



## SU2C–St. Baldrick’s Foundation Pediatric Cancer Dream Team

### “Immunogenomics to Create New Therapies for High-Risk Childhood Cancers”



*[This abstract was provided by the scientists when their application was accepted.]*

Despite progress, many children currently diagnosed with cancer have less than a 50 percent chance of survival, and survival rates have plateaued over the last decade. In addition, standard therapies are exceedingly toxic, leaving childhood cancer survivors with life threatening morbidities. Although our understanding of the biology of childhood cancer has advanced substantially in the last two decades, new precision therapies have not yet significantly improved childhood cancer outcomes or allowed for the development of less toxic therapies.

The **SU2C–St. Baldrick’s Foundation Pediatric Cancer Dream Team (PCDT)** brought together pediatric genomics and immunotherapy experts to establish a collaborative and multidisciplinary program to develop scientifically rigorous immunotherapeutic approaches for the most refractory childhood cancers.

The Dream Team has amassed comprehensive datasets spanning normal pediatric and adult tissues and pediatric cancers and developed novel algorithms to yield an entirely new platform through which systematic and unbiased exploration of the cell surface of pediatric cancers can be performed.

The genomic platform is complemented by protein-based analyses of tissue arrays and novel proteomics technologies, designed to discover promising targets for the range of monoclonal antibody (mAb)-derived therapeutics currently available. This has generated a pipeline of new immunotherapeutic targets prioritized for further development.

Beyond identifying novel targets, the team's work has also established expression patterns across the spectrum of pediatric cancers, allowing for biomarker (rather than histology)-defined clinical trial designs.

The Dream Team has created several novel mAb based therapeutics, spanning antibodies, antibody drug conjugates and chimeric antigen receptors, with several showing promising activity in preclinical models and poised for clinical translation. Work in Aim 2 has also advanced our understanding of fundamental biology that drives success or failure of emerging immunotherapeutics.





## Scientific Abstract

In Aim 3, the PCDT has launched 22 SU2C-SBF clinical trials of cell therapy for childhood cancer, enrolling 593 patients to date. This work has provided some spectacular successes, including complete response rates of >70% in children with B-ALL treated with CD19-directed CAR therapy. But, it has also identified mechanisms of immune escape that limit the effectiveness of these therapeutics, including resistance to CD19 based targeting following CD19-CAR therapy due to selection of variants lacking the CD19 target. Our team has also identified several biomarkers of toxicity and have developed guidelines that are currently in wide clinical use.

More sobering, few children with solid malignancies have benefited from immunotherapies today, and checkpoint blockade approaches have been especially disappointing. However, Dream Team investigators have learned from both the clinical successes and failures, and our efforts now are largely focused on novel immunotherapeutic strategies for solid malignancies including brain tumors, including multi-targeted approaches, novel therapeutic engineering advances, and innovative regional delivery strategies.