UNIVERSITY OF LOUISVILLE

raiseRED
2022-2024 Impact Report
and 2024-2025 Research Initiatives

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2022-2024 Report on Research Fund Utilization

Introduction

We are profoundly grateful to raiseRED for your generous support of pediatric oncology and hematology research. Your funding has been pivotal in advancing our understanding and treatment of childhood cancers, allowing us to make significant strides in innovative therapies. Your support assisted in groundbreaking research conducted by Dr. William Tse and the leading translational research conducted by Dr. Michael Huang.

Dr. William Tse's Research

Dr. William Tse's groundbreaking work focuses on developing novel human Chimeric Antigen Receptor T cells (CAR-T cells) aimed at eradicating hard-to-treat pediatric tumors, particularly advanced neuroblastoma and high-grade gliomas. Through the incorporation of cutting-edge technologies, Dr. Tse's research group has pioneered several innovative strategies:

1. CRISPR-Cas9 Gene Editing: By controlling the expression of CAR receptors at the endogenous T cell receptor locus, the team has enhanced CAR-T cell functionality, reducing cellular exhaustion and improving anti-tumor responses.
2. Cytokine-Based Activation: The integration of elements from the STAT3/5 signaling pathway has significantly improved the persistence and effectiveness of CAR-T cells in vivo.
3. Non-Viral Gene Transfer: Employing ribonucleoprotein and electroporation techniques, the research avoids the complications associated with lentivirus-mediated gene transfer, thereby streamlining the process and minimizing risks.
4. Dual Targeting of Tumor Antigens: Utilizing CRISPR-Cas9 technology, the team has engineered CAR-T cells that can target multiple tumor antigens, effectively reducing the chance of treatment failure due to "antigen escape."

The success of these innovative CAR-T cells (designated CRISPR-STAT3/5-CAR-T cells) has been demonstrated in a xenograft mouse model of human diffuse intrinsic pontine glioma (DIPG). Remarkably, after a single treatment, over 75% of the mice showed complete tumor disappearance, with no recurrence observed over three months. This extraordinary progress represents a significant breakthrough in pediatric oncology, laying the foundation for future clinical trials aimed at treating children afflicted with aggressive tumors.

Dr. Michael Huang's Research

Dr. Michael Huang serves as the Study Chair for a multi-institutional protocol investigating the efficacy of DFMO/eflornithine, an anti-parasitic drug, for treating molecular high-risk medulloblastoma—the most prevalent form of childhood brain cancer. His work exemplifies the potential of repurposing existing medications to combat aggressive pediatric tumors.

Additionally, Dr. Huang is spearheading translational research into radioimmunotherapy, a novel approach that leverages the targeting capabilities of antibodies to deliver low doses of focused radiation specifically to tumor cells. This method holds promise for treating pediatric glioblastoma and DIPG, both of which currently lack effective therapies.

Moreover, Dr. Huang's research delves into the immunosuppressive properties of the tumor immune microenvironment in pediatric high-grade brain tumors. Understanding these dynamics is crucial for developing strategies that can enhance the efficacy of existing treatments and foster better patient outcomes.

Conclusion

The transformative research being conducted by Dr. Tse and Dr. Huang, supported by the generous contributions from raiseRED, represents a beacon of hope in the fight against pediatric cancers. Their innovative approaches and groundbreaking findings not only enhance our understanding of these diseases but also pave the way for future clinical applications that could change the lives of countless children and their families. We are sincerely grateful for the unwavering support of raiseRED, which is instrumental in driving these vital research initiatives forward. ***Together, we are making strides towards a brighter future in pediatric oncology.***

2024-2025 Research Initiatives

Now that Dr. Michael Ferguson has arrived at Norton Children's Hospital/University of Louisville School of Medicine beginning his tenure as the Division Chief for Pediatric Hematology Oncology and Bone Marrow Transplant (BMT), he has two research initiatives slated to utilize RaiseRed funds for the July 2024 to June 2025 period.

The first is investing in Oxford Biodynamics EpiSwitch™ technology to develop a blood-based biomarker of disease remanence or recurrence in pediatric solid tumors and brain tumors.

Too often patients that complete treatment for a variety of solid tumors are left with residual lesions that can be detected with radiographic imaging (i.e. CT scans, PET scans, MRIs, etc.) and it is difficult to discern if any active cancer cells remain. EpiSwitch™ technology a proprietary industrial platform for the discovery, evaluation, validation and monitoring of a novel class of epigenetic biomarkers known as 'chromosome conformation signatures' ("CCSs"). CCSs can provide a compelling, stable framework from which changes in the regulation of a genome can be analyzed, long before the results of these epigenetic changes manifest themselves as obvious abnormalities. The EpiSwitch™ platform has been investigated in multiple cancer types to determine the presence of cancer from small blood samples [1, 2] and has been utilized in adult cancer to predict response to immunotherapy [3]. This innovative technology will be utilized to determine if blood biomarkers can determine if pediatric cancer relapse is occurring before radiographic imaging, thus making it a non-invasive and radiation-free methodology to predict recurrence and the need for change in therapy. The plan is to start investigating in osteosarcoma with other tumor types to follow and likely utilizing the Beat Childhood Cancer Group for greater access to patient samples. Initial meetings with Oxford Biodynamics will take place in September 2024 and Dr. Ferguson anticipates having the project approved and running by the first or second quarter of 2025.

The second is to help grow our pipeline of pediatric cancer mouse and cell models for the study of novel therapies in the lab.

Dr. William Tse is currently working with several brain tumor models to study his novel CAR T cell therapy. As his research blossoms, we will need to build our pipeline of both brain tumor mouse and cell models while additionally developing and building models in sarcoma. This effort may require additional staff members for mouse model creation and maintenance for a variety of studies. Dr. Ferguson has begun talks regarding lab space and building out a version of the pediatric cancer biorepository. These talks are in their infancy, much of this work will be planned to start late in the 2nd quarter of 2025.

References

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