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RNA-based strategies to target T cells to melanoma

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T cells that have been reprogrammed to be tumor-specific by expressing a chimeric antigen receptor (CAR-T cells) or T-cell receptor (TCR-T cells) are increasingly being used. CAR-T cells targeting hematologic tumors induced impressive clinical regressions and have been approved by the FDA and EMA. However, the development of CAR-T cells against solid tumors is lagging behind. This is partly due to the lack of tumor specificity of suitable antigens that can be targeted by CAR-T cells. This can result in on-target/off-tumor toxicity, inadvertently killing non-malignant cells that also express the target antigen. This underlines that there is a great need to identify new specific antigens on tumors.
We have establish a combined *in silico / in vitro* platform for the identification of new tumor-specific antigens on the cell surface of melanoma. The platform uses a computing algorithm to evaluate RNA sequencing data from patient samples and uses this information to propose targets for the generation of new CARs. Using the above-described pipeline, we have identified two new antigens as suitable target antigens for CARs on uveal and cutaneous melanoma. We have designed four new CARs using published sequences of scFvs binding to the target antigens and transferred these CARs to primary human T cells by mRNA electroporation. We analyzed the expression and functionality of these CARs in the T cells after antigen-specific stimulation with melanoma cell lines.
In addition, we used another *in silico* platform to predict tumor peptides that arise from aberrant splicing in uveal melanoma. We tested the immunogenicity of these peptides and cloned the TCRs reacting to them, to be able to transfect T cells with mRNA encoding these TCRs, thereby re-targeting them to uveal melanoma.