ABSTRACT
Down syndrome (DS) children with leukemia display unique clinical features as well as significant differences in treatment response including toxicity profiles and outcome compared to children without DS. In vitro drug sensitivity assays have demonstrated that blast cells from DS children with acute myeloid leukemia (AML) are more sensitive to cytarabine (ara-C) and daunorubicin compared to blast cells from children without DS. Interestingly, the same patterns of increased chemotherapy sensitivity are not seen in blast cells from DS children with acute lymphoblastic leukemia (ALL) compared to lymphoblasts from non-DS children. The treatment related toxicity observed in DS children with ALL, suggests that the host is a critical factor (e.g. infectious complications secondary to immunesuppression from corticosteroids; methotrexate-induced mucositis due in part to increased intracellular transport of methotrexate into cells via the reduced folate carrier whose gene is localized to chromosome 21). The high event-free survival (EFS) rates of DS AML patients and in particular, patients with megakaryocytic leukemia (AMkL), partially reflects an increased sensitivity to ara-C secondary to increased expression of the chromosome 21-localized gene, cystathionine-β-synthase, and potentially global mechanisms which increase the susceptibility of cells to undergo apoptosis. Somatic mutations of the GATA1 gene in DS AMkL cases, results in altered expression of GATA1 target genes including genes involved in the metabolism of ara-C (e.g. cytidine deaminase). Ongoing correlative biology studies will help to identify methods to balance curative leukemia therapy while minimizing toxicity including reducing the risks of treatment-related deaths in DS children.

EDUCATIONAL OBJECTIVES:
1) To describe the relationship of both chromosome 21-localized genes and somatic GATA1 gene mutations and their role in chemotherapy sensitivity in Down syndrome acute myeloid leukemia cases,
2) To describe the relationship of treatment-related toxicity in Down syndrome children with acute lymphoblastic leukemia in relationship to chromosome 21.

REFERENCES