St. Baldrick's Foundation – Stand Up to Cancer Pediatric Cancer Dream Team with generous support from Hope4ATRT
Stewardship Report

Lead Researchers:

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Dr. Crystal Mackall, Professor, Stanford University

Title of Research Project:

Formerly known as the St. Baldrick's – Stand Up to Cancer Pediatric Cancer Dream Team (SBF-Su2C PCDT), this team is now the St. Baldrick's EPICC Team (Empowering Pediatric Immunotherapies for Childhood Cancer).

Lay Summary of PCDT Grant

The SBF-Su2C PCDT addressed the paradox that while 80% of children with cancer can be cured, there has been little progress in improving outcomes for the 20% of pediatric oncology patients with high-risk and refractory malignancies over the last two decades. In addition, the intensive chemoradiotherapies that make up our current standard of care results in life-threatening morbidity for many childhood cancer survivors, thus illustrating a pressing need for more precise and less toxic therapies for all pediatric malignancies.

The overall **hypothesis** being tested is that childhood cancers express lineage restricted cell surface molecules that are not present on normal tissues and which can be targeted with synthetic immunotherapeutics. The overall **objective** of our multinstitutional team from ten institutions is to develop and conduct paradigm changing early phase clinical trials of immunotherapies directed toward prioritized targets emerging from the first phase of our project.

In addition to the continued support from St. Baldrick's and HOPE4ATRT and other St. Baldrick's charity partners, as well as matching funds from our home institutions, we have leveraged two recent NCI initiatives emerging out of the Biden Moonshot Initiative to accelerate efforts towards our main objective: 1) creation of the Pediatric Cancer Immunotherapy Discovery and Development network (PI-DDN) and 2) the Pediatric Cancer Immunotherapy Trials Network (PedCITN). While the PedCITN will only be transiently funded, several PCDT investigators recently received a large CRUK-NCI grant to further the CAR T cell work in several of our labs.

The past several years provided unprecedented challenges to our team, but under the theme of "Childhood cancer does not stop in a pandemic," we were able to not only keep our ongoing trials open and accruing, continue to open trials and now have 45 early phase clinical trials in the PCDT portfolio. Over the now 8.5 years of the PCDT, we have enrolled 1,371 children on PCDT-branded trials (71 in

the past six months). We published 21 papers in the last 6 months, including many in the highest profile journals, and now have 423 total publications since the initiation of this project citing the SBF-Su2C and AACR. The PCDT has also filed 56 patent applications and has licensed technology to several companies. St. Baldrick's has recommitted to continue to fund our team, along with charity partners like HOPE4ATRT, now rebranded as the St. Baldrick's Foundation Empowering Pediatric Immunotherapies for Childhood Cancer Team (SBF-EPICC Team), to continue to continue an evidence- based immunotherapy revolution for children, adolescents and young adults with cancer.

Please summarize your research related to ATRT in everyday language.

The Seattle CAR T cell portfolio continues with a broad trial portfolio for leukemia, solid tumor, and central nervous system (CNS) tumors. Specifically for pediatric CNS tumors, we have 3 active trials (BrainChild-01, -02, and -03 targeting HER2, EGFR, and B7-H3, respectively) as well as a 4th trial (BrainChild-04) that was recently FDA approved using a multi-antigen targeting approach and will open in the Spring.

Overall, our Brainchild trials have now enrolled over 70 children, including 6 children with ATRT, along with others diagnosed with DIPG, DMG, ependymoma, HGG, and medulloblastoma.

As of February 2023, we have delivered over 350 intracranial CAR T cell doses and established preliminary feasibility and tolerability of delivering repeated intracranial doses of CAR T cells in an outpatient clinic setting. Currently, because of the varying dose levels and variability in disease groups on our studies, including the subdivision of individual pathology types, we have yet to analyze correlative studies or potential clinical benefit in specific disease type.

BrainChild-03 is the first-in-human B7-H3 CAR T cell trial delivering B7-H3 CAR T cells to children with recurrent and refractory CNS tumors and DMG/DIPG, with an Arm C dedicated to DIPG due to the clinical intricacies of that anatomic location. Therefore, our greatest clinical experience is with DIPG with over 150 doses delivered to over 20 enrolled patients. As BrainChild-03 nears accrual, we are opening FDA-approved expansion cohorts to treat further patients at the highest dose level and that group will include patients with ATRT and DIPG.

Across our trials, we have found CAR T cells detectable in the Cerebral Spinal Fluid (CSF) for up to 2 weeks post infusion and found correlative markers, such as cytokines and proteins, in the CSF that support local immune inflammation is happening. Some treated patients have experienced clinical improvement and radiographic improvement, and some patients have had long standing stable disease such as one child with histone 3.3 mutant DIPG who has now received 36 doses over 18 months on trial. We have given 15 intracranial CAR T cell doses to multiple patients with DIPG who have enrolled and all of those patients have been able to complete their planned dosing without significant toxicity.

Future trials will build off this initial experience and continue to enroll patients of all high grade CNS pathologies and improving the therapeutic targeting of B7-H3, a very relevant target on ATRT, remains a central interest of our program, along with future combinatorial studies for these patients.

We are also applying technology initially focused on neuroblastoma (2) to brain tumors including AT/RT in collaboration with Dr. Jessica Foster at CHOP. We have already built two CAR's focused on peptides derived from proteins called PRAME and IGFBPL1. The former has shown cure of glioblastoma models in mice, and we hope to get to other brain tumor models for both CARs, including ATRTs in the coming year.

Is there anything else you'd like to say to St. Baldrick's and HOPE4ATRT?

We think that we have achieved a lot, but also know that for the majority of patients with high-risk solid pediatric cancers, we do not have an effective immunotherapy. We think that we have the infrastructure and thought leadership in place to change this current reality, and we thank the St. Baldrick's Foundation and HOPE4ATRT for the privilege of doing this work we believe will ultimately help improve outcomes for ATRT patients and others.

Publications/References

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