS-CoV-2 were mainly tested in rhesus macaques (Williamson et al., 2020). One drawback of this model is that the SARS-CoV-2-infected rhesus macaques are mainly asymptomatic or show mild clinical disease (Chandrashekar et al., 2020; Munster et al., 2020), despite most COVID-19 patients also show asymptomatic, which is not conducive to severe SARS-CoV-2 pathogenesis. In this regard, marmosets seem to be the best model for studying SARS-CoV and MERS-CoV because they reproduce pulmonary and extrapulmonary manifestations of SARS and MERS patients (Falzarano et al., 2014; Greenough et al., 2005b). However, MERS-CoV does not cause damage to marmoset's kidneys, and thus the model is not suitable for studying the clinical MERS-associated renal disease (Falzarano et al., 2014). WT mice are not suitable for MERS and COVID-19 studies as they do not have suitable viral entry receptors. Furthermore, although infected transgenic mice often show severe clinical symptoms that are conducive to studying highly pathogenic coronaviruses pathogenesis, sometimes their symptoms might be more severe than those in humans, hindering drug and vaccine development. For instance, MERS-CoV infection has been demonstrated to cause a mortality rate of 100% in CAG-hDPP4 transgenic mice (Agrawal et al., 2015). Theoretically, this may represent an ideal animal model that can effectively recapitulate the disease, and thus the model should be highly recommended. However, the presence and distribution of viral receptors in the transgenic mouse brain, as indicated by the detection of viral RNA and damage in the brain following MERS-CoV infection (Sheahan et al., 2020), could potentially limit its use for the evaluation of vaccines and antivirals developed to target the infection in the lungs. K18-hACE2/hDPP4 (Li et al., 2016; McCray et al., 2007; Winkler et al., 2020) and HFH4/FOXJ-HACE2 (Jiang et al., 2020) transgenic mouse models also have such limitations. In contrast, infected receptor-transduced mice couldn't show severe clinical symptoms, to some extent, this model is useful for antiviral drug and vaccine development since the majority of COVID-19 patients in the real world will not have fatal clinical manifestations. However, the receptor-transduced mice using adenoviral vectors mainly express hACE2 in the respiratory tract of mice, which makes mice susceptible to SARS-CoV-2. By this way, viral vector-mediated expression of hACE2 is local and temporary, but not systemic and permanent expression like transgenic method(Bi et al., 2021; Han et al., 2021).Therefore, the receptor-transduced mice are not conducive to studying highly pathogenic coronaviruses pathogenesis, especially extrapulmonary pathogenicity (Sun et al., 2020a).

Hamsters and ferrets support viral replication of SARS-CoV and SARS-CoV-2 but not MERS-CoV, therefore, hamsters and ferrets are

rarely used as animal models to evaluate vaccines and antivirals specifically targeting MERS-CoV. The advantage of hamsters and ferrets over other animal models is that SARS-CoV-2 can be transmitted via both direct contact and indirect aerosol routes in them, hence these two models are better for SARS-CoV-2 transmission studies (Richard et al., 2020; Sia et al., 2020). Of note, ferrets are much more expensive than hamsters and CoV-infected ferrets do not show classical clinical symptoms as those in human. In this respect hamsters are more suitable for studying SARS-CoV and SARS-CoV-2.

6. Concluding remarks

We have been witnessing the enormous impact of COVID-19 pandemic on global public health since the end of 2019. Currently, the newly emerging SARS-CoV-2 variants, such as the Delta and Omicron, coupled with the relatively slow vaccination pose a continuous threat worldwide. It is therefore extremely important to effectively sped up the vaccination process globally and to urgently and rigorously evaluate current vaccines since their safety and efficacy are still debated. Furthermore, to develop the next generation vaccines and novel therapeutics, we need to have a detailed understanding of the SARS-CoV, MERS-CoV, and SARS-CoV-2 infections, host immune responses, and immune pathology. These could be greatly speeded up by using preclinical tests in animal models. To this end, the present review provides an overview of animal models, their suitable applications, and their advantages and limitations in the studies of SARS-CoV, MERS-CoV, and SARS-CoV-2 infections. Whether an animal model is suitable for vaccine and antiviral development depends on how well it recapitulates the relevant human disease. This includes firstly the successful virus entry and replication in the animals and subsequently the development of measurable clinical symptoms. In humans, some severe COVID-19 patients are found to suffer chronic diseases such as diabetes, hypertension, and obesity. It would be ideal that these diseases could be taken into consideration in developing and optimizing future animal models. Ideally, suitable animal models would also support the evaluation of vaccines and antivirals. If vaccine and antiviral candidates could all be tested rigorously in such animals to determine their effectiveness and side effects, this would surely minimize the risk posed by the vaccines and antivirals to the clinical trial patients and volunteers. Since the outbreak of COVID-19, many animal models have been successfully developed as summarized in this review. We firmly believe that many ground-breaking studies will follow using these precious models. We anticipate a much better understanding of the coronaviruses, especially SARS-CoV2 and COVID-19 in the near future, which ultimately will help us to bring the current pandemics under control.

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Declaration of competing interest

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

References

Abdelnabi, R., Foo, C.S., De Jonghe, S., Maes, P., Weynand, B., Neyts, J., 2021a. Molnupiravir inhibits replication of the emerging SARS-CoV-2 variants of concern in a hamster infection model. J. Infect. Dis. 224, 749–753.

Abdelnabi, R., Foo, C.S., Kaptein, S.J.F., Zhang, X., Do, T.N.D., Langendries, L., Vangeel, L., Breuer, J., Pang, J., Williams, R., Vergote, V., Heylen, E., Leyssen, P., Dallmeier, K., Coelmont, L., Chatterjee, A.K., Mols, R., Augustijns, P., De Jonghe, S., Jochmans, D., Weynand, B., Neyts, J., 2021b. The combined treatment of Molnupiravir and Favipiravir results in a potentiation of antiviral efficacy in a SARS-CoV-2 hamster infection model. EBioMedicine 72, 103595.

Abdelnabi, R., Foo, C.S., Jochmans, D., Vangeel, L., De Jonghe, S., Augustijns, P., Mols, R., Weynand, B., Wattanakul, T., Hoglund, R.M., Tarning, J., Mowbray, C.E., Sjö, P., Escudié, F., Scandale, I., Chatelain, E., Neyts, J., 2022. The oral protease inhibitor (PF-07321332) protects Syrian hamsters against infection with SARS-CoV-2 variants of concern. Nat. Commun. 13, 719.

Agrawal, A.S., Garron, T., Tao, X., Peng, B.H., Wakamiya, M., Chan, T.S., Couch, R.B., Tseng, C.T., 2015. Generation of a transgenic mouse model of Middle East respiratory syndrome coronavirus infection and disease. J. Virol. 89, 3659–3670.

Arabi, Y.M., Harthi, A., Hussein, J., Bouchama, A., Johani, S., Hajeer, A.H., Saeed, B.T., Wahbi, A., Saedy, A., AlDabbagh, T., Okaili, R., Sadat, M., Balkhy, H., 2015. Severe neurologic syndrome associated with Middle East respiratory syndrome corona virus (MERS-CoV). Infection 43, 495–501.

Assiri, A., Al-Tawfiq, J.A., Al-Rabeeah, A.A., Al-Rabiah, F.A., Al-Hajjar, S., Al-Barrak, A., Flemban, H., Al-Nassir, W.N., Balkhy, H.H., Al-Hakeem, R.F., Makhdoom, H.Q., Zumla, A.I., Memish, Z.A., 2013. Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study. Lancet Infect. Dis. 13, 752–761.

Báez-Santos, Y.M., St John, S.E., Mesecar, A.D., 2015. The SARS-coronavirus papain-like protease: structure, function and inhibition by designed antiviral compounds. Antivir. Res. 115, 21–38.

Bao, L., Deng, W., Gao, H., Xiao, C., Liu, J., Xue, J., Lv, Q., Liu, J., Yu, P., Xu, Y., Qi, F., Qu, Y., Li, F., Xiang, Z., Yu, H., Gong, S., Liu, M., Wang, G., Wang, S., Song, Z., Liu, Y., Zhao, W., Han, Y., Zhao, L., Liu, X., Wei, Q., Qin, C., 2020. Reinfection Could Not Occur in SARS-CoV-2 Infected Rhesus Macaques, bioRxiv : the Preprint Server for Biology.

Bao, L., Deng, W., Qi, F., Lv, Q., Song, Z., Liu, J., Gao, H., Wei, Q., Yu, P., Xu, Y., Qu, Y., Li, F., Xue, J., Gong, S., Liu, M., Wang, G., Wang, S., Zhao, B., Cong, B., Qin, C., 2021. Sequential infection with H1N1 and SARS-CoV-2 aggravated COVID-19 pathogenesis in a mammalian model, and co-vaccination as an effective method of prevention of COVID-19 and influenza. Signal Transduct. Targeted Ther. 6, 200.

Barnard, D.L., Day, C.W., Bailey, K., Heiner, M., Montgomery, R., Lauridsen, L., Chan, P. K., Sidwell, R.W., 2006. Evaluation of immunomodulators, interferons and known in vitro SARS-coV inhibitors for inhibition of SARS-coV replication in BALB/c mice. Antivir. Chem. Chemother. 17, 275–284.

Baum, A., Ajithdoss, D., Copin, R., Zhou, A., Lanza, K., Negron, N., Ni, M., Wei, Y., Mohammadi, K., Musser, B., Atwal, G.S., Oyejide, A., Goez-Gazi, Y., Dutton, J., Clemmons, E., Staples, H.M., Bartley, C., Klaffke, B., Alfson, K., Gazi, M., Gonzalez, O., Dick Jr., E., Carrion Jr., R., Pessaint, L., Porto, M., Cook, A., Brown, R., Ali, V., Greenhouse, J., Taylor, T., Andersen, H., Lewis, M.G., Stahl, N., Murphy, A.J., Yancopoulos, G.D., Kyratsous, C.A., 2020. REGN-COV2 antibodies prevent and treat SARS-CoV-2 infection in rhesus macaques and hamsters. Science (New York, N.Y.) 370, 1110–1115.

Beigel, J.H., Tomashek, K.M., Dodd, L.E., 2020. Remdesivir for the treatment of covid-19 - preliminary report. Reply. N. Engl. J. Med. 383, 994.

Bertoglio, F., Fühner, V., Ruschig, M., Heine, P.A., Abassi, L., Klünemann, T., Rand, U., Meier, D., Langreder, N., Steinke, S., Ballmann, R., Schneider, K.T., Roth, K.D.R., Kuhn, P., Riese, P., Schäckermann, D., Korn, J., Koch, A., Chaudhry, M.Z., Eschke, K., Kim, Y., Zock-Emmenthal, S., Becker, M., Scholz, M., Moreira, G., Wenzel, E.V., Russo, G., Garritsen, H.S.P., Casu, S., Gerstner, A., Roth, G., Adler, J., Trimpert, J., Hermann, A., Schirrmann, T., Dübel, S., Frenzel, A., Van den Heuvel, J., Čičin-Šain, L., Schubert, M., Hust, M., 2021. A SARS-CoV-2 neutralizing antibody selected from COVID-19 patients binds to the ACE2-RBD interface and is tolerant to most known RBD mutations. Cell Rep. 36, 109433.

Bi, Z., Hong, W., Yang, J., Lu, S., Peng, X., 2021. Animal models for SARS-CoV-2 infection and pathology. MedComm 2, 548–568.

Bisht, H., Roberts, A., Vogel, L., Bukreyev, A., Collins, P.L., Murphy, B.R., Subbarao, K., Moss, B., 2004. Severe acute respiratory syndrome coronavirus spike protein expressed by attenuated vaccinia virus protectively immunizes mice. Proc. Natl. Acad. Sci. U. S. A 101, 6641–6646.

Bisht, H., Roberts, A., Vogel, L., Subbarao, K., Moss, B., 2005. Neutralizing antibody and protective immunity to SARS coronavirus infection of mice induced by a soluble recombinant polypeptide containing an N-terminal segment of the spike glycoprotein. Virology 334, 160–165.

Blanchard, E.L., Vanover, D., Bawage, S.S., Tiwari, P.M., Rotolo, L., Beyersdorf, J., Peck, H.E., Bruno, N.C., Hincapie, R., Michel, F., Murray, J., Sadhwani, H., Vanderheyden, B., Finn, M.G., Brinton, M.A., Lafontaine, E.R., Hogan, R.J., Zurla, C., Santangelo, P.J., 2021. Treatment of influenza and SARS-CoV-2 infections via mRNA-encoded Cas13a in rodents. Nat. Biotechnol. 39, 717–726.

Bobrowski, T., Chen, L., Eastman, R.T., Itkin, Z., Shinn, P., Chen, C.Z., Guo, H., Zheng, W., Michael, S., Simeonov, A., Hall, M.D., Zakharov, A.V., Muratov, E.N., 2021. Synergistic and antagonistic drug combinations against SARS-CoV-2. Mol. Ther. : J. Am. Soc. Gene. Ther. 29, 873–885.

Booth, C., Matukas, L., Tomlinson, G., Rachlis, A., Rose, D., Dwosh, H., Walmsley, S., Mazzulli, T., Avendano, M., Derkach, P., Ephtimios, I., Kitai, I., Mederski, B., Shadowitz, S., Gold, W., Hawryluck, L., Rea, E., Chenkin, J., Cescon, D.,

