Position statement of the ZKBS
on the classification of genetic engineering operations, in which genes for immunomodulating proteins are inserted into the genome of replication-competent microorganisms

Introduction
A large number of immunomodulatory proteins are currently known (> 60 cytokines and about 50 chemokines). Due to their pleiotropic and redundant mode of action and strong contextual dependence of their properties [1], some of these modulators can have antagonistic effects in immune responses, i.e. they can stimulate or suppress the immune reaction to a certain pathogen.

Interleukin-4 (IL-4) is known as an activator of immune responses. For example, the administration of IL-4 expressing tumour cells can induce a systemic T cell-dependent immune response against these cells [2]. However, a study by Jackson et al. found that IL-4 can significantly suppress the cellular immune response against Ectromelia virus (ECTV) [3]. After infection of mice with a recombinant, replication-competent ECTV, in whose genome the murine il-4 gene had been inserted, the existing immunity was circumvented. Mice infected with this recominant ECTV died, while mice infected with an appropriate control virus survived the infection. Thus, insertion of the murine il-4 gene significantly increased the hazard potential of ECTV.

Recommendation
For genetic engineering operations, in which immunomodulating proteins are expressed by replication-competent microorganisms, a statement about the mode of action of these proteins cannot be made based on general criteria, but only for individual cases. These works are thus basically not considered to be comparable in terms of the Genetic Engineering Act (GenTG). This also includes corresponding works with chemokines whose expression by a replication-competent microorganism can also lead to an increase in its hazard potential [2].

Thus, a case-by-case assessment by the ZKBS of genetic engineering operations, in which genes for immunomodulating proteins are inserted into the genome of replication-competent microorganisms, is generally required.

However, a case-by-case assessment by the ZKBS is dispensable in the following cases:

1. Recipient organisms recognized as part of a biological safety measure in accordance with § 6 (4) of the GenTSV (Genetic Engineering Safety Regulations) are used.
2. Combinations of recipient organisms and immunomodulating genes that have already been assessed by the ZKBS are used (e.g. transfer of the gene for the human protein TRAIL to Human mastadenovirus C).

The current data do not allow to provide a final list of genes for immunomodulatory proteins that do not require a case-by-case assessment.
References


