Characterizing the role of structural genomic instability in generating actionable neoantigens in pediatric solid tumors

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Abstract**:** Pediatric cancers are characterized by a paucity of nonsynonymous somatic mutations and thus have achieved suboptimal responses to immune checkpoint blockade (ICB) therapy to date. However, pediatric tumors are enriched in structural variants (SVs) which may generate immunogenic neoantigens through transcribed gene fusions or rearrangements. Our central hypothesis is that SVs may represent an alternative source of therapeutically actionable neoantigens in childhood cancers. To test this, we will first perform an integrative immunogenomic analysis across 4000+ whole genome and RNA sequencing datasets to define the SV-derived neoantigen landscape of pediatric solid tumors and identify both recurrent and private neoepitope candidates (Aim1). Beginning with 10 candidate recurrent neo peptides identified in our preliminary analysis, we will employ a rigorous validation workflow to experimentally confirm neoantigen presentation and immunogenicity using state-of-the-art HLA stabilization, immuno-peptidomic, and patient immune monitoring assays (Aim 2). We will leverage a unique pediatric biospecimen repository from MSK Kids to facilitate these studies. This work will deliver the largest compendium of functionally validated SV-derived neoantigens reported to date in pediatric cancers. We expect our findings to pinpoint patients and tumor subtypes that may benefit from existing ICB therapies. Further, this work will define optimal SV-derived targets for novel immunotherapeutic strategies, including individualized cancer vaccines and engineered cellular therapies, to bring the promise of cancer immunotherapy to children.