Poutanen, S., Detsky, A.J.J., 2003. Clinical Features and Short-Term Outcomes of 144 Patients with SARS in the Greater Toronto Area, vol. 289, pp. 2801–2809.
Bourgonje, A.R., Abdulle, A.E., Timens, W., Hillebrands, J.L., Navis, G.J., Gordijn, S.J., Bolling, M.C., Dijkstra, G., Voors, A.A., Osterhaus, A.D., van der Voort, P.H., Mulder, D.J., van Goor, H., 2020. Angiotensin-converting enzyme 2 (ACE2), SARS-CoV-2 and the pathophysiology of coronavirus disease 2019 (COVID-19). J. Pathol. 251, 228–248.
Brocato, R.L., Kwilas, S.A., Kim, R.K., Zeng, X., Principe, L.M., Smith, J.M., Hooper, J.W., 2021. Protective efficacy of a SARS-CoV-2 DNA vaccine in wild-type and immunosuppressed Syrian hamsters. NPJ Vaccine 6, 16.
Brouwer, P.J.M., Brinkkemper, M., Maisonnasse, P., Dereuddre-Bosquet, N., Grobben, M., Claireaux, M., de Gast, M., Marlin, R., Chesnais, V., Diry, S., Allen, J.D., Watanabe, Y., Giezen, J.M., Kerster, G., Turner, H.L., van der Straten, K., van der Linden, C.A., Aldon, Y., Naninck, T., Bontjer, I., Burger, J.A., Poniman, M., Mykytyn, A.Z., Okba, N.M.A., Schermer, E.E., van Breemen, M.J., Ravichandran, R., Caniels, T.G., van Schooten, J., Kahlaoui, N., Contreras, V., Lemaître, J., Chapon, C., Fang, R.H.T., Villaudy, J., Sliepen, K., van der Velden, Y.U., Haagmans, B.L., de Bree, G.J., Ginoux, E., Ward, A.B., Crispin, M., King, N.P., van der Werf, S., van Gils, M.J., Le Grand, R., Sanders, R.W., 2021. Two-component spike nanoparticle vaccine protects macaques from SARS-CoV-2 infection. Cell 184, 1188–1200 e1119.
Buchholz, U.J., Bukreyev, A., Yang, L., Lamirande, E.W., Murphy, B.R., Subbarao, K., Collins, P.L., 2004. Contributions of the structural proteins of severe acute respiratory syndrome coronavirus to protective immunity. Proc. Natl. Acad. Sci. U. S. A 101, 9804–9809.
Callaway, E., 2021. Heavily mutated Omicron variant puts scientists on alert. Nature 600, 21.
Campbell, F., Archer, B., Laurenson-Schafer, H., Jinnai, Y., Konings, F., Batra, N., Pavlin, B., Vandemaele, K., Van Kerkhove, M.D., Jombart, T., Morgan, O., le Polain de Waroux, O., 2021. Increased transmissibility and global spread of SARS-CoV-2 variants of concern as at June 2021. Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin, vol. 26.
Cao, X., 2020. COVID-19: immunopathology and its implications for therapy. Nat. Rev. Immunol. 20, 269–270.
Cao, Y., Su, B., Guo, X., Sun, W., Deng, Y., Bao, L., Zhu, Q., Zhang, X., Zheng, Y., Geng, C., Chai, X., He, R., Li, X., Lv, Q., Zhu, H., Deng, W., Xu, Y., Wang, Y., Qiao, L., Tan, Y., Song, L., Wang, G., Du, X., Gao, N., Liu, J., Xiao, J., Su, X.D., Du, Z., Feng, Y., Qin, C., Qin, C., Jin, R., Xie, X.S., 2020. Potent neutralizing antibodies against SARS-CoV-2 identified by high-throughput single-cell sequencing of convalescent patients' B cells. Cell 182, 73–84 e16.
Case, J.B., Rothlauf, P.W., Chen, R.E., Kafai, N.M., Fox, J.M., Smith, B.K., Shrihari, S., McCune, B.T., Harvey, I.B., Keeler, S.P., Bloyet, L.M., Zhao, H., Ma, M., Adams, L.J., Winkler, E.S., Holtzman, M.J., Fremont, D.H., Whelan, S.P.J., Diamond, M.S., 2020. Replication-competent vesicular stomatitis virus vaccine vector protects against SARS-CoV-2-mediated pathogenesis in mice. Cell Host Microbe 28, 465–474 e464.
Chan, J.F., Yao, Y., Yeung, M.L., Deng, W., Bao, L., Jia, L., Li, F., Xiao, C., Gao, H., Yu, P., Cai, J.P., Chu, H., Zhou, J., Chen, H., Qin, C., Yuen, K.Y., 2015. Treatment with lopinavir/ritonavir or interferon-beta1b improves outcome of MERS-CoV infection in a nonhuman primate model of common marmoset. J. Infect. Dis. 212, 1904–1913.
Chan, J.F., Zhang, A.J., Yuan, S., Poon, V.K., Chan, C.C., Lee, A.C., Chan, W.M., Fan, Z., Tsoi, H.W., Wen, L., Liang, R., Cao, J., Chen, Y., Tang, K., Luo, C., Cai, J.P., Kok, K. H., Chu, H., Chan, K.H., Sridhar, S., Chen, Z., Chen, H., To, K.K., Yuen, K.Y., 2020. Simulation of the Clinical and Pathological Manifestations of Coronavirus Disease 2019 (COVID-19) in Golden Syrian Hamster Model: Implications for Disease Pathogenesis and Transmissibility. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.
Chandrashekar, A., Liu, J., Martinot, A.J., McMahan, K., Mercado, N.B., Peter, L., Tostanoski, L.H., Yu, J., Maliga, Z., Nekorchuk, M., Busman-Sahay, K., Terry, M., Wrijil, L.M., Ducat, S., Martinez, D.R., Atyeo, C., Fischinger, S., Burke, J.S., Slein, M. D., Pessaint, L., Van Ry, A., Greenhouse, J., Taylor, T., Blade, K., Cook, A., Finneyfrock, B., Brown, R., Teow, E., Velasco, J., Zahn, R., Wegmann, F., Abbink, P., Bondzie, E.A., Dagotto, G., Gebre, M.S., He, X., Jacob-Dolan, C., Kordana, N., Li, Z., Lifton, M.A., Mahrokhian, S.H., Maxfield, L.F., Nityanandam, R., Nkolola, J.P., Schmidt, A.G., Miller, A.D., Baric, R.S., Alter, G., Sorger, P.K., Estes, J.D., Andersen, H., Lewis, M.G., Barouch, D.H., 2020. SARS-CoV-2 infection protects against rechallenge in rhesus macaques. Science (New York, N.Y.) 369, 812–817.
Chen, Z., Zhang, L., Qin, C., Ba, L., Yi, C.E., Zhang, F., Wei, Q., He, T., Yu, W., Yu, J., Gao, H., Tu, X., Gettie, A., Farzan, M., Yuen, K.Y., Ho, D.D., 2005. Recombinant modified vaccinia virus Ankara expressing the spike glycoprotein of severe acute respiratory syndrome coronavirus induces protective neutralizing antibodies primarily targeting the receptor binding region. J. Virol. 79, 2678–2688.
Chen, Z., Bao, L., Chen, C., Zou, T., Xue, Y., Li, F., Lv, Q., Gu, S., Gao, X., Cui, S., Wang, J., Qin, C., Jin, Q., 2017. Human neutralizing monoclonal antibody inhibition of Middle East respiratory syndrome coronavirus replication in the common marmoset. J. Infect. Dis. 215, 1807–1815.
Chen, Y., Zhang, Y.N., Yan, R., Wang, G., Zhang, Y., Zhang, Z.R., Li, Y., Ou, J., Chu, W., Liang, Z., Wang, Y., Chen, Y.L., Chen, G., Wang, Q., Zhou, Q., Zhang, B., Wang, C., 2021. ACE2-targeting monoclonal antibody as potent and broad-spectrum coronavirus blocker. Signal Transduct. Targeted Ther. 6, 315.
Cockrell, A.S., Peck, K.M., Yount, B.L., Agnihothram, S.S., Scobey, T., Curnes, N.R., Baric, R.S., Heise, M.T., 2014. Mouse dipeptidyl peptidase 4 is not a functional receptor for Middle East respiratory syndrome coronavirus infection. J. Virol. 88, 5195–5199.
Cockrell, A.S., Yount, B.L., Scobey, T., Jensen, K., Douglas, M., Beall, A., Tang, X.C., Marasco, W.A., Heise, M.T., Baric, R.S., 2016. A mouse model for MERS coronavirus-induced acute respiratory distress syndrome. Nat. Microbiol. 2, 16226.
Corbett, K.S., Flynn, B., Foulds, K.E., Francica, J.R., Boyoglu-Barnum, S., Werner, A.P., Flach, B., O'Connell, S., Bock, K.W., Minai, M., Nagata, B.M., Andersen, H., Martinez, D.R., Noe, A.T., Douek, N., Donaldson, M.M., Nji, N.N., Alvarado, G.S., Edwards, D.K., Flebbe, D.R., Lamb, E., Doria-Rose, N.A., Lin, B.C., Louder, M.K., O'Dell, S., Schmidt, S.D., Phung, E., Chang, L.A., Yap, C., Todd, J.M., Pessaint, L., Van Ry, A., Browne, S., Greenhouse, J., Putman-Taylor, T., Strasbaugh, A., Campbell, T.A., Cook, A., Dodson, A., Steingrebe, K., Shi, W., Zhang, Y., Abiona, O. M., Wang, L., Pegu, A., Yang, E.S., Leung, K., Zhou, T., Teng, I.T., Widge, A., Gordon, I., Novik, L., Gillespie, R.A., Loomis, R.J., Moliva, J.I., Stewart-Jones, G., Himansu, S., Kong, W.P., Nason, M.C., Morabito, K.M., Ruckwardt, T.J., Ledgerwood, J.E., Gaudinski, M.R., Kwong, P.D., Mascola, J.R., Carfi, A., Lewis, M. G., Baric, R.S., McDermott, A., Moore, I.N., Sullivan, N.J., Roederer, M., Seder, R.A., Graham, B.S., 2020. Evaluation of the mRNA-1273 vaccine against SARS-CoV-2 in nonhuman primates. N. Engl. J. Med. 383, 1544–1555.
Corbett, K.S., Gagne, M., Wagner, D.A., S, O.C., Narpala, S.R., Flebbe, D.R., Andrew, S.F., Davis, R.L., Flynn, B., Johnston, T.S., Stringham, C.D., Lai, L., Valentin, D., Van Ry, A., Flinchbaugh, Z., Werner, A.P., Moliva, J.I., Sriparna, M., O'Dell, S., Schmidt, S.D., Tucker, C., Choi, A., Koch, M., Bock, K.W., Minai, M., Nagata, B.M., Alvarado, G.S., Henry, A.R., Laboune, F., Schramm, C.A., Zhang, Y., Yang, E.S., Wang, L., Choe, M., Boyoglu-Barnum, S., Wei, S., Lamb, E., Nurmukhambetova, S.T., Provost, S.J., Donaldson, M.M., Marquez, J., Todd, J.M., Cook, A., Dodson, A., Pekosz, A., Boritz, E., Ploquin, A., Doria-Rose, N., Pessaint, L., Andersen, H., Foulds, K.E., Misasi, J., Wu, K., Carfi, A., Nason, M.C., Mascola, J., Moore, I.N., Edwards, D.K., Lewis, M.G., Suthar, M.S., Roederer, M., McDermott, A., Douek, D.C., Sullivan, N.J., Graham, B.S., Seder, R.A., 2021a. Protection against SARS-CoV-2 Beta variant in mRNA-1273 vaccine-boosted nonhuman primates. Science (New York, N. Y.) 374, 1343–1353.
Corbett, K.S., Nason, M.C., Flach, B., Gagne, M., O'Connell, S., Johnston, T.S., Shah, S.N., Edara, V.V., Floyd, K., Lai, L., McDanal, C., Francica, J.R., Flynn, B., Wu, K., Choi, A., Koch, M., Abiona, O.M., Werner, A.P., Moliva, J.I., Andrew, S.F., Donaldson, M.M., Fintzi, J., Flebbe, D.R., Lamb, E., Noe, A.T., Nurmukhambetova, S.T., Provost, S.J., Cook, A., Dodson, A., Faudree, A., Greenhouse, J., Kar, S., Pessaint, L., Porto, M., Steingrebe, K., Valentin, D., Zouantcha, S., Bock, K.W., Minai, M., Nagata, B.M., van de Wetering, R., Boyoglu-Barnum, S., Leung, K., Shi, W., Yang, E.S., Zhang, Y., Todd, J.M., Wang, L., Alvarado, G.S., Andersen, H., Foulds, K.E., Edwards, D.K., Mascola, J.R., Moore, I.N., Lewis, M.G., Carfi, A., Montefiori, D., Suthar, M.S., McDermott, A., Roederer, M., Sullivan, N.J., Douek, D.C., Graham, B.S., Seder, R.A., 2021b. Immune correlates of protection by mRNA-1273 vaccine against SARS-CoV-2 in nonhuman primates. Science (New York, N.Y.) 373, eabj0299.
Corbett, K.S., Werner, A.P., Connell, S.O., Gagne, M., Lai, L., Moliva, J.I., Flynn, B., Choi, A., Koch, M., Foulds, K.E., Andrew, S.F., Flebbe, D.R., Lamb, E., Nurmukhambetova, S.T., Provost, S.J., Bock, K.W., Minai, M., Nagata, B.M., Ry, A. V., Flinchbaugh, Z., Johnston, T.S., Mokhtari, E.B., Mudvari, P., Henry, A.R., Laboune, F., Chang, B., Porto, M., Wear, J., Alvarado, G.S., Boyoglu-Barnum, S., Todd, J.M., Bart, B., Cook, A., Dodson, A., Pessaint, L., Steingrebe, K., Elbashir, S., Sriparna, M., Pekosz, A., Andersen, H., Wu, K., Edwards, D.K., Kar, S., Lewis, M.G., Boritz, E., Moore, I.N., Carfi, A., Suthar, M.S., McDermott, A., Roederer, M., Nason, M.C., Sullivan, N.J., Douek, D.C., Graham, B.S., Seder, R.A., 2021c. mRNA-1273 protects against SARS-CoV-2 beta infection in nonhuman primates. Nat. Immunol. 22, 1306–1315.
Cox, R.M., Wolf, J.D., Lieber, C.M., Sourimant, J., Lin, M.J., Babusis, D., DuPont, V., Chan, J., Barrett, K.T., Lye, D., Kalla, R., Chun, K., Mackman, R.L., Ye, C., Cihlar, T., Martinez-Sobrido, L., Greninger, A.L., Bilello, J.P., Plemper, R.K., 2021a. Oral prodrug of remdesivir parent GS-441524 is efficacious against SARS-CoV-2 in ferrets. Nat. Commun. 12, 6415.
Cox, R.M., Wolf, J.D., Plemper, R.K., 2021b. Therapeutically administered ribonucleoside analogue MK-4482/EIDD-2801 blocks SARS-CoV-2 transmission in ferrets. Nat. Microbiol. 6, 11–18.
Cui, J., Li, F., Shi, Z.L., 2019. Origin and evolution of pathogenic coronaviruses. Nat. Rev. Microbiol. 17, 181–192.
COVID-19 vaccines WHO EUL issued, 2022b. https://extranet.who.int/pqweb/vaccines/vaccinescovid-19-vaccine-eul-issued.
de Vries, R.D., Rockx, B., Haagmans, B.L., Herfst, S., Koopmans, M.P., de Swart, R.L., 2021. Animal models of SARS-CoV-2 transmission. Curr. Opin. Virol. 50, 8–16.
de Wit, E., Prescott, J., Baseler, L., Bushmaker, T., Thomas, T., Lackemeyer, M.G., Martellaro, C., Milne-Price, S., Haddock, E., Haagmans, B.L., Feldmann, H., Munster, V.J., 2013a. The Middle East respiratory syndrome coronavirus (MERS-CoV) does not replicate in Syrian hamsters. PLoS One 8, e69127.
de Wit, E., Rasmussen, A.L., Falzarano, D., Bushmaker, T., Feldmann, F., Brining, D.L., Fischer, E.R., Martellaro, C., Okumura, A., Chang, J., Scott, D., Benecke, A.G., Katze, M.G., Feldmann, H., Munster, V.J., 2013b. Middle East respiratory syndrome coronavirus (MERS-CoV) causes transient lower respiratory tract infection in rhesus macaques. Proc. Natl. Acad. Sci. U. S. A 110, 16598–16603.
Dejnirattisai, W., Shaw, R.H., Supasa, P., Liu, C., Stuart, A.S., Pollard, A.J., Liu, X., Lambe, T., Crook, D., Stuart, D.I., Mongkolsapaya, J., Nguyen-Van-Tam, J.S., Snape, M.D., Screaton, G.R., 2021. Reduced Neutralisation of SARS-CoV-2 Omicron B.1.1.529 Variant by Post-immunisation Serum. Lancet (London, England).
Dhakal, S., Ruiz-Bedoya, C.A., Zhou, R., Creisher, P.S., Villano, J.S., Littlefield, K., Ruelas Castillo, J., Marinho, P., Jedlicka, A.E., Ordonez, A.A., Bahr, M., Majewska, N., Betenbaugh, M.J., Flavahan, K., Mueller, A.R.L., Looney, M.M., Quijada, D., Mota, F., Beck, S.E., Brockhurst, J., Braxton, A.M., Castell, N., Stover, M., D'Alessio, F.R., Metcalf Pate, K.A., Karakousis, P.C., Mankowski, J.L., Pekosz, A., Jain, S.K., Klein, S.L., 2021. Sex differences in lung imaging and SARS-CoV-2 antibody responses in a COVID-19 golden Syrian hamster model. mBio 12, e0097421.

Dhama, K., Patel, S.K., Sharun, K., Pathak, M., Tiwari, R., Yatoo, M.I., Malik, Y.S., Sah, R., Rabaan, A.A., Panwar, P.K., Singh, K.P., Michalak, I., Chaicumpa, W., Martinez-Pulgarin, D.F., Bonilla-Aldana, D.K., Rodriguez-Morales, A.J., 2020. SARS-CoV-2 jumping the species barrier: zoonotic lessons from SARS, MERS and recent advances to combat this pandemic virus. Trav. Med. Infect. Dis. 37, 101830.

Ding, Y., Wang, H., Shen, H., Li, Z., Geng, J., Han, H., Cai, J., Li, X., Kang, W., Weng, D., Lu, Y., Wu, D., He, L., Yao, K., 2003. The clinical pathology of severe acute respiratory syndrome (SARS): a report from China. J. Pathol. 200, 282–289.

DiPiazza, A.T., Leist, S.R., Abiona, O.M., Moliva, J.I., Werner, A., Minai, M., Nagata, B. M., Bock, K.W., Phung, E., Schäfer, A., Dinnon 3rd, K.H., Chang, L.A., Loomis, R.J., Boyoglu-Barnum, S., Alvarado, G.S., Sullivan, N.J., Edwards, D.K., Morabito, K.M., Mascola, J.R., Carfi, A., Corbett, K.S., Moore, I.N., Baric, R.S., Graham, B.S., Ruckwardt, T.J., 2021. COVID-19 vaccine mRNA-1273 elicits a protective immune profile in mice that is not associated with vaccine-enhanced disease upon SARS-CoV-2 challenge. Immunity 54, 1869–1882 e1866.

Du, L., Kou, Z., Ma, C., Tao, X., Wang, L., Zhao, G., Chen, Y., Yu, F., Tseng, C.T., Zhou, Y., Jiang, S., 2013. A truncated receptor-binding domain of MERS-CoV spike protein potently inhibits MERS-CoV infection and induces strong neutralizing antibody responses: implication for developing therapeutics and vaccines. PLoS One 8, e81587.

Du, S., Cao, Y., Zhu, Q., Yu, P., Qi, F., Wang, G., Du, X., Bao, L., Deng, W., Zhu, H., Liu, J., Nie, J., Zheng, Y., Liang, H., Liu, R., Gong, S., Xu, H., Yisimayi, A., Lv, Q., Wang, B., He, R., Han, Y., Zhao, W., Bai, Y., Qu, Y., Gao, X., Ji, C., Wang, Q., Gao, N., Huang, W., Wang, Y., Xie, X.S., Su, X.D., Xiao, J., Qin, C., 2020. Structurally resolved SARS-CoV-2 antibody shows high efficacy in severely infected hamsters and provides a potent cocktail pairing strategy. Cell 183, 1013–1023 e1013.

Du, Y., Shi, R., Zhang, Y., Duan, X., Li, L., Zhang, J., Wang, F., Zhang, R., Shen, H., Wang, Y., Wu, Z., Peng, Q., Pan, T., Sun, W., Huang, W., Feng, Y., Feng, H., Xiao, J., Tan, W., Wang, Y., Wang, C., Yan, J., 2021. A broadly neutralizing humanized ACE2-targeting antibody against SARS-CoV-2 variants. Nat. Commun. 12, 5000.

Emergency use authorization, 2022c. https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs.

Enkirch, T., von Messling, V., 2015. Ferret models of viral pathogenesis. Virology 479–480, 259–270.

Falzarano, D., de Wit, E., Rasmussen, A.L., Feldmann, F., Okumura, A., Scott, D.P., Brining, D., Bushmaker, T., Martellaro, C., Baseler, L., Benecke, A.G., Katze, M.G., Munster, V.J., Feldmann, H., 2013. Treatment with interferon-alpha2b and ribavirin improves outcome in MERS-CoV-infected rhesus macaques. Nat. Med. 19, 1313–1317.

Falzarano, D., de Wit, E., Feldmann, F., Rasmussen, A.L., Okumura, A., Peng, X., Thomas, M.J., van Doremalen, N., Haddock, E., Nagy, L., LaCasse, R., Liu, T., Zhu, J., McLellan, J.S., Scott, D.P., Katze, M.G., Feldmann, H., Munster, V.J., 2014. Infection with MERS-CoV causes lethal pneumonia in the common marmoset. PLoS Pathog. 10, e1004250.

Feng, L., Wang, Q., Shan, C., Yang, C., Feng, Y., Wu, J., Liu, X., Zhou, Y., Jiang, R., Hu, P., Liu, X., Zhang, F., Li, P., Niu, X., Liu, Y., Zheng, X., Luo, J., Sun, J., Gu, Y., Liu, B., Xu, Y., Li, C., Pan, W., Zhao, J., Ke, C., Chen, X., Xu, T., Zhong, N., Guan, S., Yuan, Z., Chen, L., 2020. An adenovirus-vectored COVID-19 vaccine confers protection from SARS-COV-2 challenge in rhesus macaques. Nat. Commun. 11, 4207.

Fischer, R.J., van Doremalen, N., Adney, D.R., Yinda, C.K., Port, J.R., Holbrook, M.G., Schulz, J.E., Williamson, B.N., Thomas, T., Barbian, K., Anzick, S.L., Ricklefs, S., Smith, B.J., Long, D., Martens, C., Saturday, G., de Wit, E., Gilbert, S.C., Lambe, T., Munster, V.J., 2021a. ChAdOx1 nCoV-19 (AZD1222) Protects Hamsters against SARS-CoV-2 B.1.351 and B.1.1.7 Disease. bioRxiv : the Preprint Server for Biology.

Fischer, R.J., van Doremalen, N., Adney, D.R., Yinda, C.K., Port, J.R., Holbrook, M.G., Schulz, J.E., Williamson, B.N., Thomas, T., Barbian, K., Anzick, S.L., Ricklefs, S., Smith, B.J., Long, D., Martens, C., Saturday, G., de Wit, E., Gilbert, S.C., Lambe, T., Munster, V.J., 2021b. ChAdOx1 nCoV-19 (AZD1222) protects Syrian hamsters against SARS-CoV-2 B.1.351 and B.1.1.7. Nat. Commun. 12, 5868.

Gao, W., Tamin, A., Soloff, A., D'Aiuto, L., Nwanegbo, E., Robbins, P.D., Bellini, W.J., Barratt-Boyes, S., Gambotto, A., 2003. Effects of a SARS-associated coronavirus vaccine in monkeys. Lancet (London, England) 362, 1895–1896.

