Background Cancer testis antigens (CTAs) are considered attractive targets for T cell receptor (TCR)-based cellular therapies as their expression in healthy adults is considered restricted to the immune-privileged testis. However, low-level expression of some CTAs in healthy tissue has been observed, resulting in significant on-target/off-cancer toxicity. Melanoma associated antigen 1 (MAGE-A1) is a member of the MAGE-A CTA family, whose members are known to influence cellular signaling pathways through their E3 ubiquitin ligase-binding MAGE homology domain. MAGE-A proteins are frequently expressed in different cancer types, have been linked to oncogenic activity and their expression has been associated with poor prognosis. Literature data suggest that in healthy tissues MAGE-A1 is detected in testis, only, with one exception suggesting MAGE-A1 RNA expression in cerebellum and cerebrum. Therefore, to evaluate MAGE-A1 as a potential target for cellular immunotherapies, an in-depth analysis of MAGE-A1 expression in > 70 different healthy tissue types and > 5,000 cancer biopsies was conducted, aiming to assess if MAGE-A1 represents a valid and safe target.

Methods A MAGE-A1 antibody with high specificity (TK-AbMA1P) was identified and characterized for immunohistochemistry. A large panel of > 70 different healthy tissue types and > 5,000 tumor biopsies was explored and scored for MAGE-A1 expression by tissue microarray. Identified cancer entities with relevant MAGE-A1 expression were further investigated to assess spatial intratumoral MAGE-A1 expression distribution and expression consistency between primary tumor and lymph node/distant metastases.

Results Characterization of TK-AbMA1P demonstrated fully paralog-selective staining for MAGE-A1. Analysis of MAGE-A1 expression in over 70 different healthy tissues confirmed strictly selective expression of MAGE-A1 in testis. An extended analysis of various CNS tissues including cerebellum and cerebrum did not reveal any expression in CNS. The analysis of > 5,000 tumor biopsies showed significant MAGE-A1 expression in distinct subgroups of multiple major tumor types with high unmet medical need. Substantial expression was detected for example in non-small-cell lung cancer, various breast cancer subtypes, gastrointestinal and urogenital cancers, among others. Extended analysis of the MAGE-A1 positive tumors demonstrated highly homogenous and consistent spatial intratumoral distribution of MAGE-A1 expression as well as between primary tumor and metastases.

Conclusions This analysis confirms that MAGE-A1 is a highly selectively expressed CTA and demonstrates relevant expression in various indications with high unmet medical need, suggesting that MAGE-A1 is an ideal target for highly potent TCR-based adoptive cell therapy.

REFERENCES