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T-cell receptor engineered T cell therapy in solid cancers: an antigen-agnostic approach to the identification of therapeutic TCRs from tumor-infiltrating lymphocytes

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The unprecedented efficacy of CAR-T cell therapy in patients with B cell malignancies and Multiple Myeloma has unleashed a surge of preclinical and clinical research testing CARs against a multitude of antigens in hematological and solid cancers. Although first clinical trials of CAR-T cell therapy were conducted in solid cancers (ovarian, renal cell cancer) and despite encouraging preclinical studies, the clinical activity of CAR-T in patients with solid cancers is still unsatisfactory. TCR-engineered T cells are regarded a promising therapeutic alternative. The selection of all therapeutic CARs/TCRs in clinical development so far has been based on the antigens they target. For TCRs, epitopes from shared antigens (cancer/germline, overexpressed) associated with frequent HLA alleles have been prioritized. Yet, only a minority of patients is eligible for therapy and study results so far have fallen short of expectations. Direct identification of therapeutic TCRs from blood or TILs would make more patients eligible for therapy but requires personalization. We have developed a method for the direct selection of tumor-specific T cell clonotypes from TILs through comparative TCR repertoire profiling of clonotypes from TILs and adjacent normal tissue and scRNA-Seq of the TIL-clonotypes. Tumor-specific clonotypes are determined by (1) high abundance among TILs, (2) a high TIL versus normal tissue clonotype frequency ratio, and (3) a sc-gene expression profile indicative of a differentiation trajectory ranging from tumor-reactivity to exhaustion. We have produced predicted tumor-specific TCRs from different NSCLC patients. Ectopically expressed by retroviral transduction in (endogenous) TCR-depleted donor T cells, we show that the recombinant TCR-T cells recognize the corresponding patients' tumor cells and/or allogeneic HLA-matched tumor lines. In one patient a comprehensive antigen screening resulted in the identification of a neoepitope processed from a common KRAS driver mutation as target of three of four TCRs tested. In addition to the personalized strategy, the TCR profiling of >100 tumor patient samples enabled us to build and screen a database comprising >650.000 TCRs using a proprietary algorithm that effectively gathers paired TRAV/TRBV-CDR3 sequences with tumor specificity and high sequence homologies. Donor T cells transduced with several of the TCRs per specificity group showed identical recognition patterns against HLA-matched NSCLC cell lines. These "cluster TCRs" are candidates for off-the-shelf adoptive cell therapies with TCR-engineered TCR-T cells of HLA- and TCR-matched patient