Gao, Q., Bao, L., Mao, H., Wang, L., Xu, K., Yang, M., Li, Y., Zhu, L., Wang, N., Lv, Z., Gao, H., Ge, X., Kan, B., Hu, Y., Liu, J., Cai, F., Jiang, D., Yin, Y., Qin, C., Li, J., Gong, X., Lou, X., Shi, W., Wu, D., Zhang, H., Zhu, L., Deng, W., Li, Y., Lu, J., Li, C., Wang, X., Yin, W., Zhang, Y., Qin, C., 2020. Development of an inactivated vaccine candidate for SARS-CoV-2. Science (New York, N.Y.) 369, 77–81.

Gebhard, C., Regitz-Zagrosek, V., Neuhauser, H.K., Morgan, R., Klein, S.L., 2020. Impact of sex and gender on COVID-19 outcomes in Europe. Biol. Sex Differ. 11, 29.

Genzel, L., Adan, R., Berns, A., van den Beucken, J., Blokland, A., Boddeke, E., Bogers, W. M., Bontrop, R., Bulthuis, R., Bousema, T., Clevers, H., Coenen, T., van Dam, A.M., Deen, P.M.T., van Dijk, K.W., Eggen, B.J.L., Elgersma, Y., Erdogan, I., Englitz, B., Fentener van Vlissingen, J.M., la Fleur, S., Fouchier, R., Fitzsimons, C.P., Frieling, W., Haagmans, B., Heesters, B.A., Henckens, M., Herfst, S., Hol, E., van den Hove, D., de Jonge, M.I., Jonkers, J., Joosten, L.A.B., Kalsbeek, A., Kamermans, M., Kampinga, H.H., Kas, M.J., Keijer, J.A., Kersten, S., Kiliaan, A.J., Kooij, T.W.A., Kooijman, S., Koopman, W.J.H., Korosi, A., Krugers, H.J., Kuiken, T., Kushner, S.A., Langermans, J.A.M., Lesscher, H.M.B., Lucassen, P.J., Lutgens, E., Netea, M.G., Noldus, L., van der Meer, J.W.M., Meye, F.J., Mul, J.D., van Oers, K., Olivier, J.D.A., Pasterkamp, R.J., Philippens, I., Prickaerts, J., Pollux, B.J.A., Rensen, P.C.N., van Rheenen, J., van Rij, R.P., Ritsma, L., Rockx, B.H.G., Roozendaal, B., van Schothorst, E.M., Stittelaar, K., Stockhofe, N., Swaab, D.F., de Swart, R.L., Vanderschuren, L., de Vries, T.J., de Vrij, F., van Wezel, R., Wierenga, C.J., Wiesmann, M., Willuhn, I., de Zeeuw, C.I., Homberg, J.R., 2020. How the COVID-19 pandemic highlights the necessity of animal research. Curr. Biol. : CB 30, R1014–r1018.

Greenough, T.C., Babcock, G.J., Roberts, A., Hernandez, H.J., Thomas Jr., W.D., Coccia, J.A., Graziano, R.F., Srinivasan, M., Lowy, I., Finberg, R.W., Subbarao, K., Vogel, L., Somasundaran, M., Luzuriaga, K., Sullivan, J.L., Ambrosino, D.M., 2005a. Development and characterization of a severe acute respiratory syndrome-associated coronavirus-neutralizing human monoclonal antibody that provides effective immunoprophylaxis in mice. J. Infect. Dis. 191, 507–514.

Greenough, T.C., Carville, A., Coderre, J., Somasundaran, M., Sullivan, J.L., Luzuriaga, K., Mansfield, K., 2005b. Pneumonitis and multi-organ system disease in common marmosets (Callithrix jacchus) infected with the severe acute respiratory syndrome-associated coronavirus. Am. J. Pathol. 167, 455–463.

Gretebeck, L.M., Subbarao, K., 2015. Animal models for SARS and MERS coronaviruses. Curr. Opin. Virol. 13, 123–129.

Gu, C., Wu, Y., Guo, H., Zhu, Y., Xu, W., Wang, Y., Zhou, Y., Sun, Z., Cai, X., Li, Y., Liu, J., Huang, Z., Yuan, Z., Zhang, R., Deng, Q., Qu, D., Xie, Y., 2020a. Protoporphyrin IX and verteporfin potently inhibit SARS-CoV-2 infection in vitro and in a mouse model expressing human ACE2. Sci. Bull.

Gu, H., Chen, Q., Yang, G., He, L., Fan, H., Deng, Y.Q., Wang, Y., Teng, Y., Zhao, Z., Cui, Y., Li, Y., Li, X.F., Li, J., Zhang, N.N., Yang, X., Chen, S., Guo, Y., Zhao, G., Wang, X., Luo, D.Y., Wang, H., Yang, X., Li, Y., Han, G., He, Y., Zhou, X., Geng, S., Sheng, X., Jiang, S., Sun, S., Qin, C.F., Zhou, Y., 2020b. Adaptation of SARS-CoV-2 in BALB/c mice for testing vaccine efficacy. Science (New York, N.Y.) 369, 1603–1607.

Guebre-Xabier, M., Patel, N., Tian, J.H., Zhou, B., Maciejewski, S., Lam, K., Portnoff, A. D., Massare, M.J., Frieman, M.B., Piedra, P.A., Ellingsworth, L., Glenn, G., Smith, G., 2020. NVX-CoV2373 vaccine protects cynomolgus macaque upper and lower airways against SARS-CoV-2 challenge. Vaccine 38, 7892–7896.

Guery, B., Poissy, J., el Mansouf, L., Sejourne, C., Ettahar, N., Lemaire, X., Vuotto, F., Goffard, A., Behillil, S., Enouf, V., Caro, V., Mailles, A., Che, D., Manuguerra, J.C., Mathieu, D., Fontanet, A., van der Werf, S., group, M.E.-C.s., 2013. Clinical features and viral diagnosis of two cases of infection with Middle East Respiratory Syndrome coronavirus: a report of nosocomial transmission. Lancet (London, England) 381, 2265–2272.

Guo, Q., Zhao, Y., Li, J., Liu, J., Yang, X., Guo, X., Kuang, M., Xia, H., Zhang, Z., Cao, L., Luo, Y., Bao, L., Wang, X., Wei, X., Deng, W., Wang, N., Chen, L., Chen, J., Zhu, H., Gao, R., Qin, C., Wang, X., You, F., 2021. Induction of alarmin S100A8/A9 mediates activation of aberrant neutrophils in the pathogenesis of COVID-19. Cell Host Microbe 29, 222–235 e224.

Han, K., Blair, R.V., Iwanaga, N., Liu, F., Russell-Lodrigue, K.E., Qin, Z., Midkiff, C.C., Golden, N.A., Doyle-Meyers, L.A., Kabir, M.E., Chandler, K.E., Cutrera, K.L., Ren, M., Monjure, C.J., Lehmicke, G., Fischer, T., Beddingfield, B., Wanek, A.G., Birnbaum, A., Maness, N.J., Roy, C.J., Datta, P.K., Rappaport, J., Kolls, J.K., Qin, X., 2021. Lung expression of human angiotensin-converting enzyme 2 sensitizes the mouse to SARS-CoV-2 infection. Am. J. Respir. Cell Mol. Biol. 64, 79–88.

Hassan, A.O., Case, J.B., Winkler, E.S., Thackray, L.B., Kafai, N.M., Bailey, A.L., McCune, B.T., Fox, J.M., Chen, R.E., Alsoussi, W.B., Turner, J.S., Schmitz, A.J., Lei, T., Shrihari, S., Keeler, S.P., Fremont, D.H., Greco, S., McCray Jr., P.B., Perlman, S., Holtzman, M.J., Ellebedy, A.H., Diamond, M.S., 2020a. A SARS-CoV-2 infection model in mice demonstrates protection by neutralizing antibodies. Cell 182, 744-753 e744.

Hassan, A.O., Kafai, N.M., Dmitriev, I.P., Fox, J.M., Smith, B.K., Harvey, I.B., Chen, R.E., Winkler, E.S., Wessel, A.W., Case, J.B., Kashentseva, E., McCune, B.T., Bailey, A.L., Zhao, H., VanBlargan, L.A., Dai, Y.N., Ma, M., Adams, L.J., Shrihari, S., Danis, J.E., Gralinski, L.E., Hou, Y.J., Schafer, A., Kim, A.S., Keeler, S.P., Weiskopf, D., Baric, R. S., Holtzman, M.J., Fremont, D.H., Curiel, D.T., Diamond, M.S., 2020b. A single-dose intranasal Chad vaccine protects upper and lower respiratory tracts against SARS-CoV-2. Cell 183, 169-184 e113.

He, X., Chandrashekar, A., Zahn, R., Wegmann, F., Yu, J., Mercado, N.B., McMahan, K., Martinot, A.J., Piedra-Mora, C., Beecy, S., Ducat, S., Chamanza, R., Huber, S.R., van Heerden, M., van der Fits, L., Borducchi, E.N., Lifton, M., Liu, J., Nampanya, F., Patel, S., Peter, L., Tostanoski, L.H., Pessaint, L., Van Ry, A., Finneyfrock, B., Velasco, J., Teow, E., Brown, R., Cook, A., Andersen, H., Lewis, M.G., Schuitemaker, H., Barouch, D.H., 2021. Low-dose Ad26.COV2.S protection against SARS-CoV-2 challenge in rhesus macaques. Cell 184, 3467–3473 e3411.

Heskin, J., Pallett, S.J.C., Mughal, N., Davies, G.W., Moore, L.S.P., Rayment, M., Jones, R., 2022. Caution required with use of ritonavir-boosted PF-07321332 in COVID-19 management. Lancet (London, England) 399, 21–22.

Ho, J.S.Y., Mok, B.W., Campisi, L., Jordan, T., Yildiz, S., Parameswaran, S., Wayman, J. A., Gaudreault, N.N., Meekins, D.A., Indran, S.V., Morozov, I., Trujillo, J.D., Fstkchyan, Y.S., Rathnasinghe, R., Zhu, Z., Zheng, S., Zhao, N., White, K., Ray-Jones, H., Malysheva, V., Thiecke, M.J., Lau, S.Y., Liu, H., Zhang, A.J., Lee, A.C., Liu, W.C., Jangra, S., Escalera, A., Aydillo, T., Melo, B.S., Guccione, E., Sebra, R., Shum, E., Bakker, J., Kaufman, D.A., Moreira, A.L., Carossino, M., Balasuriya, U.B.R., Byun, M., Albrecht, R.A., Schotsaert, M., Garcia-Sastre, A., Chanda, S.K., Miraldi, E. R., Jeyasekharan, A.D., TenOever, B.R., Spivakov, M., Weirauch, M.T., Heinz, S., Chen, H., Benner, C., Richt, J.A., Marazzi, I., 2021. TOP1 inhibition therapy protects against SARS-CoV-2-induced lethal inflammation. Cell.

Hoang, T.N., Pino, M., Boddapati, A.K., Viox, E.G., Starke, C.E., Upadhyay, A.A., Gumber, S., Nekorchuk, M., Busman-Sahay, K., Strongin, Z., Harper, J.L., Tharp, G. K., Pellegrini, K.L., Kirejczyk, S., Zandi, K., Tao, S., Horton, T.R., Beagle, E.N., Mahar, E.A., Lee, M.Y.H., Cohen, J., Jean, S.M., Wood, J.S., Connor-Stroud, F., Stammen, R.L., Delmas, O.M., Wang, S., Cooney, K.A., Sayegh, M.N., Wang, L., Filev, P.D., Weiskopf, D., Silvestri, G., Waggoner, J., Piantadosi, A., Kasturi, S.P., Al-Shakhshir, H., Ribeiro, S.P., Sekaly, R.P., Levit, R.D., Estes, J.D., Vanderford, T.H., Schinazi, R.F., Bosinger, S.E., Paiardini, M., 2021. Baricitinib treatment resolves

