THE HARTWELL FOUNDATION

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Daniel R. Matson MD, Ph.D.

Assistant Professor
Department of Pathology and Laboratory Medicine

University of Wisconsin-Madison

Defining the Role of GATA2 Deficiency Syndrome in Predisposing Acute Leukemia

Leukemia, a cancer of the body's blood-forming tissues characterized by an overproduction of immature blood cells from the bone marrow and the lymphatic system, is the most common cancer in children. There are no known risk factors, but some occur due to inherited genetic mutations. Accounting for 1 in 3 new cancer diagnoses or about 4,000 new cases each year in the US, about 75% of childhood leukemias are acute lymphocytic leukemia (ALL). By contrast, acute non-lymphocytic leukemia accounts for most of the remaining cases, which are aggressive and fast growing, and described on a continuous disease spectrum starting with early-stage myelodysplastic syndromes (MDS) that typically progress to subtypes of acute myeloid leukemia (AML). Although the overall survival rate for these cancers has improved significantly during past decades, there is no cure for MDS. Some medications can help slow the progression of the disease but cures typically require years-long treatment courses with toxic chemotherapies. Inherited mutations in the transcription factor GATA Binding Protein 2 (GATA2) cause a rare debilitating syndrome characterized by immunodeficiency and bone marrow failure and where strikingly, 40% have a predisposition to develop MDS and AML prior to age 20. While it remains unclear how GATA2 mutations lead to immunodeficiency and promote the development of malignancy, it is known that GATA2 orchestrates transcriptional regulation; and depletion of GATA2 leads to defects in mitosis and chromosomal instability. Unfortunately, credible animal models of GATA2 Deficiency Syndrome that could enable the development and testing of diagnostics and therapies do not exist. To explain how GATA2 mutations lead to leukemias in children, I have explored its role in aggressive cancers of the uterus (endometrial carcinoma), where I observed it can prevent errors during cell division. By extension, if GATA2 has the same function in bone marrow, it would explain why mutations in GATA2 create genetic errors that lead to childhood leukemias.

To analyze GATA2 Deficiency Syndrome I will generate mouse and human cell lines, and transgenic mouse models in which target GATA2 protein levels can be precisely controlled via the use of an enzyme with a drug-inducible small molecule assisted shutoff tag. In the absence of the drug the tag undergoes enzymatic self-cleavage and degradation leaving the untagged protein intact; with drug addition, self-cleavage is inhibited, and the protein target is rapidly degraded. This system will enable dynamic control of GATA2 levels in order to assess the effect on chromosomal instability before cells stop growing and die. If I succeed in understanding how GATA2 mutations lead to leukemia, clinicians will be better positioned for early identification of children whose bone marrow may appear normal when in fact it harbors genetic evidence of GATA2 Deficiency Syndrome; and who could benefit from therapeutic intervention before it develops into acute leukemia.