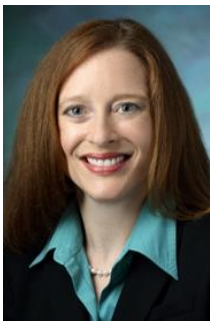
THE HARTWELL FOUNDATION

2016 Individual Biomedical Research Award

Jill A. Fahrner, MD, Ph.D.

Assistant Professor
Department of Pediatrics

Johns Hopkins University



Altering Epigenetics to Treat Growth Abnormalities

Growth and intellectual disability are the most fundamental aspects of child health and both are disrupted in thousands of individually rare, but collectively common genetic conditions. These include inherited disorders of the *epigenetic* machinery related to or arising from non-genetic influences on gene expression induced by alterations in gene function or regulation, unrelated to changes in DNA, RNA or protein sequence. Epigenetic alterations are most commonly caused by external chemical modification (epigenetic marks) to the physical structure of the particular molecule that affects how genes are turned on or off. Epigenetic modifications play a major role in tissue-type and cell-type specific differences in gene expression and cellular processes, with the balance between systems that add and remove marks being important to the genesis of any pathology. It is thought most epigenetic marks that occur in sperm and egg cells get erased when the two combine to form a fertilized egg. Two to five million U.S. children are estimated to have epigenetic growth abnormalities; and up to 1.5 million have intellectual limitations covering a range of everyday social and practical skills, often contributing to delayed development of motor skills. Unfortunately, few clinical interventions exist for short stature and even fewer exist for overgrowth; moreover, the interventions are unpredictable and often associated with morbidity. Intervention for children with developmental delays and intellectual disabilities is limited to special education and remains inadequate. To address the unmet need for intervention strategies for epigenetic disorders Jill hypothesizes that it should be possible to treat such syndromes by regulating the opposing process of writing or erasing epigenetic marks, rather than by trying to cure the defect itself. She will seek to neutralize a single H3K27me3 epigenetic mark in two different mouse models that will normalize growth by restoring precise expression of genes in cell type-specific programs under transcriptional control: *Kabuki Syndrome 2*, which exhibits growth retardation; and *Weaver Syndrome*, which exhibits overgrowth. Remarkably, both syndromes result from errors related to the same epigenetic mark responsible for turning off genes. Specifically, Kabuki syndrome 2 is a deficiency of an eraser of the H3K27me3 mark, which leads to an excess of the mark and a lower expression of implicated genes. By contrast, Weaver syndrome is a deficiency of the writer of the H3K27me3 mark, which leads to lack of the mark and elevated expression of the implicated genes. If Jill is successful, proper gene expression will be restored with normalization of growth, providing a novel treatment for those affected children that will inform the translation of novel drug therapies. Because the H3K27me3 mark also plays an important role in the fundamental processes of growth and neurologic development, manipulating it therapeutically may be strategically useful in a broader range of other congenital conditions, as well.