lower-airway macrophage inflammation and neutrophil recruitment in SARS-CoV-2-infected rhesus macaques. Cell 184, 460–475 e421.
Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., Schiergens, T.S., Herrler, G., Wu, N.H., Nitsche, A., Müller, M.A., Drosten, C., Pöhlmann, S., 2020. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 181, 271–280 e278.
Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X., Cheng, Z., Yu, T., Xia, J., Wei, Y., Wu, W., Xie, X., Yin, W., Li, H., Liu, M., Xiao, Y., Gao, H., Guo, L., Xie, J., Wang, G., Jiang, R., Gao, Z., Jin, Q., Wang, J., Cao, B., 2020. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet (London, England) 395, 497–506.
Hwang, Y.C., Lu, R.M., Su, S.C., Chiang, P.Y., Ko, S.H., Ke, F.Y., Liang, K.H., Hsieh, T.Y., Wu, H.C., 2022. Monoclonal antibodies for COVID-19 therapy and SARS-CoV-2 detection. J. Biomed. Sci. 29, 1.
Imai, M., Iwatsuki-Horimoto, K., Hatta, M., Loeber, S., Halfmann, P.J., Nakajima, N., Watanabe, T., Ujie, M., Takahashi, K., Ito, M., Yamada, S., Fan, S., Chiba, S., Kuroda, M., Guan, L., Takada, K., Armbrust, T., Balogh, A., Furusawa, Y., Okuda, M., Ueki, H., Yasuhara, A., Sakai-Tagawa, Y., Lopes, T.J.S., Kiso, M., Yamayoshi, S., Kinoshita, N., Ohmagari, N., Hattori, S.I., Takeda, M., Mitsuya, H., Krammer, F., Suzuki, T., Kawaoka, Y., 2020. Syrian hamsters as a small animal model for SARS-CoV-2 infection and countermeasure development. Proc. Natl. Acad. Sci. U. S. A 117, 16587–16595.
Ji, R.R., Qu, Y., Zhu, H., Yang, Y., Vogel, A.B., Sahin, U., Qin, C., Hui, A., 2021. BNT162b2 vaccine encoding the SARS-CoV-2 P2 S protects transgenic hACE2 mice against COVID-19. Vaccines 9.
Jiang, R.D., Liu, M.Q., Chen, Y., Shan, C., Zhou, Y.W., Shen, X.R., Li, Q., Zhang, L., Zhu, Y., Si, H.R., Wang, Q., Min, J., Wang, X., Zhang, W., Li, B., Zhang, H.J., Baric, R. S., Zhou, P., Yang, X.L., Shi, Z.L., 2020. Pathogenesis of SARS-CoV-2 in transgenic mice expressing human angiotensin-converting enzyme 2. Cell 182, 50–58 e58.
Johansen, M.D., Irving, A., Montagutelli, X., Tate, M.D., Rudloff, I., Nold, M.F., Hansbro, N.G., Kim, R.Y., Donovan, C., Liu, G., Faiz, A., Short, K.R., Lyons, J.G., McCaughan, G.W., Gorrell, M.D., Cole, A., Moreno, C., Couteur, D., Hesselson, D., Triccas, J., Neely, G.G., Gamble, J.R., Simpson, S.J., Saunders, B.M., Oliver, B.G., Britton, W.J., Wark, P.A., Nold-Petry, C.A., Hansbro, P.M., 2020. Animal and translational models of SARS-CoV-2 infection and COVID-19. Mucosal Immunol. 13, 877–891.
Jones, B.E., Brown-Augsburger, P.L., Corbett, K.S., Westendorf, K., Davies, J., Cujec, T.P., Wiethoff, C.M., Blackbourne, J.L., Heinz, B.A., Foster, D., Higgs, R.E., Balasubramaniam, D., Wang, L., Zhang, Y., Yang, E.S., Bidshahri, R., Kraft, L., Hwang, Y., Žentelis, S., Jepson, K.R., Goya, R., Smith, M.A., Collins, D.W., Hinshaw, S.J., Tycho, S.A., Pellacani, D., Xiang, P., Muthuraman, K., Sobhanifar, S., Piper, M.H., Triana, F.J., Hendle, J., Pustilnik, A., Adams, A.C., Berens, S.J., Baric, R. S., Martinez, D.R., Cross, R.W., Geisbert, T.W., Borisevich, V., Abiona, O., Belli, H. M., de Vries, M., Mohamed, A., Dittmann, M., Samanovic, M.I., Mulligan, M.J., Goldsmith, J.A., Hsieh, C.L., Johnson, N.V., Wrapp, D., McLellan, J.S., Barnhart, B. C., Graham, B.S., Mascola, J.R., Hansen, C.L., Falconer, E., 2021. The neutralizing antibody, LY-CoV555, protects against SARS-CoV-2 infection in non-human primates. Sci. Transl. Med.
Jung, C., Kmiec, D., Koepke, L., Zech, F., Jacob, T., Sparrer, K.M.J., Kirchhoff, F., 2022. Omicron: what makes the latest SARS-CoV-2 variant of concern so concerning? J. Virol. 96, e0207721.
Kandeil, A., Mostafa, A., Hegazy, R.R., El-Shesheny, R., El Taweel, A., Gomaa, M.R., Shehata, M., Elbaset, M.A., Kayed, A.E., Mahmoud, S.H., Moatasim, Y., Kutkat, O., Yassen, N.N., Shabana, M.E., GabAllah, M., Kamel, M.N., Abo Shama, N.M., El Sayes, M., Ahmed, A.N., Elalfy, Z.S., Mohamed, B.M., Abd El-Fattah, S.N., El Hariri, H.M., Abdel Kader, M., Azmy, O., Kayali, G., Ali, M.A., 2021. Immunogenicity and safety of an inactivated SARS-CoV-2 vaccine: preclinical studies. Vaccines 9.
Kaptein, S.J.F., Jacobs, S., Langendries, L., Seldeslachts, L., Ter Horst, S., Liesenborghs, L., Hens, B., Vergote, V., Heylen, E., Barthelemy, K., Maas, E., De Keyzer, C., Bervoets, L., Rymenants, J., Van Buyten, T., Zhang, X., Abdelnabi, R., Pang, J., Williams, R., Thibaut, H.J., Dallmeier, K., Boudewijns, R., Wouters, J., Augustijns, P., Verougstraete, N., Cawthorne, C., Breuer, J., Solas, C., Weynand, B., Annaert, P., Spriet, I., Vande Velde, G., Neyts, J., Rocha-Pereira, J., Delang, L., 2020. 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 117, 26955–26965.
Kato, H., Takayama-Ito, M., Iizuka-Shiota, I., Fukushi, S., Posadas-Herrera, G., Horiya, M., Satoh, M., Yoshikawa, T., Yamada, S., Harada, S., Fujii, H., Shibamura, M., Inagaki, T., Morimoto, K., Saijo, M., Lim, C.K., 2019. Development of a recombinant replication-deficient rabies virus-based bivalent-vaccine against MERS-CoV and rabies virus and its humoral immunogenicity in mice. PLoS One 14, e0223684.
Kausar, S., Said Khan, F., Ishaq Mujeeb Ur Rehman, M., Akram, M., Riaz, M., Rasool, G., Hamid Khan, A., Saleem, I., Shamim, S., Malik, A., 2021. A review: mechanism of action of antiviral drugs. Int. J. Immunopathol. Pharmacol. 35, 20587384211002621.
Kim, Y.I., Kim, S.G., Kim, S.M., Kim, E.H., Park, S.J., Yu, K.M., Chang, J.H., Kim, E.J., Lee, S., Casel, M.A.B., Um, J., Song, M.S., Jeong, H.W., Lai, V.D., Kim, Y., Chin, B.S., Park, J.S., Chung, K.H., Foo, S.S., Poo, H., Mo, I.P., Lee, O.J., Webby, R.J., Jung, J.U., Choi, Y.K., 2020. Infection and rapid transmission of SARS-CoV-2 in ferrets. Cell Host Microbe 27, 704–709 e702.
Kim, C., Ryu, D.K., Lee, J., Kim, Y.I., Seo, J.M., Kim, Y.G., Jeong, J.H., Kim, M., Kim, J.I., Kim, P., Bae, J.S., Shim, E.Y., Lee, M.S., Kim, M.S., Noh, H., Park, G.S., Park, J.S., Son, D., An, Y., Lee, J.N., Kwon, K.S., Lee, J.Y., Lee, H., Yang, J.S., Kim, K.C., Kim, S. S., Woo, H.M., Kim, J.W., Park, M.S., Yu, K.M., Kim, S.M., Kim, E.H., Park, S.J., Jeong, S.T., Yu, C.H., Song, Y., Gu, S.H., Oh, H., Koo, B.S., Hong, J.J., Ryu, C.M., Park, W.B., Oh, M.D., Choi, Y.K., Lee, S.Y., 2021. A therapeutic neutralizing antibody targeting receptor binding domain of SARS-CoV-2 spike protein. Nat. Commun. 12, 288.
Kobinger, G.P., Figueredo, J.M., Rowe, T., Zhi, Y., Gao, G., Sanmiguel, J.C., Bell, P., Wivel, N.A., Zitzow, L.A., Flieder, D.B., Hogan, R.J., Wilson, J.M., 2007. Adenovirus-based vaccine prevents pneumonia in ferrets challenged with the SARS coronavirus and stimulates robust immune responses in macaques. Vaccine 25, 5220–5231.
Koo, B.S., Oh, H., Kim, G., Hwang, E.H., Jung, H., Lee, Y., Kang, P., Park, J.H., Ryu, C.M., Hong, J.J., 2020. Transient lymphopenia and interstitial pneumonia with endotheliitis in SARS-CoV-2-infected macaques. J. Infect. Dis. 222, 1596–1600.
Kreye, J., Reincke, S.M., Kornau, H.C., Sánchez-Sendin, E., Corman, V.M., Liu, H., Yuan, M., Wu, N.C., Zhu, X., Lee, C.D., Trimpert, J., Höltje, M., Dietert, K., Stöffler, L., von Wardenburg, N., van Hoof, S., Homeyer, M.A., Hoffmann, J., Abdelgawad, A., Gruber, A.D., Bertzbach, L.D., Vladimirova, D., Li, L.Y., Barthel, P. C., Skriner, K., Hocke, A.C., Hippenstiel, S., Witzenrath, M., Suttorp, N., Kurth, F., Franke, C., Endres, M., Schmitz, D., Jeworowski, L.M., Richter, A., Schmidt, M.L., Schwarz, T., Müller, M.A., Drosten, C., Wendisch, D., Sander, L.E., Osterrieder, N., Wilson, I.A., Prüss, H., 2020. A therapeutic non-self-reactive SARS-CoV-2 antibody protects from lung pathology in a COVID-19 hamster model. Cell 183, 1058–1069 e1019.
Kuba, K., Imai, Y., Rao, S., Gao, H., Guo, F., Guan, B., Huan, Y., Yang, P., Zhang, Y., Deng, W., Bao, L., Zhang, B., Liu, G., Wang, Z., Chappell, M., Liu, Y., Zheng, D., Leibbrandt, A., Wada, T., Slutsky, A.S., Liu, D., Qin, C., Jiang, C., Penninger, J.M., 2005. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat. Med. 11, 875–879.
Kumaki, Y., Wandersee, M.K., Smith, A.J., Zhou, Y., Simmons, G., Nelson, N.M., Bailey, K.W., Vest, Z.G., Li, J.K., Chan, P.K., Smee, D.F., Barnard, D.L., 2011. Inhibition of severe acute respiratory syndrome coronavirus replication in a lethal SARS-CoV BALB/c mouse model by stinging nettle lectin, Urtica dioica agglutinin. Antivir. Res. 90, 22–32.
Kupferschmidt, K., Wadman, M., 2021. Delta Variant Triggers New Phase in the Pandemic, vol. 372, pp. 1375–1376.
Kurup, D., Malherbe, D.C., Wirblich, C., Lambert, R., Ronk, A.J., Zabihi Diba, L., Bukreyev, A., Schnell, M.J., 2021. Inactivated rabies virus vectored SARS-CoV-2 vaccine prevents disease in a Syrian hamster model. PLoS Pathog. 17, e1009383.
Kutter, J.S., de Meulder, D., Bestebroer, T.M., Lexmond, P., Mulders, A., Richard, M., Fouchier, R.A.M., Herfst, S., 2021. SARS-CoV and SARS-CoV-2 are transmitted through the air between ferrets over more than one meter distance. Nat. Commun. 12, 1653.
Lambe, T., Spencer, A.J., Thomas, K.M., Gooch, K.E., Thomas, S., White, A.D., Humphries, H.E., Wright, D., Belij-Rammerstorfer, S., Thakur, N., Conceicao, C., Watson, R., Alden, L., Allen, L., Aram, M., Bewley, K.R., Brunt, E., Brown, P., Cavell, B.E., Cobb, R., Fotheringham, S.A., Gilbride, C., Harris, D.J., Ho, C.M.K., Hunter, L., Kennard, C.L., Leung, S., Lucas, V., Ngabo, D., Ryan, K.A., Sharpe, H., Sarfas, C., Sibley, L., Slack, G.S., Ulaszewska, M., Wand, N., Wiblin, N.R., Gleeson, F. V., Bailey, D., Sharpe, S., Charlton, S., Salguero, F.J., Carroll, M.W., Gilbert, S.C., 2021. ChAdOx1 nCoV-19 protection against SARS-CoV-2 in rhesus macaque and ferret challenge models. Commun. Biol. 4, 915.
Lan, J., Yao, Y., Deng, Y., Chen, H., Lu, G., Wang, W., Bao, L., Deng, W., Wei, Q., Gao, G. F., Qin, C., Tan, W., 2015. Recombinant receptor binding domain protein induces partial protective immunity in rhesus macaques against Middle East respiratory syndrome coronavirus challenge. EBioMedicine 2, 1438–1446.
Lawler, J.V., Endy, T.P., Hensley, L.E., Garrison, A., Fritz, E.A., Lesar, M., Baric, R.S., Kulesh, D.A., Norwood, D.A., Wasieloski, L.P., Ulrich, M.P., Slezak, T.R., Vitalis, E., Huggins, J.W., Jahrling, P.B., Paragas, J., 2006. Cynomolgus macaque as an animal model for severe acute respiratory syndrome. PLoS Med. 3, e149.
Lee, N., Hui, D., Wu, A., Chan, P., Cameron, P., Joynt, G.M., Ahuja, A., Yung, M.Y., Leung, C.B., To, K.F., Lui, S.F., Szeto, C.C., Chung, S., Sung, J.J., 2003. A major outbreak of severe acute respiratory syndrome in Hong Kong. N. Engl. J. Med. 348, 1986–1994.
Leung, W.K., To, K.F., Chan, P.K., Chan, H.L., Wu, A.K., Lee, N., Yuen, K.Y., Sung, J.J., 2003. Enteric involvement of severe acute respiratory syndrome-associated coronavirus infection. Gastroenterology 125, 1011–1017.
Li, S.S., Cheng, C.W., Fu, C.L., Chan, Y.H., Lee, M.P., Chan, J.W., Yiu, S.F., 2003. Left ventricular performance in patients with severe acute respiratory syndrome: a 30-day echocardiographic follow-up study. Circulation 108, 1798–1803.
Li, B.J., Tang, Q., Cheng, D., Qin, C., Xie, F.Y., Wei, Q., Xu, J., Liu, Y., Zheng, B.J., Woodle, M.C., Zhong, N., Lu, P.Y., 2005a. Using siRNA in prophylactic and therapeutic regimens against SARS coronavirus in Rhesus macaque. Nat. Med. 11, 944–951.
Li, F., Li, W., Farzan, M., Harrison, S.C., 2005b. Structure of SARS coronavirus spike receptor-binding domain complexed with receptor. Science (New York, N.Y.) 309, 1864–1868.
Li, Y., Wan, Y., Liu, P., Zhao, J., Lu, G., Qi, J., Wang, Q., Lu, X., Wu, Y., Liu, W., Zhang, B., Yuen, K.Y., Perlman, S., Gao, G.F., Yan, J., 2015. A humanized neutralizing antibody against MERS-CoV targeting the receptor-binding domain of the spike protein. Cell Res. 25, 1237–1249.
Li, K., Wohlford-Lenane, C., Perlman, S., Zhao, J., Jewell, A.K., Reznikov, L.R., Gibson-Corley, K.N., Meyerholz, D.K., McCray Jr., P.B., 2016. Middle East respiratory syndrome coronavirus causes multiple organ damage and lethal disease in mice transgenic for human dipeptidyl peptidase 4. J. Infect. Dis. 213, 712–722.
Li, W., Chen, C., Drelich, A., Martinez, D.R., Gralinski, L.E., Sun, Z., Schäfer, A., Kulkarni, S.S., Liu, X., Leist, S.R., Zhelev, D.V., Zhang, L., Kim, Y.J., Peterson, E.C., Conard, A., Mellors, J.W., Tseng, C.K., Falzarano, D., Baric, R.S., Dimitrov, D.S., 2020a. Rapid identification of a human antibody with high prophylactic and therapeutic efficacy in three animal models of SARS-CoV-2 infection. In: Proceedings

