



2018 ACS-IRG Pilot Project

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PROJECT TITLE: SINGLE CELL TRANSCRIPTOMICS AND EPIGENOMIC PROFILING TO REVEAL IMMUNE LANDSCAPE IN PEDIATRIC SARCOMAS

ABSTRACT:

SARCOMAS ARE A HETEROGENEOUS GROUP OF MALIGNANT TUMORS THAT ARISE FROM MESENCHYMAL TISSUES AND CONSTITUTE ABOUT 15% OF ALL PEDIATRIC CANCERS. THOUGH RELATIVELY INFREQUENT, A SIGNIFICANT PROPORTION OF PEDIATRIC SARCOMAS REMAIN INCURABLE AND FATAL DESPITE MEDICAL AND SURGICAL ADVANCES IN CANCER TREATMENT. HENCE, NEWER TREATMENTS ARE URGENTLY NEEDED. NUMEROUS LINES OF EVIDENCE SUPPORT A POTENTIALLY IMPORTANT ROLE FOR T CELL-MEDIATED IMMUNOSURVEILLANCE IN MEDIATING PROTECTION AGAINST CANCER. IMMUNOTHERAPIES THAT BOOST THE ANTI-TUMOR RESPONSES OF T CELLS HAVE SHOWN PROMISE IN MANY ADULT CANCERS, HOWEVER TRANSLATION OF THEIR CLINICAL SUCCESS TO PEDIATRIC TUMORS IS HINDERED BY A LACK OF UNDERSTANDING OF THE TUMOR IMMUNE MICROENVIRONMENT WITHIN THESE TUMORS. WE HYPOTHEZIZE THAT THE IMMUNE INFILTRATE VARIES BETWEEN PEDIATRIC SARCOMA TYPES AND THE COMPOSITION OF TUMOR-INFILTRATING ANTITUMOR *VERSUS* PRO-TUMOR IMMUNE CELL TYPES AND PATHWAYS ARE DISTINCT. TRANSCRIPTOMIC AND EPIGENOMIC PROFILING OF SARCOMA TUMOR-INFILTRATING IMMUNE CELLS WILL REVEAL NOVEL AND UNIQUE TARGETS FOR IMMUNOTHERAPY FOR DIFFERENT SARCOMA TUMOR TYPES.

THE GOAL OF THIS PROJECT IS TO DEFINE THE MOLECULAR PLAYERS AND MECHANISMS INVOLVED IN ANTI-TUMOR IMMUNE RESPONSE IN PEDIATRIC SARCOMAS WITH THE SPECIFIC AIMS TO CHARACTERIZE THE TRANSCRIPTOME AND EPIGENOME OF: (I) TUMOR-INFILTRATING CD4⁺ T CELL, CD8⁺ T CELL AND CD19⁺ B CELL TO REVEAL THEIR FUNCTIONAL PHENOTYPE, TCR/BCR SEQUENCE AND CLONALITY IN PEDIATRIC SARCOMAS; (II) TUMOR-ASSOCIATED MACROPHAGE AND OTHER KEY IMMUNE CELL SUBSETS TO UNRAVEL THEIR CO-REGULATORY RELATIONSHIP AND TUMOR REGULATORY MECHANISMS. WE WILL UNDERTAKE AN UNBIASED AND COMPREHENSIVE APPROACH TO DEFINE TRANSCRIPTOMIC AND EPIGENOMIC PROFILE OF PURIFIED TUMOR-INFILTRATING LYMPHOCYTES (TILS), MACROPHAGES AND OTHER IMMUNE CELL SUBSETS IN A WELL CHARACTERIZED COHORT OF PEDIATRIC PATIENTS WITH SARCOMAS. UTILIZING STATE-OF-THE-ART GENOMIC TOOLS SUCH AS SINGLE-CELL RNA SEQUENCING, ATAC-SEQUENCING AND HISTONE CHIP-SEQ, WE WILL EVALUATE THE TIL FUNCTIONAL PHENOTYPE, TCR/BCR SEQUENCE AND CLONALITY IN PEDIATRIC SARCOMAS. IN ADDITION, SIMILAR ANALYSIS IN TUMOR-ASSOCIATED MACROPHAGE AND OTHER KEY IMMUNE CELL SUBSETS WILL UNRAVEL THEIR CO-REGULATORY RELATIONSHIP AND TUMOR REGULATORY MECHANISMS. INTEGRATED BIOINFORMATICS ANALYSES OF THESE DATASETS WILL REVEAL NOVEL IMMUNE PATHWAYS THAT MAY BE TARGETED IN IMMUNOTHERAPEUTIC STRATEGIES AGAINST PEDIATRIC SARCOMAS.