

TARGETING SOLID TUMORS WITH MULTI-ANTIGEN-SPECIFIC T CELLS

IDENTIFYING GENETIC AND EPIGENETIC DETERMINANTS OF THERAPEUTIC RESPONSE

Children with solid tumors that do not respond to standard therapy, or who relapse despite standard therapy, have a very poor prognosis. Even with the rapid increase in the number of targeted therapies for adult cancer, similar development of such agents for pediatric cancer has unfortunately progressed slowly. Furthermore, only a small number of existing adult targeted therapies show activity against childhood cancers, limiting crossover use, and those that can be used benefit only a small number of pediatric cancer patients.

Midhat Farooqi, MD, PhD, Director of Molecular Oncology at Children's Mercy Kansas City, is leading one part of a collaborative effort to find an effective therapy for pediatric patients with specific types of solid tumors: neuroblastoma, Wilms tumor, Ewing sarcoma and rhabdomyosarcoma. The focus is on a therapy that uses a patient's own immune cells to combat a tumor.

PHASE I TRIAL

Preceding the initiation of Dr. Farooqi's study, a team at Children's National Hospital in Washington, D.C., conducted an early phase I clinical trial to test the safety and efficacy of specially derived T cells in pediatric patients. They tested 15 patients with the specific types of solid tumors noted above, where the tumors had relapsed or were refractory to standard treatment. They took T cells from the peripheral blood of patients and stimulated them with antigen-presenting cells and three antigens commonly found on

the surface of pediatric solid tumors. T cells with the ability to recognize these antigens (tumor-associated antigen-specific T cells, or TAA-Ts), were selected and infused back into patients. At day 45 after receiving T cells, the study looked for responders (patients who had stable or reduced disease) versus nonresponders (those with progressive disease). Eleven of the 15 patients, or 75%, were responders with no disease progression at six months. Without this therapy, historical cohorts have less than 40% progression-free survival at six months. Details of the study were recently published in the *Journal of Clinical Oncology*¹.

CHILDREN'S MERCY SUPPORTS TRIAL EXPANSION

When phase I trial data showed no toxicity from the T cell therapy and positive results, the team at Children's National Hospital applied for an expansion to enroll up to 20 more patients in the trial. While the main trial continues to be conducted at Children's National Hospital, Dr. Farooqi and Children's Mercy are collaborating to provide crucial support and correlative biologic data to the trial.

Dr. Farooqi proposed that the Center for Genomic Medicine at Children's Mercy conduct genetic sequencing of as many trial participants as possible on a range of sample types. In his proposal, Dr. Farooqi outlined three key questions he seeks to answer in his study:

1. By performing genetic sequencing on participant tumor cells, can we figure out genetic markers that track whether patients respond or not? Could these data then help the trial team figure out which patients will and will not benefit from the therapy upfront?

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CHILDREN'S MERCY SUPPORTS TRIAL EXPANSION

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2. If we graft tumors onto mice and pretreat them with known agents that alter DNA methylation prior to TAA-T cell infusion, can we convert nonresponsive tumors into responsive tumors?
3. Can we find DNA that is shed by the tumor in a participant's blood and use it as a biomarker of disease progression or stabilization, especially as compared to imaging data? Can we eventually replace scans with a blood draw, or liquid biopsy, to perform disease status checks?

Dr. Farooqi began this phase of study in December 2019, at the same time the expansion trial began at Children's National Hospital. His goal is to receive samples from every child in the trial for sequencing. The study will continue for the next three years. His team will provide a report of its findings after the three-year period is complete.

BIOREPOSITORY BROADENS OPPORTUNITY FOR GENETIC UNDERSTANDING

In 2017, under the leadership of Dr. Erin Guest and Dr. Alex Kats, Children's Mercy created an oncology biorepository and has since been collecting voluntary patient samples. Dr. Farooqi and his team are actively sequencing all tumor samples contained in the biorepository to create a library of tumor genomes. In addition, two other children's hospitals, Children's Health in Dallas and Cook Children's Medical Center in

Fort Worth, have agreed to send a cohort of solid tumor samples to Children's Mercy for sequencing. Dr. Farooqi will use the sequencing data to identify molecular subtypes of cancers, paying particular attention to their different responses to treatment.

In his proposal, Dr. Farooqi shared plans for sequencing up to 100 cases in total, including those from Children's National Hospital, samples in the biorepository and those from the other two children's hospitals. His work is supported by a \$1 million grant from Braden's Hope for Childhood Cancer.

DREAM TEAM FIGHTS CHILDHOOD CANCER

Braden's Hope believes that institutions should not work in silos. The Foundation urged Children's Mercy to form a dream team to fight pediatric cancer. This request was the impetus for Dr. Farooqi and his team to work with the three other pediatric hospitals, along with support and guidance from The University of Kansas Cancer Center.

SOURCES

¹ Immunotherapy of Relapsed and Refractory Solid Tumors With Ex Vivo Expanded Multi-Tumor Associated Antigen Specific Cytotoxic T Lymphocytes: A Phase I Study. Hont AB, Cruz CR, Ulrey R, O'Brien B, Stanojevic M, Datar A, Albihani S, Saunders D, Hanajiri R, Panchapakesan K, Darko S, Banerjee P, Fortiz MF, Hoq F, Lang H, Wang Y, Hanley PJ, Dome JS, Bollard CM, Meany HJ. *Journal of Clinical Oncology* 2019 Sep 10;37(26):2349-2359. doi: 10.1200/JCO.19.00177. Epub 2019 Jul 29.

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