of the National Academy of Sciences of the United States of America, vol. 117, pp. 29832–29838.
Li, W., Schäfer, A., Kulkarni, S.S., Liu, X., Martinez, D.R., Chen, C., Sun, Z., Leist, S.R., Drelich, A., Zhang, L., Ura, M.L., Berezuk, A., Chittori, S., Leopold, K., Mannar, D., Srivastava, S.S., Zhu, X., Peterson, E.C., Tseng, C.T., Mellors, J.W., Falzarano, D., Subramaniam, S., Baric, R.S., Dimitrov, D.S., 2020b. High potency of a bivalent human V(H) domain in SARS-CoV-2 animal models. Cell 183, 429–441 e416.
Li, J.Q., Zhang, Z.R., Zhang, H.Q., Zhang, Y.N., Zeng, X.Y., Zhang, Q.Y., Deng, C.L., Li, X. D., Zhang, B., Ye, H.Q., 2021a. Intranasal delivery of replicating mRNA encoding neutralizing antibody against SARS-CoV-2 infection in mice. Signal Transduct. Targeted Ther. 6, 369.
Li, K., Meyerholz, D.K., Bartlett, J.A., McCray Jr., P.B., 2021b. The TMPRSS2 inhibitor nafamostat reduces SARS-CoV-2 pulmonary infection in mouse models of COVID-19. mBio 12, e0097021.
Li, T., Han, X., Gu, C., Guo, H., Zhang, H., Wang, Y., Hu, C., Wang, K., Liu, F., Luo, F., Zhang, Y., Hu, J., Wang, W., Li, S., Hao, Y., Shen, M., Huang, J., Long, Y., Song, S., Wu, R., Mu, S., Chen, Q., Gao, F., Wang, J., Long, S., Li, L., Wu, Y., Gao, Y., Xu, W., Cai, X., Qu, D., Zhang, Z., Zhang, H., Li, N., Gao, Q., Zhang, G., He, C., Wang, W., Ji, X., Tang, N., Yuan, Z., Xie, Y., Yang, H., Zhang, B., Huang, A., Jin, A., 2021c. Potent SARS-CoV-2 neutralizing antibodies with protective efficacy against newly emerged mutational variants. Nat. Commun. 12, 6304.
Li, Y., Bi, Y., Xiao, H., Yao, Y., Liu, X., Hu, Z., Duan, J., Yang, Y., Li, Z., Li, Y., Zhang, H., Ding, C., Yang, J., Li, H., He, Z., Liu, L., Hu, G., Liu, S., Che, Y., Wang, S., Li, Q., Lu, S., Cun, W., 2021d. A novel DNA and protein combination COVID-19 vaccine formulation provides full protection against SARS-CoV-2 in rhesus macaques. Emerg. Microb. Infect. 10, 342–355.
Li, P., Wang, Y., Lavrijsen, M., Lamers, M.M., de Vries, A.C., Rottier, R.J., Bruno, M.J., Peppelenbosch, M.P., Haagmans, B.L., Pan, Q., 2022a. SARS-CoV-2 Omicron variant is highly sensitive to molnupiravir, nirmatrelvir, and the combination. Cell Res. 32, 322–324.
Li, Y., Cao, L., Li, G., Cong, F., Li, Y., Sun, J., Luo, Y., Chen, G., Li, G., Wang, P., Xing, F., Ji, Y., Zhao, J., Zhang, Y., Guo, D., Zhang, X., 2022b. Remdesivir metabolite GS-441524 effectively inhibits SARS-CoV-2 infection in mouse models. J. Med. Chem. 65, 2785–2793.
Liang, J.G., Su, D., Song, T.Z., Zeng, Y., Huang, W., Wu, J., Xu, R., Luo, P., Yang, X., Zhang, X., Luo, S., Liang, Y., Li, X., Huang, J., Wang, Q., Huang, X., Xu, Q., Luo, M., Huang, A., Luo, D., Zhao, C., Yang, F., Han, J.B., Zheng, Y.T., Liang, P., 2021. S-Trimer, a COVID-19 subunit vaccine candidate, induces protective immunity in nonhuman primates. Nat. Commun. 12, 1346.
Lin, H.X.J., Cho, S., Meyyur Aravamudan, V., Sanda, H.Y., Palraj, R., Molton, J.S., Venkatachalam, I., 2021. Remdesivir in Coronavirus Disease 2019 (COVID-19) treatment: a review of evidence. Infection 49, 401–410.
Liu, R., Wang, J., Shao, Y., Wang, X., Zhang, H., Shuai, L., Ge, J., Wen, Z., Bu, Z., 2018. A recombinant VSV-vectored MERS-CoV vaccine induces neutralizing antibody and T cell responses in rhesus monkeys after single dose immunization. Antivir. Res. 150, 30–38.
Liu, R., Americo, J.L., Cotter, C.A., Earl, P.L., Erez, N., Peng, C., Moss, B., 2021. One or two injections of MVA-vectored vaccine shields hACE2 transgenic mice from SARS-CoV-2 upper and lower respiratory tract infection. In: Proceedings of the National Academy of Sciences of the United States of America, vol. 118.
Lu, S., Zhao, Y., Yu, W., Yang, Y., Gao, J., Wang, J., Kuang, D., Yang, M., Yang, J., Ma, C., Xu, J., Qian, X., Li, H., Zhao, S., Li, J., Wang, H., Long, H., Zhou, J., Luo, F., Ding, K., Wu, D., Zhang, Y., Dong, Y., Liu, Y., Zheng, Y., Lin, X., Jiao, L., Zheng, H., Dai, Q., Sun, Q., Hu, Y., Ke, C., Liu, H., Peng, X., 2020. Comparison of nonhuman primates identified the suitable model for COVID-19. Signal Transduct. Targeted Ther. 5, 157.
Lu, M., Dravid, P., Zhang, Y., Trivedi, S., Li, A., Harder, O., Kc, M., Chaiwatpongsakorn, S., Zani, A., Kenney, A., Zeng, C., Cai, C., Ye, C., Liang, X., Shimamura, M., Liu, S.L., Mejias, A., Ramilo, O., Boyaka, P.N., Qiu, J., Martinez-Sobrido, L., Yount, J.S., Peeples, M.E., Kapoor, A., Niewiesk, S., Li, J., 2021a. A safe and highly efficacious measles virus-based vaccine expressing SARS-CoV-2 stabilized prefusion spike. In: Proceedings of the National Academy of Sciences of the United States of America, vol. 118.
Lu, S., Zhao, J., Dong, J., Liu, H., Zhu, Y., Li, H., Liu, L., Yang, Y., Sun, S., Song, Y., Zhao, Y., She, R., Luo, T., Deng, H., Peng, X., 2021b. Effective treatment of SARS-CoV-2-infected rhesus macaques by attenuating inflammation. Cell Res. 31, 229–232.
Luke, T., Wu, H., Zhao, J., Channappanavar, R., Coleman, C.M., Jiao, J.A., Matsushita, H., Liu, Y., Postnikova, E.N., Ork, B.L., Glenn, G., Flyer, D., Defang, G., Raviprakash, K., Kochel, T., Wang, J., Nie, W., Smith, G., Hensley, L.E., Olinger, G. G., Kuhn, J.H., Holbrook, M.R., Johnson, R.F., Perlman, S., Sullivan, E., Frieman, M. B., 2016. Human polyclonal immunoglobulin G from transchromosomic bovines inhibits MERS-CoV in vivo. Sci. Transl. Med. 8, 326ra321.
Ma, X., Zou, F., Yu, F., Li, R., Yuan, Y., Zhang, Y., Zhang, X., Deng, J., Chen, T., Song, Z., Qiao, Y., Zhan, Y., Liu, J., Zhang, J., Zhang, X., Peng, Z., Li, Y., Lin, Y., Liang, L., Wang, G., Chen, Y., Chen, Q., Pan, T., He, X., Zhang, H., 2020. Nanoparticle vaccines based on the receptor binding domain (RBD) and heptad repeat (HR) of SARS-CoV-2 elicit robust protective immune responses. Immunity 53, 1315–1330 e1319.
Mahase, E., 2021a. Covid-19: molnupiravir reduces risk of hospital admission or death by 50% in patients at risk, MSD reports. BMJ (Clin. Res. Ed.) 375, n2422.
Mahase, E., 2021b. Covid-19: pfizer's paxlovid is 89% effective in patients at risk of serious illness, company reports. BMJ (Clin. Res. Ed.) 375, n2713.
Maisonnasse, P., Aldon, Y., Marc, A., Marlin, R., Dereuddre-Bosquet, N., Kuzmina, N.A., Freyn, A.W., Snitselaar, J.L., Gonçalves, A., Caniels, T.G., Burger, J.A., Poniman, M., Bontjer, I., Chesnais, V., Diry, S., Iershov, A., Ronk, A.J., Jangra, S., Rathnasinghe, R., Brouwer, P.J.M., Bijl, T.P.L., van Schooten, J., Brinkkemper, M., Liu, H., Yuan, M., Mire, C.E., van Breemen, M.J., Contreras, V., Naninck, T., Lemaître, J., Kahlaoui, N., Relouzat, F., Chapon, C., Ho Tsong Fang, R., McDanal, C., Osei-Twum, M., St-Amant, N., Gagnon, L., Montefiori, D.C., Wilson, I.A., Ginoux, E., de Bree, G.J., García-Sastre, A., Schotsaert, M., Coughlan, L., Bukreyev, A., van der Werf, S., Guedj, J., Sanders, R.W., van Gils, M.J., Le Grand, R., 2021. COVA1-18 neutralizing antibody protects against SARS-CoV-2 in three preclinical models. Nat. Commun. 12, 6097.
Malczyk, A.H., Kupke, A., Prufer, S., Scheuplein, V.A., Hutzler, S., Kreuz, D., Beissert, T., Bauer, S., Hubich-Rau, S., Tondera, C., Eldin, H.S., Schmidt, J., Vergara-Alert, J., Suzer, Y., Seifried, J., Hanschmann, K.M., Kalinke, U., Herold, S., Sahin, U., Cichutek, K., Waibler, Z., Eickmann, M., Becker, S., Muhlebach, M.D., 2015. A highly immunogenic and protective Middle East respiratory syndrome coronavirus vaccine based on a recombinant measles virus vaccine platform. J. Virol. 89, 11654–11667.
Marsh, G.A., McAuley, A.J., Au, G.G., Riddell, S., Layton, D., Singanallur, N.B., Layton, R., Payne, J., Durr, P.A., Bender, H., Barr, J.A., Bingham, J., Boyd, V., Brown, S., Bruce, M.P., Burkett, K., Eastwood, T., Edwards, S., Gough, T., Halpin, K., Harper, J., Holmes, C., Horman, W.S.J., van Vuren, P.J., Lowther, S., Maynard, K., McAuley, K.D., Neave, M.J., Poole, T., Rootes, C., Rowe, B., Soldani, E., Stevens, V., Stewart, C.R., Suen, W.W., Tachedjian, M., Todd, S., Trinidad, L., Walter, D., Watson, N., Drew, T.W., Gilbert, S.C., Lambe, T., Vasan, S.S., 2021a. ChAdOx1 nCoV-19 (AZD1222) vaccine candidate significantly reduces SARS-CoV-2 shedding in ferrets. NPJ Vaccine 6, 67.
Marsh, G.A., McAuley, A.J., Brown, S., Pharo, E.A., Crameri, S., Au, G.G., Baker, M.L., Barr, J.A., Bergfeld, J., Bruce, M.P., Burkett, K., Durr, P.A., Holmes, C., Izzard, L., Layton, R., Lowther, S., Neave, M.J., Poole, T., Riddell, S.J., Rowe, B., Soldani, E., Stevens, V., Suen, W.W., Sundaramoorthy, V., Tachedjian, M., Todd, S., Trinidad, L., Williams, S.M., Druce, J.D., Drew, T.W., Vasan, S.S., 2021b. In vitro characterisation of SARS-CoV-2 and susceptibility of domestic ferrets (Mustela putorius furo). Transboundary Emerg. Dis.
McAuliffe, J., Vogel, L., Roberts, A., Fahle, G., Fischer, S., Shieh, W.J., Butler, E., Zaki, S., St Claire, M., Murphy, B., Subbarao, K., 2004. Replication of SARS coronavirus administered into the respiratory tract of African Green, rhesus and cynomolgus monkeys. Virology 330, 8–15.
McCray Jr., P.B., Pewe, L., Wohlford-Lenane, C., Hickey, M., Manzel, L., Shi, L., Netland, J., Jia, H.P., Halabi, C., Sigmund, C.D., Meyerholz, D.K., Kirby, P., Look, D. C., Perlman, S., 2007. Lethal infection of K18-hACE2 mice infected with severe acute respiratory syndrome coronavirus. J. Virol. 81, 813–821.
Menachery, V.D., Yount Jr., B.L., Sims, A.C., Debbink, K., Agnihothram, S.S., Gralinski, L. E., Graham, R.L., Scobey, T., Plante, J.A., Royal, S.R., Swanstrom, J., Sheahan, T.P., Pickles, R.J., Corti, D., Randell, S.H., Lanzavecchia, A., Marasco, W.A., Baric, R.S., 2016. SARS-like WIV1-CoV poised for human emergence. Proc. Natl. Acad. Sci. U. S. A. 113, 3048–3053.
Meo, S.A., Alhowikan, A.M., Al-Khlaiwi, T., Meo, I.M., Halepoto, D.M., Iqbal, M., Usmani, A.M., Hajjar, W., Ahmed, N., 2020. Novel coronavirus 2019-nCoV: prevalence, biological and clinical characteristics comparison with SARS-CoV and MERS-CoV. Eur. Rev. Med. Pharmacol. Sci. 24, 2012–2019.
Mercado, N.B., Zahn, R., Wegmann, F., Loos, C., Chandrashekar, A., Yu, J., Liu, J., Peter, L., McMahan, K., Tostanoski, L.H., He, X., Martinez, D.R., Rutten, L., Bos, R., van Manen, D., Vellinga, J., Custers, J., Langedijk, J.P., Kwaks, T., Bakkers, M.J.G., Zuijdgeest, D., Rosendahl Huber, S.K., Atyeo, C., Fischinger, S., Burke, J.S., Feldman, J., Hauser, B.M., Caradonna, T.M., Bondzie, E.A., Dagotto, G., Gebre, M.S., Hoffman, E., Jacob-Dolan, C., Kirilova, M., Li, Z., Lin, Z., Mahrokhian, S.H., Maxfield, L.F., Nampanya, F., Nityanandam, R., Nkolola, J.P., Patel, S., Ventura, J. D., Verrington, K., Wan, H., Pessaint, L., Van Ry, A., Blade, K., Strasbaugh, A., Cabus, M., Brown, R., Cook, A., Zouantchangadou, S., Teow, E., Andersen, H., Lewis, M.G., Cai, Y., Chen, B., Schmidt, A.G., Reeves, R.K., Baric, R.S., Lauffenburger, D.A., Alter, G., Stoffels, P., Mammen, M., Van Hoof, J., Schuitemaker, H., Barouch, D.H., 2020. Single-shot Ad26 vaccine protects against SARS-CoV-2 in rhesus macaques. Nature 586, 583–588.
Meyer, M., Wang, Y., Edwards, D., Smith, G.R., Rubenstein, A.B., Ramanathan, P., Mire, C.E., Pietzsch, C., Chen, X., Ge, Y., Cheng, W.S., Henry, C., Woods, A., Ma, L., Stewart-Jones, G.B., Bock, K.W., Minai, M., Nagata, B.M., Periasamy, S., Shi, P.Y., Graham, B.S., Moore, I.N., Ramos, I., Troyanskaya, O.G., Zaslavsky, E., Carfi, A., Sealfon, S.C., Bukreyev, A., 2021. Attenuated activation of pulmonary immune cells in mRNA-1273-vaccinated hamsters after SARS-CoV-2 infection. J. Clin. Invest. 131.
Mohandas, S., Yadav, P.D., Shete-Aich, A., Abraham, P., Vadrevu, K.M., Sapkal, G., Mote, C., Nyayanit, D., Gupta, N., Srinivas, V.K., Kadam, M., Kumar, A., Majumdar, T., Jain, R., Deshpande, G., Patil, S., Sarkale, P., Patil, D., Ella, R., Prasad, S.D., Sharma, S., Ella, K.M., Panda, S., Bhargava, B., 2021. Immunogenicity and protective efficacy of BBV152, whole virion inactivated SARS- CoV-2 vaccine candidates in the Syrian hamster model. iScience 24, 102054.
Monchatre-Leroy, E., Lesellier, S., Wasniewski, M., Picard-Meyer, E., Richomme, C., Boué, F., Lacôte, S., Murri, S., Pulido, C., Vulin, J., Salguero, F.J., Gouilh, M.A., Servat, A., Marianneau, P., 2021. Hamster and ferret experimental infection with intranasal low dose of a single strain of SARS-CoV-2. J. Gen. Virol. 102.
Moore, J.B., June, C.H., 2020. Cytokine release syndrome in severe COVID-19. Science 368, 473–474.
Munster, V.J., Feldmann, F., Williamson, B.N., van Doremalen, N., Pérez-Pérez, L., Schulz, J., Meade-White, K., Okumura, A., Callison, J., Brumbaugh, B., Avanzato, V. A., Rosenke, R., Hanley, P.W., Saturday, G., Scott, D., Fischer, E.R., de Wit, E., 2020. Respiratory disease in rhesus macaques inoculated with SARS-CoV-2. Nature 585, 268–272.
Muthumani, K., Falzarano, D., Reuschel, E.L., Tingey, C., Flingai, S., Villarreal, D.O., Wise, M., Patel, A., Izmirly, A., Aljuaid, A., Seliga, A.M., Soule, G., Morrow, M., Kraynyak, K.A., Khan, A.S., Scott, D.P., Feldmann, F., LaCasse, R., Meade-White, K., Okumura, A., Ugen, K.E., Sardesai, N.Y., Kim, J.J., Kobinger, G., Feldmann, H., Weiner, D.B., 2015. A synthetic consensus anti-spike protein DNA vaccine induces

protective immunity against Middle East respiratory syndrome coronavirus in nonhuman primates. Sci. Transl. Med. 7, 301ra132.
Nargis, T., Chakrabarti, P., 2018. Significance of circulatory DPP4 activity in metabolic diseases. IUBMB Life 70, 112–119.
Nemet, I., Kliker, L., Lustig, Y., Zuckerman, N., Erster, O., Cohen, C., Kreiss, Y., Alroy-Preis, S., Regev-Yochay, G., Mendelson, E., Mandelboim, M., 2021. Third BNT162b2 vaccination neutralization of SARS-CoV-2 Omicron infection. N. Engl. J. Med.
Ning, L., Abagna, H.B., Jiang, Q., Liu, S., Huang, J., 2021. Development and application of therapeutic antibodies against COVID-19. Int. J. Biol. Sci. 17, 1486–1496.
Nuñez, I.A., Lien, C.Z., Selvaraj, P., Stauft, C.B., Liu, S., Starost, M.F., Wang, T.T., 2021. SARS-CoV-2 B.1.1.7 Infection of Syrian Hamster Does Not Cause More Severe Disease, and Naturally Acquired Immunity Confers Protection. mSphere, e0050721.
Owen, D.R., Allerton, C.M.N., Anderson, A.S., Aschenbrenner, L., Avery, M., Berritt, S., Boras, B., Cardin, R.D., Carlo, A., Coffman, K.J., Dantonio, A., Di, L., Eng, H., Ferre, R., Gajiwala, K.S., Gibson, S.A., Greasley, S.E., Hurst, B.L., Kadar, E.P., Kalgutkar, A.S., Lee, J.C., Lee, J., Liu, W., Mason, S.W., Noell, S., Novak, J.J., Obach, R.S., Ogilvie, K., Patel, N.C., Pettersson, M., Rai, D.K., Reese, M.R., Sammons, M.F., Sathish, J.G., Singh, R.S.P., Steppan, C.M., Stewart, A.E., Tuttle, J. B., Updyke, L., Verhoest, P.R., Wei, L., Yang, Q., Zhu, Y., 2021. An oral SARS-CoV-2 M(pro) inhibitor clinical candidate for the treatment of COVID-19. Science (New York, N.Y.) 374, 1586–1593.
Pan, Y., Du, J., Liu, J., Wu, H., Gui, F., Zhang, N., Deng, X., Song, G., Li, Y., Lu, J., Wu, X., Zhan, S., Jing, Z., Wang, J., Yang, Y., Liu, J., Chen, Y., Chen, Q., Zhang, H., Hu, H., Duan, K., Wang, M., Wang, Q., Yang, X., 2021. Screening of potent neutralizing antibodies against SARS-CoV-2 using convalescent patients-derived phage-display libraries. Cell Discover. 7, 57.
Pandey, K., Acharya, A., Mohan, M., Ng, C.L., Reid, S.P., Byrareddy, S.N., 2021. Animal models for SARS-CoV-2 research: a comprehensive literature review. Transboundary Emerg. Dis. 68, 1868–1885.
Peckham, H., de Gruijter, N.M., Raine, C., Radziszewska, A., Ciurtin, C., Wedderburn, L. R., Rosser, E.C., Webb, K., Deakin, C.T., 2020. Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ITU admission. Nat. Commun. 11, 6317.
Peiris, J.S., Yuen, K.Y., Osterhaus, A.D., Stöhr, K., 2003a. The severe acute respiratory syndrome. N. Engl. J. Med. 349, 2431–2441.
Peiris, J.S.M., Lai, S.T., Poon, L.L.M., Guan, Y., Yam, L.Y.C., Lim, W., Nicholls, J., Yee, W. K.S., Yan, W.W., Cheung, M.T., Cheng, V.C.C., Chan, K.H., Tsang, D.N.C., Yung, R.W. H., Ng, T.K., Yuen, K.Y., Grp, S.S., 2003b. Coronavirus as a possible cause of severe acute respiratory syndrome. Lancet (London, England) 361, 1319–1325.
Planas, D., Bruel, T., Grzelak, L., Guivel-Benhassine, F., Staropoli, I., Porrot, F., Planchais, C., Buchrieser, J., Rajah, M.M., Bishop, E., Albert, M., Donati, F., Prot, M., Behillil, S., Enouf, V., Maquart, M., Smati-Lafarge, M., Varon, E., Schortgen, F., Yahyaoui, L., Gonzalez, M., De Sèze, J., Péré, H., Veyer, D., Sève, A., Simon-Lorière, E., Fafi-Kremer, S., Stefic, K., Mouquet, H., Hocqueloux, L., van der Werf, S., Prazuck, T., Schwartz, O., 2021. Sensitivity of infectious SARS-CoV-2 B.1.1.7 and B.1.351 variants to neutralizing antibodies. Nat. Med. 27, 917–924.
Plante, K.S., Dwivedi, V., Plante, J.A., Fernandez, D., Mirchandani, D., Bopp, N., Aguilar, P.V., Park, J.G., Tamayo, P.P., Delgado, J., Shivanna, V., Torrelles, J.B., Martinez-Sobrido, L., Matos, R., Weaver, S.C., Sastry, K.J., Newman, R.A., 2021. Antiviral activity of oleandrin and a defined extract of Nerium oleander against SARS-CoV-2. Biomed. Pharmacolther. 138, 111457.
Polack, F.P., Thomas, S.J., Kitchin, N., Absalon, J., Gurtman, A., Lockhart, S., Perez, J.L., Pérez Marc, G., Moreira, E.D., Zerbini, C., Bailey, R., Swanson, K.A., Roychoudhury, S., Koury, K., Li, P., Kalina, W.V., Cooper, D., Frenck Jr., R.W., Hammitt, L.L., Türeci, Ö., Nell, H., Schaefer, A., Ünal, S., Tresnan, D.B., Mather, S., Dormitzer, P.R., Şahin, U., Jansen, K.U., Gruber, W.C., 2020. Safety and efficacy of the BNT162b2 mRNA covid-19 vaccine. N. Engl. J. Med. 383, 2603–2615.
Proud, P.C., Tsitoura, D., Watson, R.J., Chua, B.Y., Aram, M.J., Bewley, K.R., Cavell, B.E., Cobb, R., Dowall, S., Fotheringham, S.A., Ho, C.M.K., Lucas, V., Ngabo, D., Rayner, E., Ryan, K.A., Slack, G.S., Thomas, S., Wand, N.I., Yeates, P., Demaison, C., Zeng, W., Holmes, I., Jackson, D.C., Bartlett, N.W., Mercuri, F., Carroll, M.W., 2021. Prophylactic intranasal administration of a TLR2/6 agonist reduces upper respiratory tract viral shedding in a SARS-CoV-2 challenge ferret model. EBioMedicine 63, 103153.
Qin, E., Shi, H., Tang, L., Wang, C., Chang, G., Ding, Z., Zhao, K., Wang, J., Chen, Z., Yu, M., Si, B., Liu, J., Wu, D., Cheng, X., Yang, B., Peng, W., Meng, Q., Liu, B., Han, W., Yin, X., Duan, H., Zhan, D., Tian, L., Li, S., Wu, J., Tan, G., Li, Y., Li, Y., Liu, Y., Liu, H., Lv, F., Zhang, Y., Kong, X., Fan, B., Jiang, T., Xu, S., Wang, X., Li, C., Wu, X., Deng, Y., Zhao, M., Zhu, Q., 2006. Immunogenicity and protective efficacy in monkeys of purified inactivated Vero-cell SARS vaccine. Vaccine 24, 1028–1034.
Qin, M., Cao, Z., Wen, J., Yu, Q., Liu, C., Wang, F., Zhang, J., Yang, F., Li, Y., Fishbein, G., Yan, S., Xu, B., Hou, Y., Ning, Z., Nie, K., Jiang, N., Liu, Z., Wu, J., Yu, Y., Li, H., Zheng, H., Li, J., Jin, W., Pang, S., Wang, S., Chen, J., Gan, Z., He, Z., Lu, Y., 2020. An Antioxidant Enzyme Therapeutic for COVID-19. Advanced Materials, vol. 32. Deerfield Beach, Fla, e2004901.
Qiu, H., Sun, S., Xiao, H., Feng, J., Guo, Y., Tai, W., Wang, Y., Du, L., Zhao, G., Zhou, Y., 2016. Single-dose treatment with a humanized neutralizing antibody affords full protection of a human transgenic mouse model from lethal Middle East respiratory syndrome (MERS)-coronavirus infection. Antivir. Res. 132, 141–148.
Raj, V.S., Mou, H., Smits, S.L., Dekkers, D.H., Muller, M.A., Dijkman, R., Muth, D., Demmers, J.A., Zaki, A., Fouchier, R.A., Thiel, V., Drosten, C., Rottier, P.J., Osterhaus, A.D., Bosch, B.J., Haagmans, B.L., 2013. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. Nature 495, 251–254.
Raj, V.S., Farag, E.A., Reusken, C.B., Lamers, M.M., Pas, S.D., Voermans, J., Smits, S.L., Osterhaus, A.D., Al-Mawlawi, N., Al-Romaihi, H.E., AlHajri, M.M., El-Sayed, A.M., Mohran, K.A., Ghobashy, H., Alhajri, F., Al-Thani, M., Al-Marri, S.A., El-Maghraby, M.M., Koopmans, M.P., Haagmans, B.L., 2014a. Isolation of MERS coronavirus from a dromedary camel, Qatar. Emerg. Infect. Dis. 20, 1339–1342, 2014.
Raj, V.S., Smits, S.L., Provacia, L.B., van den Brand, J.M., Wiersma, L., Ouwendijk, W.J., Bestebroer, T.M., Spronken, M.I., van Amerongen, G., Rottier, P.J., Fouchier, R.A., Bosch, B.J., Osterhaus, A.D., Haagmans, B.L., 2014b. Adenosine deaminase acts as a natural antagonist for dipeptidyl peptidase 4-mediated entry of the Middle East respiratory syndrome coronavirus. J. Virol. 88, 1834–1838.
Ren, W., Zhu, Y., Wang, Y., Shi, H., Yu, Y., Hu, G., Feng, F., Zhao, X., Lan, J., Wu, J., Kenney, D.J., Douam, F., Tong, Y., Zhong, J., Xie, Y., Wang, X., Yuan, Z., Zhou, D., Zhang, R., Ding, Q., 2021. Comparative analysis reveals the species-specific genetic determinants of ACE2 required for SARS-CoV-2 entry. PLoS Pathog. 17, e1009392.
Richard, M., Kok, A., de Meulder, D., Bestebroer, T.M., Lamers, M.M., Okba, N.M.A., Fentener van Vlissingen, M., Rockx, B., Haagmans, B.L., Koopmans, M.P.G., Fouchier, R.A.M., Herfst, S., 2020. SARS-CoV-2 is transmitted via contact and via the air between ferrets. Nat. Commun. 11, 3496.
Roberts, A., Paddock, C., Vogel, L., Butler, E., Zaki, S., Subbarao, K., 2005a. Aged BALB/c mice as a model for increased severity of severe acute respiratory syndrome in elderly humans. J. Virol. 79, 5833–5838.
Roberts, A., Vogel, L., Guarner, J., Hayes, N., Murphy, B., Zaki, S., Subbarao, K., 2005b. Severe acute respiratory syndrome coronavirus infection of golden Syrian hamsters. J. Virol. 79, 503–511.
Roberts, A., Thomas, W.D., Guarner, J., Lamirande, E.W., Babcock, G.J., Greenough, T. C., Vogel, L., Hayes, N., Sullivan, J.L., Zaki, S., Subbarao, K., Ambrosino, D.M., 2006. Therapy with a severe acute respiratory syndrome-associated coronavirus-neutralizing human monoclonal antibody reduces disease severity and viral burden in golden Syrian hamsters. J. Infect. Dis. 193, 685–692.
Rockx, B., Feldmann, F., Brining, D., Gardner, D., LaCasse, R., Kercher, L., Long, D., Rosenke, R., Virtaneva, K., Sturdevant, D.E., Porcella, S.F., Mattoon, J., Parnell, M., Baric, R.S., Feldmann, H., 2011. Comparative pathogenesis of three human and zoonotic SARS-CoV strains in cynomolgus macaques. PLoS One 6, e18558.
Rockx, B., Kuiken, T., Herfst, S., Bestebroer, T., Lamers, M.M., Oude Munnink, B.B., de Meulder, D., van Amerongen, G., van den Brand, J., Okba, N.M.A., Schipper, D., van Run, P., Leijten, L., Sikkema, R., Verschoor, E., Verstrepen, B., Bogers, W., Langermans, J., Drosten, C., Fentener van Vlissingen, M., Fouchier, R., de Swart, R., Koopmans, M., Haagmans, B.L., 2020. Comparative pathogenesis of COVID-19, MERS, and SARS in a nonhuman primate model. Science (New York, N.Y.) 368, 1012–1015.
Roozendaal, R., Solforosi, L., Stieh, D.J., Serroyen, J., Straetemans, R., Dari, A., Boulton, M., Wegmann, F., Rosendahl Huber, S.K., van der Lubbe, J.E.M., Hendriks, J., Le Gars, M., Dekking, L., Czapska-Casey, D.N., Guimera, N., Janssen, S., Tete, S., Chandrashekar, A., Mercado, N.B., Yu, J., Koudstaal, W., Perez-Ruixo, J.J., Sadoff, J., Barouch, D.H., Schuitemaker, H., Zahn, R., 2021. SARS-CoV-2 binding and neutralizing antibody levels after Ad26.COV2.S vaccination predict durable protection in rhesus macaques. Nat. Commun. 12, 5877.
Rosenke, K., Meade-White, K., Letko, M., Clancy, C., Hansen, F., Liu, Y., Okumura, A., Tang-Huau, T.L., Li, R., Saturday, G., Feldmann, F., Scott, D., Wang, Z., Munster, V., Jarvis, M.A., Feldmann, H., 2020. Defining the Syrian hamster as a highly susceptible preclinical model for SARS-CoV-2 infection. Emerg. Microb. Infect. 9, 2673–2684.
Rosenke, K., Hansen, F., Schwarz, B., Feldmann, F., Haddock, E., Rosenke, R., Barbian, K., Meade-White, K., Okumura, A., Leventhal, S., Hawman, D.W., Ricotta, E., Bosio, C.M., Martens, C., Saturday, G., Feldmann, H., Jarvis, M.A., 2021. Orally delivered MK-4482 inhibits SARS-CoV-2 replication in the Syrian hamster model. Nat. Commun. 12, 2295.
Routhu, N.K., Cheedarla, N., Gangadhara, S., Bollimpelli, V.S., Boddapati, A.K., Shiferaw, A., Rahman, S.A., Sahoo, A., Edara, V.V., Lai, L., Floyd, K., Wang, S., Fischinger, S., Atyeo, C., Shin, S.A., Gumber, S., Kirejczyk, S., Cohen, J., Jean, S.M., Wood, J.S., Connor-Stroud, F., Stammen, R.L., Upadhyay, A.A., Pellegrini, K., Montefiori, D., Shi, P.Y., Menachery, V.D., Alter, G., Vanderford, T.H., Bosinger, S.E., Suthar, M.S., Amara, R.R., 2021. A modified vaccinia Ankara vector-based vaccine protects macaques from SARS-CoV-2 infection, immune pathology, and dysfunction in the lungs. Immunity 54, 542–556 e549.
Rowe, T., Gao, G., Hogan, R.J., Crystal, R.G., Voss, T.G., Grant, R.L., Bell, P., Kobinger, G. P., Wivel, N.A., Wilson, J.M., 2004. Macaque model for severe acute respiratory syndrome. J. Virol. 78, 11401–11404.
Ryu, D.K., Song, R., Kim, M., Kim, Y.I., Kim, C., Kim, J.I., Kwon, K.S., Tijsma, A.S., Nuijten, P.M., van Baalen, C.A., Hermanus, T., Kgagudi, P., Moyo-Gwete, T., Moore, P.L., Choi, Y.K., Lee, S.Y., 2021. Therapeutic effect of CT-P59 against SARS-CoV-2 South African variant. Biochem. Biophys. Res. Commun. 566, 135–140.
Sakr, Y., Bensasi, H., Taha, A., Bauer, M., Ismail, K., 2021. Camostat mesylate therapy in critically ill patients with COVID-19 pneumonia. Intensive Care Med. 47, 707–709.
Salguero, F.J., White, A.D., Slack, G.S., Fotheringham, S.A., Bewley, K.R., Gooch, K.E., Longet, S., Humphries, H.E., Watson, R.J., Hunter, L., Ryan, K.A., Hall, Y., Sibley, L., Sarfas, C., Allen, L., Aram, M., Brunt, E., Brown, P., Buttigieg, K.R., Cavell, B.E., Cobb, R., Coombes, N.S., Darby, A., Daykin-Pont, O., Elmore, M.J., Garcia-Dorival, I., Gkolfinos, K., Godwin, K.J., Gouriet, J., Halkerston, R., Harris, D.J., Hender, T., Ho, C.M.K., Kennard, C.L., Knott, D., Leung, S., Lucas, V., Mabbutt, A., Morrison, A.L., Nelson, C., Ngabo, D., Paterson, J., Penn, E.J., Pullan, S., Taylor, I., Tipton, T., Thomas, S., Tree, J.A., Turner, C., Vamos, E., Wand, N., Wiblin, N.R., Charlton, S., Dong, X., Hallis, B., Pearson, G., Rayner, E.L., Nicholson, A.G., Funnell, S.G., Hiscox, J.A., Dennis, M.J., Gleeson, F.V., Sharpe, S., Carroll, M.W., 2021. Comparison of rhesus and cynomolgus macaques as an infection model for COVID-19. Nat. Commun. 12, 1260.
Sanchez-Felipe, L., Vercruysse, T., Sharma, S., Ma, J., Lemmens, V., Van Looveren, D., Arkalagud Javarappa, M.P., Boudewijns, R., Malengier-Devlies, B., Liesenborghs, L.,

