Histone deacetylase inhibition recovers neurological dysfunction in a mouse model of Kabuki syndrome

Awardee: Hans Tomas Bjornsson
Award: Early Independence Award
Awardee Institution: Johns Hopkins University
Co-authors: Joel S. Benjamin, Li Zhang, Jacqueline Weissman, Elizabeth E. Gerber, Yi-Chun Chen, Rebecca Vaurio, Michelle C. Potter, Kasper D. Hansen, Harry C. Dietz
Co-authors institutions: Johns Hopkins University School of Medicine, Kennedy Krieger Institute, Bloomberg School of Public Health, Howard Hughes Medical Institute.

There are currently few forms of intellectual disability known to be treatable in postnatal life. Kabuki syndrome (KS) is a rare genetic disorder that presents with mild to moderate intellectual disability, as well as some unique physical abnormalities, and is known to be caused by mutations in either of two genes, *KMT2D* or *KDM6A*. KMT2D is a histone-modifying enzyme that adds the open chromatin mark H3K4me3, and KDM6A is a histone demethylase which removes the closed chromatin mark H3K27me3. Given the complementary functions of these two genes, we hypothesized that some of the pathogenesis of KS may relate to an ongoing imbalance between open and closed chromatin of a subset of disease relevant target genes. If this notion is true, any ongoing deficiency may be affected by promoting open chromatin states through HDAC inhibition even in post-natal life. To this end, we have characterized a novel mouse model of KS that has a heterozygous loss of function mutation in *Kmt2d,* which leads to a global deficiency of H3K4me3 as seen by ChIP-seq. Characterization of this model has revealed behavior deficits indicative of hippocampal memory dysfunction in the Morris water maze ($P < 0.005$) and novel object recognition test ($P < 0.05$), as well as both decreased H3K4me3 ($P < 0.05$) and neurogenesis ($P < 0.001$), as measured by number of doublecortin positive cells in the dentate gyrus granule cell layer (GCL), a critical area of adult neurogenesis. After treatment with the HDAC inhibitor AR-42, both the neurogenesis ($P < 0.05$) and H3K4me3 ($P < 0.001$) deficits of the GCL were significantly reversed in the *Kmt2d* mutant mice, as well as the overall global H3K4me3 deficiency. Additionally, the treatment significantly increased the performance of the mutant mice ($P < 0.05$), and normalized their performance in platform crossings during the probe trial of the Morris water maze when compared to wild-type littermates. This work suggests the GCL may be a potentially relevant cell population for some aspects of the intellectual disability seen in KS and perhaps other causes of intellectual disability. Furthermore, manipulating epigenetic marks appears to be a potential therapeutic avenue for KS and related Mendelian disorders of the epigenetic machinery.