

and patients with HCC and BCA the lowest proportion (40.0%).

Conclusions The observed findings underline the importance of TLS as a novel biomarker and a possible association to cellular responses may even enhance their prognostic value. Our planned analyses of combined humoral immune responses will further elucidate the role of TLS in anti-tumor immune response of the analyzed cancer types. A combined targeting of a predefined or personalized set of included TAAs appears promising across the different cancer types.

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P06.03 BISPECIFIC ANTIBODY-DRIVEN SYNTHETIC AGONISTIC RECEPTOR ENGINEERED T CELLS LEAD TO SPECIFIC AND CONDITIONAL THERAPY IN MELANOMA CANCER MODELS

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Background Immunotherapeutic approaches, including immune checkpoint blockade and adoptive T cell therapy (ACT) in the form of tumor-infiltrating lymphocytes (TIL), have had marked success in the treatment of melanoma. Despite these successes, many patients are refractory to treatment or relapse with therapy-resistant disease. To overcome said limitations, we propose a controlled ACT approach, where T cells are armed with synthetic agonistic receptors (SAR) that are conditionally activated only in the presence of a target melanoma-associated antigen, and a cross-linking bispecific antibody (BiAb) specific for both SAR T cell and tumour cell.

Materials and Methods A SAR composed of an extracellular EGFRvIII, trans-membrane CD28, and intracellular CD28 and CD3z domains was fused via overlap-extension PCR cloning. T cells were retrovirally transduced to stably express our SAR construct. We validated our approach in two murine as well as two human cancer models expressing our melanoma-associated target antigens TYRP (murine) and MCSP (human). We confirmed conditional and specific stimulation and proliferation of our T cells, as well as their tumour-antigen-directed cytotoxicity, in vitro and in vivo.

Results Crosslinking TYRP-EGFRvIII (murine) and MCSP-EGFRvIII (human) BiAb, monovalently selective for our SAR, induced conditional antigen-dependent activation, proliferation of SAR-T cells and directed tumour cell lysis with specificity towards two TYRP-expressing murine melanoma and two MCSP-expressing human melanoma cancer models. In vivo, anti-tumoural activity was mediated by the co-administration

of SAR-T cells and BiAb, in A375 and MV3 melanoma xenograft models. Further, we could show that SAR T cells exhibited resistance to MDSC-induced suppression of activation and proliferation.

Conclusions Here we apply the SAR x BiAb approach in efforts to deliver specific and conditional activation of SAR transduced T cells, and targeted tumour cell lysis. The modularity of our platform is key for a targeting approach in a tumor entity with a high mutational load such as melanoma and is fundamental in our drive towards personalised immunotherapies. Further, the SAR approach has demonstrated resistance to MDSC-induced suppression, an interesting axis that requires further investigation.

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P06.04 TRANSCRIPTOME-WIDE NETWORK ANALYSIS PREDICTS THE ROLE OF LACTATE DEHYDROGENASE C IN BREAST CANCER CELL SURVIVAL AND IMMUNE DYSFUNCTION

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Background Cancer testis antigens (CTAs) are lucrative anti-cancer targets given their restricted expression patterns and known roles as mediators of cancer hallmarks, including cancer metabolism, proliferation, survival, and cell motility. Lactate dehydrogenase C (LDHC) is a CTA with upregulated expression in poor prognosis subtypes of breast cancer, however its tumorigenic role is less understood. We recently reported that silencing LDHC reduces breast cancer cell survival through a dysregulated DNA damage response, thus highlighting its potential as an anti-cancer target with limited off-target effects. This study aimed to explore the changes in the transcriptome of breast cancer cells and immune-related mediators upon *in vitro* LDHC targeting.

Materials and Methods We silenced *LDHC* expression in breast cancer cell lines and investigated the downstream effects on the tumor cell transcriptome. Differentially expressed genes were subjected to regulatory network analyses. We further assessed the secretory profile of cytokines and immune checkpoint expression in *LDHC*-silenced cells and used the Tumor Immune Dysfunction and Exclusion (TIDE) algorithm to determine the effect of the interaction between *LDHC* expression and cytotoxic T lymphocyte (CTL) infiltration in the METABRIC breast cancer cohort.

Results Network analysis to investigate the effects of silencing *LDHC* on the tumor cell transcriptome identified 47 up- and 55 down-regulated transcripts (2.0-fold change, adj $p < 0.05$). Differentially expressed genes in the *LDHC*-silenced cells were particularly enriched in canonical pathways regulating cell cycle checkpoint control, BRCA1-mediated DNA damage response and NF- κ B signaling in response to infection. Upstream regulator analyses revealed the altered expression profile was associated with mTOR ($p = 1.27 \times 10^{-5}$, $z = 2.242$) and CASP3 ($p = 3.2 \times 10^{-4}$, $z = 2.250$) pathways, which in the presence of LDHC are predicted to activate TP53, Myc, NF- κ B complex, STAT1/3, PRKC, CDK2, FOXO3 and HIF-1 α while