Kaptein, S.J.F., De Keyzer, C., Bervoets, L., Debaveye, S., Rasulova, M., Seldeslachts, L., Li, L.H., Jansen, S., Yakass, M.B., Verstrepen, B.E., Böszörményi, K. P., Kiemenyi-Kayere, G., van Driel, N., Quaye, O., Zhang, X., Ter Horst, S., Mishra, N., Deboutte, W., Matthijnssens, J., Coelmont, L., Vandermeulen, C., Heylen, E., Vergote, V., Schols, D., Wang, Z., Bogers, W., Kuiken, T., Verschoor, E., Cawthorne, C., Van Laere, K., Opdenakker, G., Vande Velde, G., Weynand, B., Teuwen, D.E., Matthys, P., Neyts, J., Jan Thibaut, H., Dallmeier, K., 2021. A single-dose live-attenuated YF17D-vectored SARS-CoV-2 vaccine candidate. Nature 590, 320–325.

Schäfer, A., Muecksch, F., Lorenzi, J.C.C., Leist, S.R., Cipolla, M., Bournazos, S., Schmidt, F., Maison, R.M., Gazumyan, A., Martinez, D.R., Baric, R.S., Robbiani, D.F., Hatziioannou, T., Ravetch, J.V., Bieniasz, P.D., Bowen, R.A., Nussenzweig, M.C., Sheahan, T.P., 2021. Antibody potency, effector function, and combinations in protection and therapy for SARS-CoV-2 infection in vivo. J. Exp. Med. 218.

Shan, C., Yao, Y.F., Yang, X.L., Zhou, Y.W., Gao, G., Peng, Y., Yang, L., Hu, X., Xiong, J., Jiang, R.D., Zhang, H.J., Gao, X.X., Peng, C., Min, J., Chen, Y., Si, H.R., Wu, J., Zhou, P., Wang, Y.Y., Wei, H.P., Pang, W., Hu, Z.F., Lv, L.B., Zheng, Y.T., Shi, Z.L., Yuan, Z.M., 2020. Infection with novel coronavirus (SARS-CoV-2) causes pneumonia in Rhesus macaques. Cell Res. 30, 670–677.

Sheahan, T.P., Sims, A.C., Leist, S.R., Schafer, A., Won, J., Brown, A.J., Montgomery, S. A., Hogg, A., Babusis, D., Clarke, M.O., Spahn, J.E., Bauer, L., Sellers, S., Porter, D., Feng, J.Y., Cihlar, T., Jordan, R., Denison, M.R., Baric, R.S., 2020. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat. Commun. 11, 222.

Shi, Z., Hu, Z., 2008. A review of studies on animal reservoirs of the SARS coronavirus. Virus Res. 133, 74–87.

Shi, J., Wen, Z., Zhong, G., Yang, H., Wang, C., Huang, B., Liu, R., He, X., Shuai, L., Sun, Z., Zhao, Y., Liu, P., Liang, L., Cui, P., Wang, J., Zhang, X., Guan, Y., Tan, W., Wu, G., Chen, H., Bu, Z., 2020a. Susceptibility of ferrets, cats, dogs, and other domesticated animals to SARS-coronavirus 2. Science (New York, N.Y.) 368, 1016–1020.

Shi, R., Shan, C., Duan, X., Chen, Z., Liu, P., Song, J., Song, T., Bi, X., Han, C., Wu, L., Gao, G., Hu, X., Zhang, Y., Tong, Z., Huang, W., Liu, W.J., Wu, G., Zhang, B., Wang, L., Qi, J., Feng, H., Wang, F.S., Wang, Q., Gao, G.F., Yuan, Z., Yan, J., 2020b. A human neutralizing antibody targets the receptor-binding site of SARS-CoV-2. Nature 584, 120–124.

Shi, Y., Shuai, L., Wen, Z., Wang, C., Yan, Y., Jiao, Z., Guo, F., Fu, Z.F., Chen, H., Bu, Z., Peng, G., 2021. The preclinical inhibitor GS441524 in combination with GC376 efficaciously inhibited the proliferation of SARS-CoV-2 in the mouse respiratory tract. Emerg. Microb. Infect. 10, 481–492.

Sia, S.F., Yan, L.M., Chin, A.W.H., Fung, K., Choy, K.T., Wong, A.Y.L., Kaewpreedee, P., Perera, R., Poon, L.L.M., Nicholls, J.M., Peiris, M., Yen, H.L., 2020. Pathogenesis and transmission of SARS-CoV-2 in golden hamsters. Nature 583, 834–838.

Singh, D.K., Singh, B., Ganatra, S.R., Gazi, M., Cole, J., Thippeshappa, R., Alfson, K.J., Clemmons, E., Gonzalez, O., Escobedo, R., Lee, T.H., Chatterjee, A., Goez-Gazi, Y., Sharan, R., Gough, M., Alvarez, C., Blakley, A., Ferdin, J., Bartley, C., Staples, H., Parodi, L., Callery, J., Mannino, A., Klaffke, B., Escareno, P., Platt 2nd, R.N., Hodara, V., Scordo, J., Gautam, S., Vilanova, A.G., Olmo-Fontanez, A., Schami, A., Oyejide, A., Ajithdoss, D.K., Copin, R., Baum, A., Kyratsous, C., Alvarez, X., Ahmed, M., Rosa, B., Goodroe, A., Dutton, J., Hall-Ursone, S., Frost, P.A., Voges, A. K., Ross, C.N., Sayers, K., Chen, C., Hallam, C., Khader, S.A., Mitreva, M., Anderson, T.J.C., Martinez-Sobrido, L., Patterson, J.L., Turner, J., Torrelles, J.B., Dick Jr., E.J., Brasky, K., Schlesinger, L.S., Giavedoni, L.D., Carrion Jr., R., Kaushal, D., 2021. Responses to acute infection with SARS-CoV-2 in the lungs of rhesus macaques, baboons and marmosets. Nat. Microbiol. 6, 73–86.

Smits, S.L., de Lang, A., van den Brand, J.M., Leijten, L.M., van, I.W.F., Eijkemans, M.J., van Amerongen, G., Kuiken, T., Andeweg, A.C., Osterhaus, A.D., Haagmans, B.L., 2010. Exacerbated innate host response to SARS-CoV in aged non-human primates. PLoS Pathog. 6, e1000756.

Solforosi, L., Kuipers, H., Jongeneelen, M., Rosendahl Huber, S.K., van der Lubbe, J.E.M., Dekking, L., Czapska-Casey, D.N., Izquierdo Gil, A., Baert, M.R.M., Drijver, J., Vaneman, J., van Huizen, E., Choi, Y., Vreugdenhil, J., Kroos, S., de Wilde, A.H., Kourkouta, E., Custers, J., van der Vlugt, R., Veldman, D., Huizingh, J., Kaszas, K., Dalebout, T.J., Myeni, S.K., Kikkert, M., Snijder, E.J., Barouch, D.H., Böszörményi, K. P., Stammes, M.A., Kondova, I., Verschoor, E.J., Verstrepen, B.E., Koopman, G., Mooij, P., Bogers, W., van Heerden, M., Muchene, L., Tolboom, J., Roozendaal, R., Brandenburg, B., Schuitemaker, H., Wegmann, F., Zahn, R.C., 2021. Immunogenicity and efficacy of one and two doses of Ad26.COV2.S COVID vaccine in adult and aged NHP. J. Exp. Med. 218.

Song, D., Wang, W., Dong, C., Ning, Z., Liu, X., Liu, C., Du, G., Sha, C., Wang, K., Lu, J., Sun, B., Zhao, Y., Wang, Q., Xu, H., Li, Y., Shen, Z., Jiao, J., Wang, R., Tian, J., Liu, W., Wang, L., Deng, Y.Q., Dou, C., 2021. Structure and function analysis of a potent human neutralizing antibody CA521(FALA) against SARS-CoV-2. Commun. Biol. 4, 500.

Strollo, R., Pozzilli, P., 2020. DPP4 Inhibition: Preventing SARS-CoV-2 Infection And/or Progression of COVID-19? Diabetes Metab Res Rev, e3330.

Subbarao, K., McAuliffe, J., Vogel, L., Fahle, G., Fischer, S., Tatti, K., Packard, M., Shieh, W.J., Zaki, S., Murphy, B., 2004. Prior infection and passive transfer of neutralizing antibody prevent replication of severe acute respiratory syndrome coronavirus in the respiratory tract of mice. J. Virol. 78, 3572–3577.

Sun, D., 2020. Remdesivir for treatment of COVID-19: combination of pulmonary and IV administration may offer aditional benefit. AAPS J. 22, 77.

Sun, J., Zhuang, Z., Zheng, J., Li, K., Wong, R.L., Liu, D., Huang, J., He, J., Zhu, A., Zhao, J., Li, X., Xi, Y., Chen, R., Alshukairi, A.N., Chen, Z., Zhang, Z., Chen, C., Huang, X., Li, F., Lai, X., Chen, D., Wen, L., Zhuo, J., Zhang, Y., Wang, Y., Huang, S., Dai, J., Shi, Y., Zheng, K., Leidinger, M.R., Chen, J., Li, Y., Zhong, N., Meyerholz, D. K., McCray Jr., P.B., Perlman, S., Zhao, J., 2020a. Generation of a broadly useful model for COVID-19 pathogenesis, vaccination, and treatment. Cell 182, 734–743 e735.

Sun, S.H., Chen, Q., Gu, H.J., Yang, G., Wang, Y.X., Huang, X.Y., Liu, S.S., Zhang, N.N., Li, X.F., Xiong, R., Guo, Y., Deng, Y.Q., Huang, W.J., Liu, Q., Liu, Q.M., Shen, Y.L., Zhou, Y., Yang, X., Zhao, T.Y., Fan, C.F., Zhou, Y.S., Qin, C.F., Wang, Y.C., 2020b. A mouse model of SARS-CoV-2 infection and pathogenesis. Cell Host Microbe 28, 124–133 e124.

Sun, W., McCroskery, S., Liu, W.C., Leist, S.R., Liu, Y., Albrecht, R.A., Slamanig, S., Oliva, J., Amanat, F., Schäfer, A., Dinnon 3rd, K.H., Innis, B.L., García-Sastre, A., Krammer, F., Baric, R.S., Palese, P., 2020c. A newcastle disease virus (NDV) expressing a membrane-anchored spike as a cost-effective inactivated SARS-CoV-2 vaccine. Vaccines 8.

