

Histone deacetylase inhibitors reverse gene silencing in Friedreich's ataxia.

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Expansion of GAA x TTC triplets within an intron in FXN (the gene encoding frataxin) leads to transcription silencing, forming the molecular basis for the neurodegenerative disease Friedreich's ataxia. Gene silencing at expanded FXN alleles is accompanied by hypoacetylation of histones H3 and H4 and trimethylation of histone H3 at Lys9, observations that are consistent with a heterochromatin-mediated repression mechanism. We describe the synthesis and characterization of a class of histone deacetylase (HDAC) inhibitors that reverse FXN silencing in primary lymphocytes from individuals with Friedreich's ataxia. We show that these molecules directly affect the histones associated with FXN, increasing acetylation at particular lysine residues on histones H3 and H4 (H3K14, H4K5 and H4K12). This class of HDAC inhibitors may yield therapeutics for Friedreich's ataxia.

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Breaking the silence in Friedreich's ataxia.

Richard Festenstein

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NINDS Friedreich's Ataxia Information Page

http://www.ninds.nih.gov/disorders/friedreichs_ataxia/friedreichs_ataxia.htm

About Friedreich's Ataxia Research Alliance (FARA)

FARA is a national, public, non-profit, tax-exempt organization dedicated to the pursuit of scientific research leading to treatments and a cure for Friedreich's ataxia. FARA's mission is to slow, stop, and reverse the damage caused by this disorder. For more information, go to www.curefa.org