THE HARTWELL FOUNDATION

2021 Individual Biomedical Research Award

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Improved Detection of Relapse in Pediatric Acute Myeloid Leukemia Using Single-Cell Genomics

Pediatric acute myelogenous leukemia (pAML) is a devastating disease affecting approximately 800 children per year in the United States. Thanks to chemotherapy and hematopoietic cell transplantation (HCT), many pAML patients have a rapid response to treatment, remain disease-free for the entirety of their life, and suffer few, if any, long-term complications. For others, the most intensive therapies fail to prevent relapse. The two types of patients can, at the outset, seem indistinguishable. Laboratory tests are employed that inventory a variety of genetic variants that might be present in a bone marrow sample of a child with pAML, and what these tests reveal is that, particularly in children, the specific genetic alterations in the marrow of pAML patients can differ in complexity and amount, even within a given patient's tissue. This cellular complexity contributes significantly to treatment failures because some cells may be resistant to chemotherapy or become resistant throughout treatment. Some cells even appear to escape chemotherapy by selectively "dialing up" or "turning down" the cellular marks that identify targets, hiding, therefore, in plain sight. This ability to engage in cellular camouflage can make it difficult to determine when a patient's leukemia is truly eradicated, leaving some patients with a false sense of confidence, and at risk for ultimate relapse. To address this problem, I propose an entirely novel approach to measuring leukemic presence in the marrow using technologies that measure which genes are turned on at a single cell level. To provide deeper insights into AML biology and therapeutic vulnerabilities, I will assemble a comprehensive molecular description of pAML cells (epigenomic, transcriptomic, and surface proteomic signatures) from 20 patients at the time of diagnosis and after induction of chemotherapy (when a bone marrow biopsy is performed). I will evaluate patients for residual disease; and rigorously identify leukemic stem cells by characterizing them for cell-surface immunophenotype, RNA, and DNA. State of the art droplet microfluidics for capturing individual cells will provide the genomic profiles of thousands of single residual leukemic cells at a time, creating a massive genetic "atlas" of residual disease cells that are chemotherapy-resistant or not. From these data, I will construct a comprehensive outline of leukemic states of differentiation, both before and after chemotherapy. To evaluate the efficacy of single-cell genomics for evaluating disease burden in patients who have received a HCT, I will retrospectively profile 30 pAML patients who went on to relapse up to 6 months after a bone marrow biopsy. If I am successful, the translation of single-cell genomics-based assays into the clinic will dramatically improve risk-stratification for pediatric leukemia patients, forming the basis for clinical decisions regarding not only their course of therapy but their quality of life.