Recommendation by the ZKBS on risk assessment of
Severe acute respiratory syndrome-related coronavirus
as donor or recipient organism according to § 5 (1) GenTSV

The Coronaviridae family comprises viruses whose genome consists of a single-stranded RNA of positive polarity with a length of 26.4 – 33.5 kb. Coronaviruses are widely distributed among animals and humans. Infections can lead to various acute or subacute diseases or can be asymptomatic. Most of the known human pathogenic coronaviruses cause mild diseases of the respiratory tract. According to European Directive 2000/54/EC (amended by Directive (EU) 2019/1833) Coronaviridae are classified in risk group 2 except for representatives of the species Severe acute respiratory syndrome-related coronavirus and Middle East respiratory syndrome-related coronavirus.

In 2002, however, a new coronavirus appeared, which causes the so-called severe acute respiratory syndrome (SARS) and was given the name SARS coronavirus (SARS-CoV). SARS spread to 33 countries and caused more than 8,000 infections, of which more than 700 were fatal [1]. The SARS pandemic was declared over by the World Health Organization (WHO) in May 2003. Since then, no new SARS cases have occurred, except for four post-pandemic cases that occurred in the winter of 2003/2004 and which were probably caused by infected mongoose [2], and isolated laboratory-acquired infections [3–5]. SARS-CoV has been assigned to a new virus species within the Betacoronavirus genus.

At the end of 2019, a wave of respiratory infections, some of them fatal, was reported from the city of Wuhan (Hubei region) in China, caused by another novel betacoronavirus. The corresponding disease was named coronavirus disease 2019 (COVID-19) by the WHO. Within a few months, it spread worldwide and led to more than 167,515 confirmed cases of infection and 6,606 deaths (as of 16 March 2020). Due to its high nucleic acid sequence similarity to SARS-CoV, the virus, initially referred to as novel (n)CoV-2019, was also assigned to the species Severe acute respiratory syndrome-related coronavirus in February 2020 and renamed SARS-CoV-2 [6].

SARS-CoV:

SARS-CoV has a broad host spectrum. The natural hosts of SARS-CoV have been identified as humans, masked palm civets, raccoon dogs, Chinese ferret-badgers, cats and pigs, with all natural hosts except humans appearing asymptomatic [7–10]. In addition, non-human primates, ferrets, hamsters, guinea pigs, mice and rats can also be infected experimentally [9, 11]. In humans, infection with SARS-CoV can cause atypical pneumonia with high fever, coughing and shortness of breath, headache, muscle pain and gastrointestinal discomfort. The incubation period is two to 16 days. Viruses are released by infected people via the nasopharynx, stool and urine. The total lethality rate is about 10 %, varying between < 1 % for those under 25 years of age and > 50 % for those over 65 years of age. Besides advanced age, risk factors for a poor clinical prognosis are underlying diseases such as diabetes [12].
Pregnant women also have a high risk of a serious course of infection [13]. A vaccine has not been approved yet because the vaccine candidates developed so far have not been shown to be sufficiently immunogenic [14].

SARS-CoV is mainly transmitted by droplets and thus primarily by close contact with an infected person. Vertical transmission from pregnant women to foetuses has not been observed [15]. Transmission by air or by contact or smear infection is also possible. For example, an outbreak developed in a residential complex in Hong Kong, where an infected person with diarrhoea lived, probably via the vacuum ventilation system of the sanitary rooms, through which virus-contaminated droplets were spread from damaged sewage pipes [16, 17]. SARS-CoV can maintain its infectivity outside a host for up to several days, depending on the prevailing environmental conditions [18, 19].

### SARS-CoV-2:

The nucleic acid sequence of the SARS-CoV-2 genome is 82 % identical to that of SARS-CoV [20]. For cell entry, SARS-CoV-2 uses the same receptor as SARS-CoV, the angiotensin-converting enzyme 2 (ACE2) [21, 22]. The receptor binding domain of the envelope protein of SARS-CoV-2 (spike protein) has a high affinity for ACE2 [23]. A polybasic furin cleavage site was also identified between the two domains of the spike protein. Polybasic furin cleavage sites within the genus of betacoronaviruses have so far only been detected in representatives of lineage b. They enable effective cleavage of the spike protein by furin and other widespread host cell proteases, so that cell entry could also be improved in the epithelium of the upper respiratory tract compared to SARS-CoV [24, 25]. This may explain the increased shedding via the upper respiratory tract compared to SARS-CoV [26], which makes SARS-CoV-2 detection of in throat swabs more reliable than SARS-CoV detection. SARS-CoV-2 is excreted by the infected person shortly after infection [26, 27], which means that other people can be infected before symptoms appear. The incubation period is usually three to seven days, but can occasionally take up to 14 days [28].

In bats and Malayan pangolins, coronaviruses were identified with a very high similarity to SARS-CoV-2 (nucleic acid sequence identity of the individual open reading frames 92.9 to 99.6% and 89.3 to 98.3% [28]); however, they do not exhibit the polybasic furin cleavage site in the spike protein. This is interpreted as an indication that the virus adapted to humans after circulation in various animal reservoirs, then possibly recombined with other coronaviruses and acquired the polybasic furin cleavage site [24, 25].

Transmission usually occurs via droplets, whereby faecal-oral infection cannot be excluded either [31]. Typical symptoms of COVID-19 are fever, dry cough, shortness of breath, atypical pneumonia and other respiratory problems as well as headaches and aching limbs, more rarely diarrhoea and vomiting. In roughly 80 % of all cases, SARS-CoV-2 infections are asymptomatic or subclinical [31, 32].

The lethality of SARS-CoV-2 in China was about 2.5 %, varying between 0.7 % in the affected Chinese regions except the Hubei region and 3 % in Wuhan where the epidemic originated (evaluation of about 45,000 Chinese cases, status: 16 February 2020). A possible explanation for this is an overload of the healthcare system in Hubei due to the very rapidly growing number of cases, so that not all seriously ill patients could be optimally treated. [33]. It can also be assumed that the lethality rate determined at an early stage of the epidemic is an overestimation, as undetected or unreported mild courses of disease are not included in the statistics. For certain risk groups the lethality rate is increased. The lethality rate of the virus is higher the older the infected persons are (under 40 years of age: 0.2 %, 70- to 79-year-olds: 8.0 %, 80-year-olds and older: 14.8 %; data from China, as of February 11, 2020). Pre-existing conditions such as high blood pressure, diabetes, diseases of the cardiovascular system, chronic respiratory diseases or malignant diseases are also associated with a worse outcome (lethality rate of 5.6 to 10.5 %) [34]. First publications on the lethality rate of SARS-CoV-2 in other world regions mention similar case fatality rates [35].
Recommendation

As a donor or recipient organism for genetic engineering operations, the *Severe acute respiratory syndrome-related coronavirus* is assigned to **risk group 3** in accordance with § 5 (1) GenTSV in conjunction with the criteria in Annex I GenTSV.

Reasoning

The viruses of the species *Severe acute respiratory syndrome-related coronavirus* are highly infectious viruses that can cause potentially fatal respiratory diseases in humans.

Note regarding necessary personal protective equipment:

In addition to the level 3 safety measures listed in Annex IIIA No. 3 GenTSV, the German Central Committee on Biological Safety recommends wearing respiratory protection with a retention capacity of class P3 for genetic engineering operation with SARS-CoV or SARS-CoV-2. For example, FFP3 protective masks, respirators with P3 filters and TH3P respirator hoods have such retention capacity. TH3P respirator hoods are particularly suitable because they are less stressful to wear and also show fewer leakage problems.

References


