THE HARTWELL FOUNDATION

2020 Individual Biomedical Research Award

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Regulating Leukemia Initiating Cells in Relapsed and Refractory T Cell Lymphoblastic Leukemia

Acute lymphoblastic leukemia is the most prevalent hematological malignancy diagnosed in children in the United States. Despite a high cure rate after intensive chemotherapy, 25% of pediatric T cell lymphoblastic leukemia (T-ALL) cases show resistance to chemotherapeutic agents and relapse months or years after remission. Currently the only curative therapy for relapsed/refractory T-ALL patients is allogeneic bone marrow transplant, which is costly and risky due to transplant-related mortality and toxicity. Thus, less than 25% of children with relapsed/refractory T-ALL survive past 5 years. Current research efforts have identified leukemia initiating cells (LIC) as the main culprit causing disease relapse and therapeutic resistance. LICs can evade chemotherapy and hide inside the bone marrow, only to emerge and cause relapse later. Therefore, biomarkers and therapies directly targeting this population can greatly increase the survival of children with T-ALL. In examining leukemia samples from children, Fay discovered that LICs often harbor increased adenosine-to-inosine RNA editing, a phenomenon by which a cell can change its RNA to improve survival and expansion. In effect, RNA editing creates an activated condition that allows the LIC to "re-invent" their own RNA to create new proteins that might help survival and evade chemotherapy and thus promote relapse. In this regard, she observed that relapsed/refractory patients often have enriched LIC with enhanced pro-survival and self-renewal capacity. She believes that RNA editing is a crucial event in the oncogenic transformation of normal progenitors to LIC and hypothesizes that RNA editing in LIC could be the weakness of these cells, like an "Achilles Heel". Building on these unique findings, she proposes aberrant edited RNA transcripts can serve as biomarkers and novel therapeutic targets for prediction of T-ALL relapse, including progression to refractory stages. Since RNA editing can change any of the thousands of transcripts in a cell, she plans to identify edited-RNA as predictive biomarkers of T-ALL relapse and resistance to therapy; validate reliability of edited-RNA biomarkers and identify RNA editing targets in T-ALL initiating cells in culture; and then test druggable RNA editing targets and verify edited-RNA biomarkers in pre-clinical humanized mouse models. If Fay is successful, her approach will set the stage for rapid translation of novel biomarkers for relapsed or refractory T-ALL. Blood-based assays for a panel of edited RNA biomarkers will enable clinicians to identify children with higher likelihood of relapse during therapy and thus, apply more targeted treatment regimens with the potential to limit any undesirable drug toxicity. The use of blood-based biomarkers will also reduce the need for painful and invasive bone marrow biopsies and improve the detection of minimal residual disease after attainment of complete remission, benefitting not only those children diagnosed with T-ALL but their families, as well.