REEXAMINATION OF MAGE-A3 AS A T-CELL THERAPEUTIC TARGET

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Background Recurrent cancer-speciﬁc targets are rare. Given the pace of genomic research over the past three decades, few are likely to lie yet undiscovered. In 2013 an innovative MAGE-A3-directed cancer therapeutic of great potential value was terminated in the clinic because of neurotoxicity.1 The safety problems were hypothesized to originate from off-target TCR activity against a closely related MAGE-A12 peptide.

Methods A combination of published and new data led us to test this hypothesis with current technology, including RNA hybridization in situ and further analysis of the clinical TCR's speciﬁcity to MAGE-A12 and other antigens.

Results We ﬁnd that a key prediction of the MAGE-A12 toxicity hypothesis, the existence of rare, high-MAGE-A12-expressing cells in the brain, is not supported by the data. Our results imply that an alternative related peptide from the EPS8L2 protein is more likely responsible for the toxicity. Therefore, it may be valuable to reconsider MAGE-A3 as a cancer target using HLA-A*02-restricted-TCRs or CARs. As a step in this direction, we isolated MAGE-A3 pMHC-directed CARs, targeting the same peptide as the clinical TCR. These CARs have high selectivity, and avoid cross-reaction with the EPS8L2 peptide that represents a significant risk for MAGE-A3-targeted therapeutics.

Conclusions Given the qualities of MAGE-A3 as an onco-testis antigen widely expressed in tumors and largely absent from normal adult tissues, our ﬁndings suggest that MAGE-A3 may deserve further consideration as a cancer target. We have identiﬁed CARs with selectivity proﬁles consistent with a cell therapeutic directed against HLA-A*02-positive, MAGE-A3-expressing cancers. The relative merits of TCRs and CARs for this target will be discussed.

REFERENCE

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