

An HDAC inhibitor ameliorates HD pathology in the R6/2 mice

A new HDAC inhibitor developed by Scripps Research Institute and licensed by Repligen Corporation has been found to ameliorate HD pathology in a mouse model of Huntington's Disease. Normal gene transcription was partially restored and the animals improved in movement and brain volume as compared to untreated HD mice.

Transcriptional dysregulation has been shown to be a major pathology in Huntington's Disease. The huntingtin's protein is usually found in the cytoplasm, making only brief visits to the nucleus of the cell in response to stress. The HD version of the protein with its expanded polyglutamine region begins to pile up in the nucleus of the cell where it interferes with the transcription of other genes. A large number of genes whose proteins are needed for the cell to do its work are down-regulated and a smaller number of genes that are not needed are up-regulated.

One approach to address this problem has been to look for histone deacetylase (HDAC) inhibitors that might partially correct the problem. During the process of gene expression, DNA winds around proteins called histones. Enzymes called histone acetylases facilitate transcription by making histones less compact while histone deacetylases inhibit transcription by making histones more compact.

Existing HDAC inhibitors have been tested in the mice. The results suggested that HDAC inhibition might be an effective therapeutic approach, but none of the drugs were as promising for the research pipeline as researchers would like given concerns about side effects and level of effectiveness.

The HDAC inhibitor developed at Scripps (HDACi 4b) has very positive results in the R6/2 mice. Body weight and movement was improved compared to untreated mice, brain atrophy was reduced, and gene expression was at least partially restored in 90 percent of the genes affected by transcription dysregulation. Interestingly, some genes were upregulated but others were down-regulated, notably genes associated with cell death and the immune response.

These results are very encouraging for the HD community. They represent an improvement over previous studies with other HDAC inhibitors and they were obtained even though HDACi 4b was administered after the animals were already symptomatic. In addition, the drug has minimal toxicity.

"The benefit seen was surprising, and immensely exciting, because it suggests this compound could form the basis of a truly relevant therapeutic treatment for Huntington's disease," says the study's lead author, Elizabeth A. Thomas, Ph.D., assistant professor in the Scripps Research Department of Molecular Biology.



"The marked reduction in symptoms achieved in the Huntington's disease model without overt toxicity defines a second disease target for our HDAC inhibitor program," stated Walter C. Herlihy, President and Chief Executive Officer of Repligen Corporation. "We plan to continue to evaluate the utility of our novel HDAC inhibitors as a potential treatment for both Friedreich's ataxia and Huntington's disease."

Reference:

Elizabeth A. Thomas, Giovanni Coppola, Paula A. Desplats, Bin Tang, Elisabetta Soragni, Ryan Burnett, Fuying Gao, Kelsey M. Fitzgerald, Jenna F. Borok, David Herman, Daniel H. Geschwind, and Joel M. Gottesfeld. **"The HDAC inhibitor 4b ameliorates the disease phenotype and transcriptional abnormalities in Huntington's disease transgenic mice."** PNAS e-published September 30, 2008.

Rene Tombley. **"Team Reverses Huntington's Disease Symptoms in Mice."** News & Views: Online Weekly of the Scripps Institute Vol 8. Issue 27, September 22, 2008.

Press Release from Repligen, **"Repligen Announces Publication of Positive Results with Proprietary HDAC Inhibitor in Huntington's Disease Model Study Published in the *Proceedings of the National Academy of Sciences*."** September 16, 2008.

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