NIH Challenge Grant Award from the National Heart, Lung, and Blood Institute

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- Project: Identification of Altered Molecular Signature of Down Syndrome Induced Pluripotent Stem Cells
- Start Date: September 30, 2009
- Total Award Amount: $1,012,411

How the results of this project will benefit society:
This research is relevant to multiple human diseases: (1) transient myeloproliferative disease in children with Down syndrome (DS), (2) acute leukemia in children with DS, and (3) multiple non-hematopoietic phenotypes that characterize human DS. For complex genetic diseases, such as Down syndrome, powerful new approaches, including the use of human induced pluripotent stem cells (iPSCs), are absolutely critical to improve our understanding of the molecular basis of the disease and the discovery of novel approaches to alleviate symptoms of this disease.

The problem the project is trying to solve:
Children with DS show a spectrum of clinical abnormalities, including a remarkable incidence of abnormal hematopoietic cell development. As many as 10 percent of newborns with DS show evidence of transient myeloproliferative disorder (TMD), a disease in which megakaryocyte precursor cells proliferate abnormally. Moreover, infants with TMD show a predisposition to leukemia. The natural history of hematologic abnormalities in children with DS suggests that trisomy 21 directly and functionally contributes to aberrant expansion of hematopoietic cells in the fetal liver during gestation. Consistent with this hypothesis, two studies have recently demonstrated that human fetuses with DS show a significant expansion in megakaryocyte erythroid progenitors and in both erythroid and megakaryocytic colony forming units. In order to better define the molecular differences between euploid and trisomy 21 hematopoietic progenitors, we propose to compare gene expression and methylation profiles of induced pluripotent stem cells (iPSCs) generated from individuals with and without DS. In addition, we will compare the hematopoietic differentiation potential of these two groups of iPSCs as another means to study the effect of DS on blood cell development and disease.

How this project will work:
Our specific aims are: (1) To generate and characterize trisomic and euploid iPSCs from individuals with and without Down syndrome, (2) To compare the expression of microRNAs and mRNAs in undifferentiated DS and wild-type iPSCs and hematopoietic progenitors derived from these groups of iPSCs, and (3) To characterize the epigenome of DS versus euploid iPSCs. Our long-term goal is to determine which of the microRNAs, mRNAs or methylation differences we detect in trisomy 21 cells contribute to aberrant hematopoiesis in DS.

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