Sutton, T.C., Subbarao, K., 2015. Development of animal models against emerging coronaviruses: from SARS to MERS coronavirus. Virology 479–480, 247–258.

Suzuki, R., Yamasoba, D., Kimura, I., Wang, L., Kishimoto, M., Ito, J., Morioka, Y., Nao, N., Nasser, H., Uriu, K., Kosugi, Y., Tsuda, M., Orba, Y., Sasaki, M., Shimizu, R., Kawabata, R., Yoshimatsu, K., Asakura, H., Nagashima, M., Sadamasu, K., Yoshimura, K., Sawa, H., Ikeda, T., Irie, T., Matsuno, K., Tanaka, S., Fukuhara, T., Sato, K., 2022. Attenuated fusogenicity and pathogenicity of SARS-CoV-2 Omicron variant. Nature 603, 700–705.

ter Meulen, J., Bakker, A.B., van den Brink, E.N., Weverling, G.J., Martina, B.E., Haagmans, B.L., Kuiken, T., de Kruif, J., Preiser, W., Spaan, W., Gelderblom, H.R., Goudsmit, J., Osterhaus, A.D., 2004. Human monoclonal antibody as prophylaxis for SARS coronavirus infection in ferrets. Lancet (London, England) 363, 2139–2141.

Tracking SARS-CoV-2 variants, 2021a. https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/.

Tian, J.H., Patel, N., Haupt, R., Zhou, H., Weston, S., Hammond, H., Logue, J., Portnoff, A.D., Norton, J., Guebre-Xabier, M., Zhou, B., Jacobson, K., Maciejewski, S., Khatoon, R., Wisniewska, M., Moffitt, W., Kluepfel-Stahl, S., Ekechukwu, B., Papin, J., Boddapati, S., Jason Wong, C., Piedra, P.A., Frieman, M.B., Massare, M.J., Fries, L., Bengtsson, K.L., Stertman, L., Ellingsworth, L., Glenn, G., Smith, G., 2021. SARS-CoV-2 spike glycoprotein vaccine candidate NVX-CoV2373 immunogenicity in baboons and protection in mice. Nat. Commun. 12, 372.

Tostanoski, L.H., Wegmann, F., Martinot, A.J., Loos, C., McMahan, K., Mercado, N.B., Yu, J., Chan, C.N., Bondoc, S., Starke, C.E., Nekorchuk, M., Busman-Sahay, K., Piedra-Mora, C., Wrijil, L.M., Ducat, S., Custers, J., Atyeo, C., Fischinger, S., Burke, J. S., Feldman, J., Hauser, B.M., Caradonna, T.M., Bondzie, E.A., Dagotto, G., Gebre, M. S., Jacob-Dolan, C., Lin, Z., Mahrokhian, S.H., Nampanya, F., Nityanandam, R., Pessaint, L., Porto, M., Ali, V., Benetiene, D., Tevi, K., Andersen, H., Lewis, M.G., Schmidt, A.G., Lauffenburger, D.A., Alter, G., Estes, J.D., Schuitemaker, H., Zahn, R., Barouch, D.H., 2020. Ad26 vaccine protects against SARS-CoV-2 severe clinical disease in hamsters. Nat. Med.

Tostanoski, L.H., Yu, J., Mercado, N.B., McMahan, K., Jacob-Dolan, C., Martinot, A.J., Piedra-Mora, C., Anioke, T., Chang, A., Giffin, V.M., Hope, D.L., Wan, H., Bondzie, E. A., Mahrokhian, S.H., Wrijil, L.M., Bauer, K., Pessaint, L., Porto, M., Piegols, J., Faudree, A., Spence, B., Kar, S., Amanat, F., Krammer, F., Andersen, H., Lewis, M.G., Wegmann, F., Zahn, R., Schuitemaker, H., Barouch, D.H., 2021. Immunity elicited by natural infection or Ad26.COV2.S vaccination protects hamsters against SARS-CoV-2 variants of concern. Sci. Transl. Med. 13, eabj3789.

Ullrich, S., Nitsche, C., 2020. The SARS-CoV-2 main protease as drug target. Bioorg. Med. Chem. Lett 30, 127377.

Vabret, A., Mourez, T., Gouarin, S., Petitjean, J., Freymuth, F., 2003. An Outbreak of Coronavirus OC43 Respiratory Infection in Normandy, France, vol. 36. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, pp. 985–989.

Vabret, N., Britton, G.J., Gruber, C., Hegde, S., Kim, J., Kuksin, M., Levantovsky, R., Malle, L., Moreira, A., Park, M.D., Pia, L., Risson, E., Saffern, M., Salome, B., Esai Selvan, M., Spindler, M.P., Tan, J., van der Heide, V., Gregory, J.K., Alexandropoulos, K., Bhardwaj, N., Brown, B.D., Greenbaum, B., Gumus, Z.H., Homann, D., Horowitz, A., Kamphorst, A.O., Curotto de Lafaille, M.A., Mehandru, S., Merad, M., Samstein, R.M., Sinai Immunology Review, P., 2020. Immunology of COVID-19: current state of the science. Immunity 52, 910–941.

van den Brand, J.M., Haagmans, B.L., Leijten, L., van Riel, D., Martina, B.E., Osterhaus, A.D., Kuiken, T., 2008. Pathology of experimental SARS coronavirus infection in cats and ferrets. Vet. Pathol. 45, 551–562.

van der Hoek, L., Pyrc, K., Berkhout, B., 2006. Human coronavirus NL63, a new respiratory virus. FEMS Microbiol. Rev. 30, 760–773.

van der Lubbe, J.E.M., Rosendahl Huber, S.K., Vijayan, A., Dekking, L., van Huizen, E., Vreugdenhil, J., Choi, Y., Baert, M.R.M., Feddes-de Boer, K., Izquierdo Gil, A., van Heerden, M., Dalebout, T.J., Myeni, S.K., Kikkert, M., Snijder, E.J., de Waal, L., Stittelaar, K.J., Tolboom, J., Serroyen, J., Muchene, L., van der Fits, L., Rutten, L., Langedijk, J.P.M., Barouch, D.H., Schuitemaker, H., Zahn, R.C., Wegmann, F., 2021. Ad26.COV2.S protects Syrian hamsters against G614 spike variant SARS-CoV-2 and does not enhance respiratory disease. NPJ Vaccine 6, 39.

van Doremalen, N., Miazgowicz, K.L., Milne-Price, S., Bushmaker, T., Robertson, S., Scott, D., Kinne, J., McLellan, J.S., Zhu, J., Munster, V.J., 2014. Host species restriction of Middle East respiratory syndrome coronavirus through its receptor, dipeptidyl peptidase 4. J. Virol. 88, 9220–9232.

van Doremalen, N., Haddock, E., Feldmann, F., Meade-White, K., Bushmaker, T., Fischer, R.J., Okumura, A., Hanley, P.W., Saturday, G., Edwards, N.J., Clark, M.H.A., Lambe, T., Gilbert, S.C., Munster, V.J., 2020a. A single dose of ChAdOx1 MERS provides protective immunity in rhesus macaques. Sci. Adv. 6, eaba8399.

van Doremalen, N., Lambe, T., Spencer, A., Belij-Rammerstorfer, S., Purushotham, J.N., Port, J.R., Avanzato, V.A., Bushmaker, T., Flaxman, A., Ulaszewska, M., Feldmann, F., Allen, E.R., Sharpe, H., Schulz, J., Holbrook, M., Okumura, A., Meade-

White, K., Pérez-Pérez, L., Edwards, N.J., Wright, D., Bissett, C., Gilbride, C., Williamson, B.N., Rosenke, R., Long, D., Ishwarbhai, A., Kailath, R., Rose, L., Morris, S., Powers, C., Lovaglio, J., Hanley, P.W., Scott, D., Saturday, G., de Wit, E., Gilbert, S.C., Munster, V.J., 2020b. ChAdOx1 nCoV-19 vaccine prevents SARS-CoV-2 pneumonia in rhesus macaques. Nature 586, 578–582.

van Doremalen, N., Purushotham, J.N., Schulz, J.E., Holbrook, M.G., Bushmaker, T., Carmody, A., Port, J.R., Yinda, C.K., Okumura, A., Saturday, G., Amanat, F., Krammer, F., Hanley, P.W., Smith, B.J., Lovaglio, J., Anzick, S.L., Barbian, K., Martens, C., Gilbert, S.C., Lambe, T., Munster, V.J., 2021. Intranasal ChAdOx1 nCoV-19/AZD1222 vaccination reduces viral shedding after SARS-CoV-2 D614G challenge in preclinical models. Sci. Transl. Med. 13.

van Hasselt, J.G.C., Iyengar, R., 2019. Systems pharmacology: defining the interactions of drug combinations. Annu. Rev. Pharmacol. Toxicol. 59, 21–40.

Van Rompay, K.K.A., Olstad, K.J., Sammak, R.L., Dutra, J., Watanabe, J.K., Usachenko, J. L., Immareddy, R., Verma, A., Shaan Lakshmanappa, Y., Schmidt, B.A., Roh, J.W., Elizaldi, S.R., Allen, A.M., Muecksch, F., Lorenzi, J.C.C., Lockwood, S., Pollard, R.E., Yee, J.L., Nham, P.B., Ardeshir, A., Deere, J.D., Patterson, J., Dang, Q., Hatziioannou, T., Bieniasz, P.D., Iyer, S.S., Hartigan-O'Connor, D.J., Nussenzweig, M.C., Reader, J.R., 2021. Early treatment with a combination of two potent neutralizing antibodies improves clinical outcomes and reduces virus replication and lung inflammation in SARS-CoV-2 infected macaques. PLoS Pathog. 17, e1009688.

VanBlargan, L.A., Adams, L.J., Liu, Z., Chen, R.E., Gilchuk, P., Raju, S., Smith, B.K., Zhao, H., Case, J.B., Winkler, E.S., Whitener, B.M., Droit, L., Aziati, I.D., Bricker, T. L., Joshi, A., Shi, P.Y., Creanga, A., Pegu, A., Handley, S.A., Wang, D., Boon, A.C.M., Crowe Jr., J.E., Whelan, S.P.J., Fremont, D.H., Diamond, M.S., 2021. A potently neutralizing SARS-CoV-2 antibody inhibits variants of concern by utilizing unique binding residues in a highly conserved epitope. Immunity 54, 2399–2416 e2396.

Vandyck, K., Abdelnabi, R., Gupta, K., Jochmans, D., Jekle, A., Deval, J., Misner, D., Bardiot, D., Foo, C.S., Liu, C., Ren, S., Beigelman, L., Blatt, L.M., Boland, S., Vangeel, L., Dejonghe, S., Chaltin, P., Marchand, A., Serebryany, V., Stoycheva, A., Chanda, S., Symons, J.A., Raboisson, P., Neyts, J., 2021. ALG-097111, a potent and selective SARS-CoV-2 3-chymotrypsin-like cysteine protease inhibitor exhibits in vivo efficacy in a Syrian Hamster model. Biochem. Biophys. Res. Commun. 555, 134–139.

Vanhove, B., Marot, S., So, R.T., Gaborit, B., Evanno, G., Malet, I., Lafrogne, G., Mevel, E., Ciron, C., Royer, P.J., Lheriteau, E., Raffi, F., Bruzzone, R., Mok, C.K.P., Duvaux, O., Marcelin, A.G., Calvez, V., 2021. XAV-19, a swine glyco-humanized polyclonal antibody against SARS-CoV-2 spike receptor-binding domain, targets multiple epitopes and broadly neutralizes variants. Front. Immunol. 12, 761250.

Views of COVID-19 studies listed on ClinicalTrials.gov (beta), 2021b. https://clinicaltrials.gov/ct2/covid_view.

Vogel, A.B., Kanevsky, I., Che, Y., Swanson, K.A., Muik, A., Vormehr, M., Kranz, L.M., Walzer, K.C., Hein, S., Güler, A., Loschko, J., Maddur, M.S., Ota-Setlik, A., Tompkins, K., Cole, J., Lui, B.G., Ziegenhals, T., Plaschke, A., Eisel, D., Dany, S.C., Fesser, S., Erbar, S., Bates, F., Schneider, D., Jesionek, B., Sänger, B., Wallisch, A.K., Feuchter, Y., Junginger, H., Krumm, S.A., Heinen, A.P., Adams-Quack, P., Schlereth, J., Schille, S., Kröner, C., de la Caridad Güimil Garcia, R., Hiller, T., Fischer, L., Sellers, R.S., Choudhary, S., Gonzalez, O., Vascotto, F., Gutman, M.R., Fontenot, J.A., Hall-Ursone, S., Brasky, K., Griffor, M.C., Han, S., Su, A.A.H., Lees, J. A., Nedoma, N.L., Mashalidis, E.H., Sahasrabudhe, P.V., Tan, C.Y., Pavliakova, D., Singh, G., Fontes-Garfias, C., Pride, M., Scully, I.L., Ciolino, T., Obregon, J., Gazi, M., Carrion Jr., R., Alfson, K.J., Kalina, W.V., Kaushal, D., Shi, P.Y., Klamp, T., Rosenbaum, C., Kuhn, A.N., Türeci, Ö., Dormitzer, P.R., Jansen, K.U., Sahin, U., 2021. BNT162b vaccines protect rhesus macaques from SARS-CoV-2. Nature 592, 283–289.

VOI/VOC profiles of Spike amino acid changes, 2021c. https://www.who.int/docs/default-source/coronaviruse/voc_voi_290921.pdf?sfvrsn=61b3acff_5.

Volz, A., Kupke, A., Song, F., Jany, S., Fux, R., Shams-Eldin, H., Schmidt, J., Becker, C., Eickmann, M., Becker, S., Sutter, G., 2015. Protective efficacy of recombinant modified vaccinia virus ankara delivering Middle East respiratory syndrome coronavirus spike glycoprotein. J. Virol. 89, 8651–8656.

Wall, E.C., Wu, M., Harvey, R., Kelly, G., Warchal, S., Sawyer, C., Daniels, R., Hobson, P., Hatipoglu, E., Ngai, Y., Hussain, S., Nicod, J., Goldstone, R., Ambrose, K., Hindmarsh, S., Beale, R., Riddell, A., Gamblin, S., Howell, M., Kassiotis, G., Libri, V., Williams, B., Swanton, C., Gandhi, S., Bauer, D.L., 2021. Neutralising antibody activity against SARS-CoV-2 VOCs B.1.617.2 and B.1.351 by BNT162b2 vaccination. Lancet (London, England) 397, 2331–2333.

Walsh, E.E., Shin, J.H., Falsey, A.R., 2013. Clinical impact of human coronaviruses 229E and OC43 infection in diverse adult populations. J. Infect. Dis. 208, 1634–1642.

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

Wang, H., Zhang, Y., Huang, B., Deng, W., Quan, Y., Wang, W., Xu, W., Zhao, Y., Li, N., Zhang, J., Liang, H., Bao, L., Xu, Y., Ding, L., Zhou, W., Gao, H., Liu, J., Niu, P., Zhao, L., Zhen, W., Fu, H., Yu, S., Zhang, Z., Xu, G., Li, C., Lou, Z., Xu, M., Qin, C., Wu, G., Gao, G.F., Tan, W., Yang, X., 2020a. Development of an inactivated vaccine candidate, BBIBP-CorV, with potent protection against SARS-CoV-2. Cell 182, 713–721 e719.

Wang, H., Zhang, Y., Huang, B., Deng, W., Quan, Y., Wang, W., Xu, W., Zhao, Y., Li, N., Zhang, J., Liang, H., Bao, L., Xu, Y., Ding, L., Zhou, W., Gao, H., Liu, J., Niu, P., Zhao, L., Zhen, W., Fu, H., Yu, S., Zhang, Z., Xu, G., Li, C., Lou, Z., Xu, M., Qin, C., Wu, G., Gao, G.F., Tan, W., Yang, X., 2020b. Development of an inactivated vaccine candidate, BBIBP-CorV, with potent protection against SARS-CoV-2. Cell 182, 713–721 e719.

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

Wang, S., Peng, Y., Wang, R., Jiao, S., Wang, M., Huang, W., Shan, C., Jiang, W., Li, Z., Gu, C., Chen, B., Hu, X., Yao, Y., Min, J., Zhang, H., Chen, Y., Gao, G., Tang, P., Li, G., Wang, A., Wang, L., Zhang, J., Chen, S., Gui, X., Yuan, Z., Liu, D., 2020d. Characterization of neutralizing antibody with prophylactic and therapeutic efficacy against SARS-CoV-2 in rhesus monkeys. Nat. Commun. 11, 5752.

Wang, W., Su, B., Pang, L., Qiao, L., Feng, Y., Ouyang, Y., Guo, X., Shi, H., Wei, F., Su, X., Yin, J., Jin, R., Chen, D., 2020e. High-dimensional immune profiling by mass cytometry revealed immunosuppression and dysfunction of immunity in COVID-19 patients. Cell. Mol. Immunol. 17, 650–652.

Wang, Y., Zhang, D., Du, G., Du, R., Zhao, J., Jin, Y., Fu, S., Gao, L., Cheng, Z., Lu, Q., Hu, Y., Luo, G., Wang, K., Lu, Y., Li, H., Wang, S., Ruan, S., Yang, C., Mei, C., Wang, Y., Ding, D., Wu, F., Tang, X., Ye, X., Ye, Y., Liu, B., Yang, J., Yin, W., Wang, A., Fan, G., Zhou, F., Liu, Z., Gu, X., Xu, J., Shang, L., Zhang, Y., Cao, L., Guo, T., Wan, Y., Qin, H., Jiang, Y., Jaki, T., Hayden, F.G., Horby, P.W., Cao, B., Wang, C., 2020f. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet (London, England) 395, 1569–1578.

Wang, G., Yang, M.L., Duan, Z.L., Liu, F.L., Jin, L., Long, C.B., Zhang, M., Tang, X.P., Xu, L., Li, Y.C., Kamau, P.M., Yang, L., Liu, H.Q., Xu, J.W., Chen, J.K., Zheng, Y.T., Peng, X.Z., Lai, R., 2021a. Dalbavancin binds ACE2 to block its interaction with SARS-CoV-2 spike protein and is effective in inhibiting SARS-CoV-2 infection in animal models. Cell Res. 31, 17–24.

Wang, P., Casner, R.G., Nair, M.S., Wang, M., Yu, J., Cerutti, G., Liu, L., Kwong, P.D., Huang, Y., Shapiro, L., Ho, D.D., 2021b. Increased resistance of SARS-CoV-2 variant P.1 to antibody neutralization. Cell Host Microbe 29, 747–751 e744.

