ID #341 Spatial dissection of targets for antibody drug conjugates and radioligands on transcriptome and protein level identifies novel therapeutic opportunities in AT/RT [Abstract]

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ID #341 SPATIAL DISSECTION OF TARGETS FOR ANTIBODY DRUG CONJUGATES AND RADIOLIGANDS ON TRANSCRIPTOME AND PROTEIN LEVEL IDENTIFIES NOVEL THERAPEUTIC OPPORTUNITIES IN AT/RT

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Background: Rhabdoid tumors (RT) are rare, highly aggressive pediatric malignancies characterized by loss of SWI/SNF complex components (SMARCB1/SMARCA4) and poor clinical outcomes. Relapsed or refractory RT remain almost uniformly fatal, targeted or immune-based therapies have shown limited efficacy.

Methods: To identify novel therapeutic vulnerabilities, we performed large-scale transcriptomic screening to prioritize clinically actionable surface antigens amenable to antibody–drug conjugates (ADCs), radiopharmaceutic herapies (RPT), or cellular immunotherapies. FAP, CXCR4, and IL13RA2 were selected for protein-level validation by immunohistochemistry in a cohort of 60 rhabdoid tumors, including 50 atypical teratoid/rhabdoid tumors (ATRT) spanning all molecular subgroups (ATRT-TYR, ATRT-SHH, ATRT-MYC) and 10 extracranial rhabdoid tumors (eMRT). Spatial and single-nucleus transcriptomic analyses were integrated to define subgroup- and cell-type–specific patterns.

Results: FAP, CXCR4, and IL13RA2 demonstrated differential expression across RT subgroups: FAP expression was detected in 51/60 tumors and was particularly strong in ATRT-SHH and ATRT-MYC subgroups, with heterogeneous localization across stromal and tumor compartments. CXCR4 expression localized almost exclusively to the stromal compartment with a strong endothelial reactivity. Although only 11/60 tumors stained positive for IL13RA2, its expression delineated a distinct niche of rhabdoid tumor cells characterized by high expression of melanosomal-and stemness-associated markers.

Conclusions: We identify multiple biologically and clinically relevant surface targets in rhabdoid tumors, including widespread FAP expression and a biologically distinct IL13RA2-positive tumor population. These findings support the rational development of ADC-and RPT-based therapeutic strategies as an additional therapy component.