

## **Inhibitors of Cytochrome c release have therapeutic potential**

Coalition for the Cure senior researcher Dr. Robert M. Friedlander and colleagues have found that an inhibitor of cytochrome c delays disease onset and significantly prolongs survival in the R6/2 mouse model of HD.



When the mitochondria, the energy factories of the cell, are damaged in neurodegenerative disease, they release cytochrome c into the cytoplasm of the cell. Cytochrome c is a small protein associated with the membrane of the mitochondria. Its release activates caspases. The word caspase comes from cysteine-aspartic-acid-proteases. These enzymes play a role in apoptosis, programmed cell death. Specifically, cytochrome c release activates caspase 9 which in turn activates caspase 3 which brings about the death of the cell.

While it seems reasonable that inhibiting cytochrome c release might therefore inhibit cell death and thus be a valid therapeutic target in Huntington's Disease, this had not been demonstrated before this study. The researchers first developed a mitochondrial assay to screen potential inhibitors. Purified mitochondria were challenged with calcium to cause cytochrome release and various compounds were screened to see if they would act as inhibitors,

The drugs screened came from the National Institute of Neurological Disorders and Stroke. Their Neurodegeneration Drug Consortium maintains a library of 1040 compounds, most of which are FDA approved for other purposes and many of which cross the blood brain barrier.

The twenty-one drugs that inhibited cytochrome c release, crossed the blood brain barrier and did not cause major side effects were then screened in a striatal cell model where the cells were challenged with temperature increases. Five of these drugs were found to be ineffective in the cell model.

The researchers selected methazolamide, a drug which crosses the blood brain barrier and is approved to treat glaucoma, to test in the R6/2 mice. Disease onset was delayed and survival time prolonged. In addition, neurodegeneration was reduced. The researchers express their hope that further testing will show that this drug to be helpful in treating neurodegenerative disorders.

### **Reference**

Zin Wang, Shan Zhu, Zhijuan Pei, Martin Drozda, Irina Stavrovskaya, Steven DelSignore, Kerry Cormier, Ethan Shimony, Hongyan Wang, Robert Ferrante, Bruce Kristal, and Robert M. Friedlander. **"Inhibitors of cytochrome c release with**

**therapeutic potential for Huntington's disease.**“ The Journal of Neuroscience 2008  
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- *Marsha L. Miller, September 20, 2008*