Position statement of the Central Biosafety Commission (ZKBS) on the risk assessment of laboratory strains of the lymphocytic choriomeningitis virus as donor or recipient organisms in genetic engineering operations according to § 5 paragraph 1 of the Genetic Engineering Safety Regulations

The lymphocytic choriomeningitis virus (LCMV) belongs to the Arenaviridae family of viruses. It was first isolated in 1933 from the liquor of a patient suffering from encephalitis. LCMV was, however, not the cause of the encephalitis (1).

Mice are the natural hosts of LCMV. However, hamsters or guinea pigs can also be carriers of the virus, and monkeys are also known to have been infected. The symptoms generated by an LCMV infection vary widely. Prenatal or neonatal infection in mice is generally asymptomatic and persistent, whereas in older mice the infection is transient and causes lymphocytic choriomeningitis (2, 3, 4). Furthermore, significant differences were detected in the pathogenicity and disease pattern in rodents, depending on the specific test animal and the LCMV strain involved (5). In monkeys, too, LCMV infections gave rise to different diseases. One case of LCMV infection of zoo monkeys, presumably transmitted by a wild mouse, resulted in fatal hepatitis (6, 7). In an experimental infection of rhesus macaques, intravenous administration of the virus led to haemorrhagic fever, whereas intragastric inoculation remained symptomless (8). Irrespective of the inoculation route, the infection of rhesus macaques caused liver disease if the LCMV strain WE was administered. By contrast, infection with the Armstrong strain commonly known as “neurotropic” remained symptomless (9).

LCMV-infected rodents can also transmit the virus to humans (4, 10, 11), probably via infected saliva, urine or faeces. In humans, the clinical course ranges from an asymptomatic infection (35%), slight to moderate symptoms (50%) through to the classic involvement of the central nervous system (CNS) with choriomeningitis or encephalopathy (15%). In immune-competent persons the infection resolves (4, 12, 13). LCMV infection following organ transplantation caused great concern in 2003 and 2005, when seven out of eight transplant recipients who contracted the virus died from the infection (13). Other horizontal transmissions from human to human have not been described to date (4). Transplacental infection can seriously harm the foetus, triggering disorders such as hydrocephalus, chorioretinitis or microcephaly (4, 15).

LCMV is prevalent worldwide (4) and the host range and cell tropism is broad. It replicates in all organs, including lymphatic tissue and the central nervous system (16, 17, 18, 19). The course of the infection is not lytic. The symptoms are caused by an LCMV-triggered immune reaction (20).

Treatment is symptomatic and supportive. To date no antiviral therapies or vaccines are available (4).

In the Guidelines for Research Involving Recombinant DNA Molecules of April 2002 (NIH Guidelines), neurotropic strains of LCMV are allocated to risk group 3 (Appendix B-III-D) and non-neurotropic strains of LCMV to risk group 2 (Appendix B-II-D). The same classification is adopted in the European Council Directive on the protection of workers from risks related to exposure to biological agents at work (2000/54/EC) of 18.09.2000 and in the list of risk-assessed donor and recipient organisms for genetic engineering operations (notification accord-
Recommendation

In accordance with § 5 paragraph 1 of the GenTSV in conjunction with the criteria listed in Appendix I of the GenTSV, the established laboratory strains of LCMV ARM, Docile, WE, UBC, Traub or Pasteur C1PV76001 are classified as donor and recipient organisms for genetic engineering operations in **risk group 2**.

The risk assessment of new isolates of LCMV as donor and recipient organisms for genetic engineering operations are dealt with on a case-to-case basis.

Pregnant women and immune-suppressed persons are disqualified from participating in genetic engineering operations with LCMV.

Reasons

LCMV has a broad host range and cell tropism. The symptoms vary widely in humans and animals. The subdivision of the strains of LCMV into neurotropic and non-neurotropic strains is not possible since, as a rule, LCMVs exhibit a broad cell tropism which includes neuronal cells. The development of neuronal diseases depends on the status of the immune system and not on the specific strain of LCMV.

The listed laboratory strains have been established and characterised. Only a few accidental laboratory infections have been described. These infections amounted to no more than passing flu-like symptoms.

The Central Biosafety Commission (ZKBS) thus recommends allocating established strains of LCMV to just one risk group irrespective of the strain. The risk posed by LCMV to persons with a healthy immune system and to the environment is low. However, a higher potential health hazard for pregnant women and immune-suppressed persons cannot be ruled out.

Transmission of the virus from infected rodents to other animals or humans occurs aerogenously or as a result of a bite. Transmission from human to human has not been documented.

For genetic engineering operations with laboratory strains of LCMV, level 2 safety measures are adequate to safeguard the goods and interests listed in § 1 of the German Genetic Engineering Act (GenTG). Additional safety precautions should be taken to minimize the risk of being bitten by an infected animal.

References

