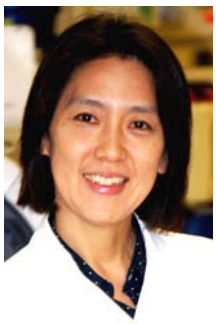
THE HARTWELL FOUNDATION

2011 Individual Biomedical Research Award

Review of Proposed Research

Investigator: **Noriko Satake, MD**
Assistant Professor
Department of Pediatrics

Institution: **University of California, Davis**



Proposal: **Targeted Therapy for Childhood Acute Lymphoblastic Leukemia: Silencing the Mxd3 Gene Using Small Interfering RNA**

Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer in the US. It is a fast-growing cancer of the blood characterized by the overproduction of white blood cells, which the body uses to fight infections. There are two types of ALL called B-cell and T-cell, based on the origin of the leukemia, with B-cell type ALL being the most common. In the US, approximately 2,900 children under age 20 are diagnosed with ALL each year and up to 25% will die or suffer relapse within 5 years. In B-cell type ALL the survival rate is only 30%. Children who survive current treatment protocols for this leukemia, which include 2-3 years of systemic chemotherapy and/or radiation therapy, suffer serious long-term side effects. Because these treatments are non-specific and highly toxic, they inevitably damage healthy cells along with the leukemia cells. Moreover, toxicity is not limited to short-term side effects, as recommended therapy may result in long-term irreversible side effects that decrease the quality of life of the growing children who survive. Unfortunately, there are no therapies that target leukemia cells that do not also harm normal cells. A few promising targeted therapies have been clinically tested in certain leukemias, but no targeted therapies have been developed for B-cell type ALL. To address this unmet need, Noriko has identified a promising new target in the ALL cells: the gene MXD3, which operates as an "on-off switch" for the regulatory (transcription factor) protein called Mxd3. This innovation is based upon her observation that a significantly higher level of MXD3 expression in B-cell type ALL cells occurs compared to normal cells. In preliminary experiments, she has demonstrated that silencing MXD3 in cultured leukemia cells using a gene silencing method called "small interfering RNA" (siRNA) rapidly inhibited the growth of leukemia cells by reducing Mxd3 by turning off the MXD3 gene. This approach is called molecular targeting and is different from conventional chemotherapy drugs, which kill cells in a non-specific manner. Using a human ALL derived mouse model, she now proposes to develop a unique method to deliver MXD3 siRNA specifically to the leukemia cells (but not to normal healthy cells). If she is successful, her narrow target approach could prove transformative by changing pediatric cancer treatment from a generally toxic therapy to one with few if any side effects.