Weingartl, H., Czub, M., Czub, S., Neufeld, J., Marszal, P., Gren, J., Smith, G., Jones, S., Proulx, R., Deschambault, Y., Grudeski, E., Andonov, A., He, R., Li, Y., Copps, J., Grolla, A., Dick, D., Berry, J., Ganske, S., Manning, L., Cao, J., 2004. Immunization with modified vaccinia virus Ankara-based recombinant vaccine against severe acute respiratory syndrome is associated with enhanced hepatitis in ferrets. J. Virol. 78, 12672–12676.

Weiss, S.R., Navas-Martin, S., 2005. Coronavirus pathogenesis and the emerging pathogen severe acute respiratory syndrome coronavirus. Microbiol. Mol. Biol. Rev. 69, 635–664.

White, J.M., Schiffer, J.T., Bender Ignacio, R.A., Xu, S., Kainov, D., Ianevski, A., Aittokallio, T., Frieman, M., Olinger, G.G., Polyak, S.J., 2021. Drug combinations as a first line of defense against coronaviruses and other emerging viruses. mBio 12, e0334721.

WHO coronavirus (COVID-19) dashboard, 2022a. https://covid19.who.int/.

Williamson, B.N., Feldmann, F., Schwarz, B., Meade-White, K., Porter, D.P., Schulz, J., van Doremalen, N., Leighton, I., Yinda, C.K., Perez-Perez, L., Okumura, A., Lovaglio, J., Hanley, P.W., Saturday, G., Bosio, C.M., Anzick, S., Barbian, K., Cihlar, T., Martens, C., Scott, D.P., Munster, V.J., de Wit, E., 2020. Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2. Nature 585, 273–276.

Winkler, E.S., Bailey, A.L., Kafai, N.M., Nair, S., McCune, B.T., Yu, J., Fox, J.M., Chen, R. E., Earnest, J.T., Keeler, S.P., Ritter, J.H., Kang, L.I., Dort, S., Robichaud, A., Head, R., Holtzman, M.J., Diamond, M.S., 2020. SARS-CoV-2 infection of human ACE2-transgenic mice causes severe lung inflammation and impaired function. Nat. Immunol.

Woo, P.C., Lau, S.K., Tsoi, H.W., Huang, Y., Poon, R.W., Chu, C.M., Lee, R.A., Luk, W.K., Wong, G.K., Wong, B.H., Cheng, V.C., Tang, B.S., Wu, A.K., Yung, R.W., Chen, H., Guan, Y., Chan, K.H., Yuen, K.Y., 2005. Clinical and molecular epidemiological features of coronavirus HKU1-associated community-acquired pneumonia. J. Infect. Dis. 192, 1898–1907.

Woo, P.C., Lau, S.K., Lam, C.S., Lau, C.C., Tsang, A.K., Lau, J.H., Bai, R., Teng, J.L., Tsang, C.C., Wang, M., Zheng, B.J., Chan, K.H., Yuen, K.Y., 2012. Discovery of seven novel Mammalian and avian coronaviruses in the genus deltacoronavirus supports bat coronaviruses as the gene source of alphacoronavirus and betacoronavirus and avian coronaviruses as the gene source of gammacoronavirus and deltacoronavirus. J. Virol. 86, 3995–4008.

Wrapp, D., Wang, N., Corbett, K.S., Goldsmith, J.A., Hsieh, C.L., Abiona, O., Graham, B. S., McLellan, J.S., 2020. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science (New York, N.Y.) 367, 1260–1263.

Wu, F., Zhao, S., Yu, B., Chen, Y.M., Wang, W., Song, Z.G., Hu, Y., Tao, Z.W., Tian, J.H., Pei, Y.Y., Yuan, M.L., Zhang, Y.L., Dai, F.H., Liu, Y., Wang, Q.M., Zheng, J.J., Xu, L., Holmes, E.C., Zhang, Y.Z., 2020a. A new coronavirus associated with human respiratory disease in China. Nature 579, 265–269.

Wu, S., Zhong, G., Zhang, J., Shuai, L., Zhang, Z., Wen, Z., Wang, B., Zhao, Z., Song, X., Chen, Y., Liu, R., Fu, L., Zhang, J., Guo, Q., Wang, C., Yang, Y., Fang, T., Lv, P., Wang, J., Xu, J., Li, J., Yu, C., Hou, L., Bu, Z., Chen, W., 2020b. A single dose of an adenovirus-vectored vaccine provides protection against SARS-CoV-2 challenge. Nat. Commun. 11, 4081.

Wu, T., Kang, S., Peng, W., Zuo, C., Zhu, Y., Pan, L., Fu, K., You, Y., Yang, X., Luo, X., Jiang, L., Deng, M., 2021. Original hosts, clinical features, transmission routes, and vaccine development for coronavirus disease (COVID-19). Front. Med. 8, 702066.

Xu, Z., Shi, L., Wang, Y., Zhang, J., Huang, L., Zhang, C., Liu, S., Zhao, P., Liu, H., Zhu, L., Tai, Y., Bai, C., Gao, T., Song, J., Xia, P., Dong, J., Zhao, J., Wang, F.S., 2020. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir. Med. 8, 420–422.

Yadav, P.D., Ella, R., Kumar, S., Patil, D.R., Mohandas, S., Shete, A.M., Vadrevu, K.M., Bhati, G., Sapkal, G., Kaushal, H., Patil, S., Jain, R., Deshpande, G., Gupta, N., Agarwal, K., Gokhale, M., Mathapati, B., Metkari, S., Mote, C., Nyayanit, D., Patil, D.

Y., Sai Prasad, B.S., Suryawanshi, A., Kadam, M., Kumar, A., Daigude, S., Gopale, S., Majumdar, T., Mali, D., Sarkale, P., Baradkar, S., Gawande, P., Joshi, Y., Fulari, S., Dighe, H., Sharma, S., Gunjikar, R., Kumar, A., Kalele, K., Srinivas, V.K., Gangakhedkar, R.R., Ella, K.M., Abraham, P., Panda, S., Bhargava, B., 2021. Immunogenicity and protective efficacy of inactivated SARS-CoV-2 vaccine candidate, BBV152 in rhesus macaques. Nat. Commun. 12, 1386.

Yahalom-Ronen, Y., Tamir, H., Melamed, S., Politi, B., Shifman, O., Achdout, H., Vitner, E.B., Israeli, O., Milrot, E., Stein, D., Cohen-Gihon, I., Lazar, S., Gutman, H., Glinert, I., Cherry, L., Vagima, Y., Lazar, S., Weiss, S., Ben-Shmuel, A., Avraham, R., Puni, R., Lupu, E., Bar-David, E., Sittner, A., Erez, N., Zichel, R., Mamroud, E., Mazor, O., Levy, H., Laskar, O., Yitzhaki, S., Shapira, S.C., Zvi, A., Beth-Din, A., Paran, N., Israely, T., 2020. A single dose of recombinant VSV-ΔG-spike vaccine provides protection against SARS-CoV-2 challenge. Nat. Commun. 11, 6402.

Yang, Z.Y., Kong, W.P., Huang, Y., Roberts, A., Murphy, B.R., Subbarao, K., Nabel, G.J., 2004. A DNA vaccine induces SARS coronavirus neutralization and protective immunity in mice. Nature 428, 561–564.

Yang, F., Shi, S., Zhu, J., Shi, J., Dai, K., Chen, X., 2020. Analysis of 92 deceased patients with COVID-19. J. Med. Virol.

Ye, Q., Wang, B., Mao, J., 2020. The pathogenesis and treatment of the 'Cytokine Storm' in COVID-19. J. Infect. 80, 607–613.

Ye, Z.W., Yuan, S., Chan, J.F., Zhang, A.J., Yu, C.Y., Ong, C.P., Yang, D., Chan, C.C., Tang, K., Cao, J., Poon, V.K., Chan, C.C., Cai, J.P., Chu, H., Yuen, K.Y., Jin, D.Y., 2021. Beneficial effect of combinational methylprednisolone and remdesivir in hamster model of SARS-CoV-2 infection. Emerg. Microb. Infect. 10, 291–304.

Yi, C., Sun, X., Ye, J., Ding, L., Liu, M., Yang, Z., Lu, X., Zhang, Y., Ma, L., Gu, W., Qu, A., Xu, J., Shi, Z., Ling, Z., Sun, B., 2020. Key residues of the receptor binding motif in the spike protein of SARS-CoV-2 that interact with ACE2 and neutralizing antibodies. Cell. Mol. Immunol. 17, 621–630.

Yu, J., Tostanoski, L.H., Peter, L., Mercado, N.B., McMahan, K., Mahrokhian, S.H., Nkolola, J.P., Liu, J., Li, Z., Chandrashekar, A., Martinez, D.R., Loos, C., Atyeo, C., Fischinger, S., Burke, J.S., Slein, M.D., Chen, Y., Zuiani, A., Lelis, F.J.N., Travers, M., Habibi, S., Pessaint, L., Van Ry, A., Blade, K., Brown, R., Cook, A., Finneyfrock, B., Dodson, A., Teow, E., Velasco, J., Zahn, R., Wegmann, F., Bondzie, E.A., Dagotto, G., Gebre, M.S., He, X., Jacob-Dolan, C., Kirilova, M., Kordana, N., Lin, Z., Maxfield, L. F., Nampanya, F., Nityanandam, R., Ventura, J.D., Wan, H., Cai, Y., Chen, B., Schmidt, A.G., Wesemann, D.R., Baric, R.S., Alter, G., Andersen, H., Lewis, M.G., Barouch, D.H., 2020. DNA vaccine protection against SARS-CoV-2 in rhesus macaques. Science (New York, N.Y.) 369, 806–811.

Yu, J., Tostanoski, L.H., Mercado, N.B., McMahan, K., Liu, J., Jacob-Dolan, C., Chandrashekar, A., Atyeo, C., Martinez, D.R., Anioke, T., Bondzie, E.A., Chang, A., Gardner, S., Giffin, V.M., Hope, D.L., Nampanya, F., Nkolola, J., Patel, S., Sanborn, O., Sellers, D., Wan, H., Hayes, T., Bauer, K., Pessaint, L., Valentin, D., Flinchbaugh, Z., Brown, R., Cook, A., Bueno-Wilkerson, D., Teow, E., Andersen, H., Lewis, M.G., Martinot, A.J., Baric, R.S., Alter, G., Wegmann, F., Zahn, R., Schuitemaker, H., Barouch, D.H., 2021. Protective efficacy of Ad26.COV2.S against SARS-CoV-2 B.1.351 in macaques. Nature 596, 423–427.

Yuan, S., Wang, R., Chan, J.F., Zhang, A.J., Cheng, T., Chik, K.K., Ye, Z.W., Wang, S., Lee, A.C., Jin, L., Li, H., Jin, D.Y., Yuen, K.Y., Sun, H., 2020. Metallodrug ranitidine bismuth citrate suppresses SARS-CoV-2 replication and relieves virus-associated pneumonia in Syrian hamsters. Nat. Microbiol. 5, 1439–1448.

Yuan, L., Zhu, H., Zhou, M., Ma, J., Chen, R., Chen, Y., Chen, L., Wu, K., Cai, M., Hong, J., Li, L., Liu, C., Yu, H., Zhang, Y., Wang, J., Zhang, T., Ge, S., Zhang, J., Yuan, Q., Chen, Y., Tang, Q., Chen, H., Cheng, T., Guan, Y., Xia, N., 2021a. Gender associates with both susceptibility to infection and pathogenesis of SARS-CoV-2 in Syrian hamster. Signal Transduct. Targeted Ther. 6, 136.

Yuan, S., Yin, X., Meng, X., Chan, J.F., Ye, Z.W., Riva, L., Pache, L., Chan, C.C., Lai, P.M., Chan, C.C., Poon, V.K., Lee, A.C., Matsunaga, N., Pu, Y., Yuen, C.K., Cao, J., Liang, R., Tang, K., Sheng, L., Du, Y., Xu, W., Lau, C.Y., Sit, K.Y., Au, W.K., Wang, R., Zhang, Y.Y., Tang, Y.D., Clausen, T.M., Pihl, J., Oh, J., Sze, K.H., Zhang, A.J., Chu, H., Kok, K.H., Wang, D., Cai, X.H., Esko, J.D., Hung, I.F., Li, R.A., Chen, H., Sun, H., Jin, D.Y., Sun, R., Chanda, S.K., Yuen, K.Y., 2021b. Clofazimine broadly inhibits coronaviruses including SARS-CoV-2. Nature 593, 418–423.

Yuan, S., Yin, X., Meng, X., Chan, J.F., Ye, Z.W., Riva, L., Pache, L., Chan, C.C., Lai, P.M., Chan, C.C., Poon, V.K., Lee, A.C., Matsunaga, N., Pu, Y., Yuen, C.K., Cao, J., Liang, R., Tang, K., Sheng, L., Du, Y., Xu, W., Lau, C.Y., Sit, K.Y., Au, W.K., Wang, R., Zhang, Y.Y., Tang, Y.D., Clausen, T.M., Pihl, J., Oh, J., Sze, K.H., Zhang, A.J., Chu, H., Kok, K.H., Wang, D., Cai, X.H., Esko, J.D., Hung, I.F., Li, R.A., Chen, H., Sun, H., Jin, D.Y., Sun, R., Chanda, S.K., Yuen, K.Y., 2021c. Clofazimine broadly inhibits coronaviruses including SARS-CoV-2. Nature.

Zaki, A.M., van Boheemen, S., Bestebroer, T.M., Osterhaus, A.D., Fouchier, R.A., 2012. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N. Engl. J. Med. 367, 1814–1820.

Zhang, N.N., Li, X.F., Deng, Y.Q., Zhao, H., Huang, Y.J., Yang, G., Huang, W.J., Gao, P., Zhou, C., Zhang, R.R., Guo, Y., Sun, S.H., Fan, H., Zu, S.L., Chen, Q., He, Q., Cao, T. S., Huang, X.Y., Qiu, H.Y., Nie, J.H., Jiang, Y., Yan, H.Y., Ye, Q., Zhong, X., Xue, X.L., Zha, Z.Y., Zhou, D., Yang, X., Wang, Y.C., Ying, B., Qin, C.F., 2020a. A thermostable mRNA vaccine against COVID-19. Cell 182, 1271–1283 e1216.

Zhang, T., Wu, Q., Zhang, Z., 2020b. Probable pangolin origin of SARS-CoV-2 associated with the COVID-19 outbreak. Curr. Biol. : CB 30, 1578.

Zhang, X., Wu, S., Wu, B., Yang, Q., Chen, A., Li, Y., Zhang, Y., Pan, T., Zhang, H., He, X., 2021. SARS-CoV-2 Omicron strain exhibits potent capabilities for immune evasion and viral entrance. Signal Transduct. Targeted Ther. 6, 430.

Zhao, J., Li, K., Wohlford-Lenane, C., Agnihothram, S.S., Fett, C., Zhao, J., Gale Jr., M.J., Baric, R.S., Enjuanes, L., Gallagher, T., McCray Jr., P.B., Perlman, S., 2014. Rapid generation of a mouse model for Middle East respiratory syndrome. Proc. Natl. Acad. Sci. U. S. A 111, 4970–4975.

Zhao, S., Zhang, H., Yang, X., Zhang, H., Chen, Y., Zhan, Y., Zhang, X., Jiang, R., Liu, M., Liu, L., Chen, L., Tang, W., Peng, C., Gao, X., Zhang, Z., Shi, Z., Gong, R., 2021. Identification of potent human neutralizing antibodies against SARS-CoV-2 implications for development of therapeutics and prophylactics. Nat. Commun. 12, 4887.

Zheng, H., Li, H., Guo, L., Liang, Y., Li, J., Wang, X., Hu, Y., Wang, L., Liao, Y., Yang, F., Li, Y., Fan, S., Li, D., Cui, P., Wang, Q., Shi, H., Chen, Y., Yang, Z., Yang, J., Shen, D., Cun, W., Zhou, X., Dong, X., Wang, Y., Chen, Y., Dai, Q., Jin, W., He, Z., Li, Q., Liu, L., 2020. Virulence and pathogenesis of SARS-CoV-2 infection in rhesus macaques: a nonhuman primate model of COVID-19 progression. PLoS Pathog. 16, e1008949.

Zhou, P., Yang, X.L., Wang, X.G., Hu, B., Zhang, L., Zhang, W., Si, H.R., Zhu, Y., Li, B., Huang, C.L., Chen, H.D., Chen, J., Luo, Y., Guo, H., Jiang, R.D., Liu, M.Q., Chen, Y., Shen, X.R., Wang, X., Zheng, X.S., Zhao, K., Chen, Q.J., Deng, F., Liu, L.L., Yan, B., Zhan, F.X., Wang, Y.Y., Xiao, G.F., Shi, Z.L., 2020. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 579, 270–273.

Zhou, D., Chan, J.F., Zhou, B., Zhou, R., Li, S., Shan, S., Liu, L., Zhang, A.J., Chen, S.J., Chan, C.C., Xu, H., Poon, V.K., Yuan, S., Li, C., Chik, K.K., Chan, C.C., Cao, J., Chan, C.Y., Kwan, K.Y., Du, Z., Lau, T.T., Zhang, Q., Zhou, J., To, K.K., Zhang, L., Ho, D.D., Yuen, K.Y., Chen, Z., 2021. Robust SARS-CoV-2 Infection in Nasal Turbinates after Treatment with Systemic Neutralizing Antibodies. Cell host & microbe.

Zhu, W., Chen, C.Z., Gorshkov, K., Xu, M., Lo, D.C., Zheng, W., 2020. RNA-dependent RNA polymerase as a target for COVID-19 drug discovery. SLAS Discover. : Adv. Life Sci. R D 25, 1141–1151.

Zost, S.J., Gilchuk, P., Case, J.B., Binshtein, E., Chen, R.E., Nkolola, J.P., Schäfer, A., Reidy, J.X., Trivette, A., Nargi, R.S., Sutton, R.E., Suryadevara, N., Martinez, D.R., Williamson, L.E., Chen, E.C., Jones, T., Day, S., Myers, L., Hassan, A.O., Kafai, N.M., Winkler, E.S., Fox, J.M., Shrihari, S., Mueller, B.K., Meiler, J., Chandrashekar, A., Mercado, N.B., Steinhardt, J.J., Ren, K., Loo, Y.M., Kallewaard, N.L., McCune, B.T., Keeler, S.P., Holtzman, M.J., Barouch, D.H., Gralinski, L.E., Baric, R.S., Thackray, L. B., Diamond, M.S., Carnahan, R.H., Crowe Jr., J.E., 2020. Potently neutralizing and protective human antibodies against SARS-CoV-2. Nature 584, 443–449.

Zu, S., Deng, Y.Q., Zhou, C., Li, J., Li, L., Chen, Q., Li, X.F., Zhao, H., Gold, S., He, J., Li, X., Zhang, C., Yang, H., Cheng, G., Qin, C.F., 2020. 25-Hydroxycholesterol is a potent SARS-CoV-2 inhibitor. Cell Res. 30, 1043–1045.