MAGE-A1 PROTEIN EXPRESSION PATTERN IN > 5,000 TUMOR AND HEALTHY TISSUE SAMPLES: VALIDATION OF MAGE-A1 AS AN IDEAL TARGET FOR TCR-BASED CELL THERAPY

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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.¹ 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.² 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

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Ethics Approval This study was approved by the Ethics Commission of the Ärztekammer Hamburg; approval number WF-049/09. Participants gave informed consent before taking part.

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