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 antitumor 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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Materials and Methods A SAR composed of an extracellular LDHC expression and 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.


P06.04 TRANSWORSTOME-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-kb signaling in response to infection. Upstream regulator analyses revealed the altered expression profile was associated with mTOR (p=1.27e-5, z=2.242) and CASP3 (p=3.2e-4, z=2.250) pathways, which in the presence of LDHC are predicted to activate TP53, Myc, NF-KB complex, STAT1/3, PRKC, CDK2, FOXO3 and HIF-1α while...