## Reduced Creatine Kinase

*Dr. Ferrante*

Robert Ferrante, *Coalition for the Cure* member Steven Hersch, and colleagues have identified a potential biomarker for Huntington's Disease progression that can be measured in blood samples. An isoenzyme of creatine kinase, CK-BB, was shown to be reduced in the blood and brains of two mouse models over time. What is exciting is that CK-BB was also found to be reduced in the blood of pre-manifest gene carriers, and reduced even more in symptomatic patients.

Creatine kinase is an enzyme that plays a crucial role in the production and maintenance of energy in cells. When the cell needs energy, creatine kinase causes the transfer of a high-energy phosphoryl group from phosphocreatine to adenosine diphosphate (ADT) to form adenosine triphostphate (ATP) which is the source of energy for cell metabolism. Creatine kinase maintains levels of ATP even when energy is consumed by the various functions of the cell. It has long been thought that there is a problem with energy production in HD and ATP levels are known to be very low in the brains of HD mice. Creatine kinase is critically important for cells to maintain energy homeostasis and deficiencies of creatine kinase are harmful.

There are three creatine kinase isoenzymes and the one which is specific to the neurons which degenerate in HD is CK-BB. Mice which have been engineered to lack the gene which produces CK-BB develop similar symptoms to those who have been engineered to develop HD. These include reduced body weight, brain atrophy and impaired spatial learning.

The researchers studied CK-BB in blood and brain samples from the R6/2 mice and the 140 CAG knock in mice. Human blood samples were obtained from the REVEAL-HD project and included premanifest gene carriers, HD patients, and spouses who served as controls. Postmortem HD brain tissue which had been donated for research was also examined.

They found that CK-BB was progressively reduced over time in the blood and the brains of both mouse models. CK-BB was reduced in the brains of premanifest gene carriers and further reduced in those who were symptomatic. CK-BB was also significantly reduced in the caudate nucleus of HD brains, with the amount of loss correlated with the stage of the disease.

If further research validates CK-BB as a biomarker throughout disease progression, it would be a valuable indicator of when future treatments should start. It could also enable clinical trials of potential new treatments in premanifest gene carriers and serve to shorten clinical trials for HD patients by providing an objective and sensitive endpoint.

In addition, this work provides additional support for the hypothesis that energy metabolism is impaired in Huntington's Disease and for the rationale behind the current Phase III clinical trial of creatine.

Dr. Steven Hersch, director of the Phase III creatine trial, is encouraged by the results. "This discovery of a progressive deficiency of creatine kinase in blood and brain is very exciting because we urgently need biomarkers to help make clinical trials more efficient, because it helps explain why creatine has been so effective in HD mice, and because it makes the case for testing creatine in HD patients all the more compelling."

*Dr. Hersch*

**Reference:**

Jimho Kim, Dnaiel J. Amante, Jennifer P. Moody, Christina K. Edgerly, Olivia L. Bordiuk, Karen Smith, Samantha A. Matson, Wayne R. Matson, Clemens R. Scherzer, H. Diana Rosas, Steven M. Hersch, and Robert J. Ferrante. **"Reduced creatine kinase as a central and peripheral biomarker in Huntington's disease."** Biochimica et biophysica acta. July-August 2010, Pages 673-681.

- *Marsha L. Miller, Ph.D., July 20, 2010*