



# CHDD Outlook 2011 Issue #3

News from the Center on Human Development and Disability at the University of Washington  
 Health Sciences Center

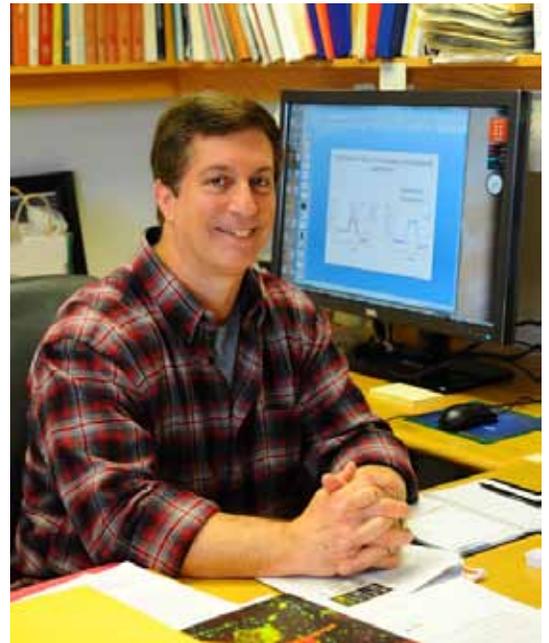
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## Enzyme Inhibitors May Block Injury from Stroke, Promote Recovery

by Joel Schwarz

It's not going to happen tomorrow, but some day patients who experience a stroke could recover more rapidly and suffer fewer lasting effects because of new University of Washington research. This work currently is exploring the potential of enzyme inhibitors called Histone deacetylase (HDAC) inhibitors which also have attracted the interest of other investigators seeking treatment for various types of cancers. While HDAC inhibitors have been found to promote the death of tumor cells, UW researchers headed by Richard Morrison, Ph.D., professor of neurological surgery, have discovered that the HDAC inhibitors also effectively block injury in the nervous system and promote recovery. Not only that, but the inhibitors work if they are given before and after experimental stroke conditions. Stroke is one of the top 10 causes of death for children and the risk of childhood stroke is greatest in the first year of life. The American Heart Association estimates that between 50 and 80 percent of children who survive a stroke will have permanent neurological deficits. The most common disabilities caused by stroke around the time of birth are total or partial paralysis on one side of the body, cognitive and sensory impairments, epilepsy, speech or communications disorders, behavior problems, poor attention, and visual disturbances.

From his work in proteomics, Morrison, who is a research affiliate of the Center on Human Development and Disability (CHDD), thought HDAC inhibitors had promise in blocking cell death in neurons despite their cell death inducing actions in tumor cells. Their initial findings in fact, demonstrated that HDAC inhibitors could prevent cell death induced in cultured neurons by DNA damage and oxidative stress. "Based on these findings we were interested in determining if these inhibitors could also promote functional recovery in neurons," he said. Since Morrison had two UW collaborators working with stroke and white matter injury, the newest research focused on white matter cells something that most previous stroke research didn't look at because these cells only make up 10 to 14 percent of the rodent brain on which most stroke experiments are conducted. The human brain, however, contains about 50 percent white matter. Because of this and other anatomical differences between the rodent and human brain, most experimental stroke research showed extensive gray matter cell death in the rodent brain while sparing white matter. As a consequence, drugs that proved useful in rodent models failed in clinical trials.



Devon Bacon

Richard Morrison is investigating the potential of Histone deacetylase inhibitors to block cell death in the nervous system caused by stroke as well as assisting white matter cells to recover.

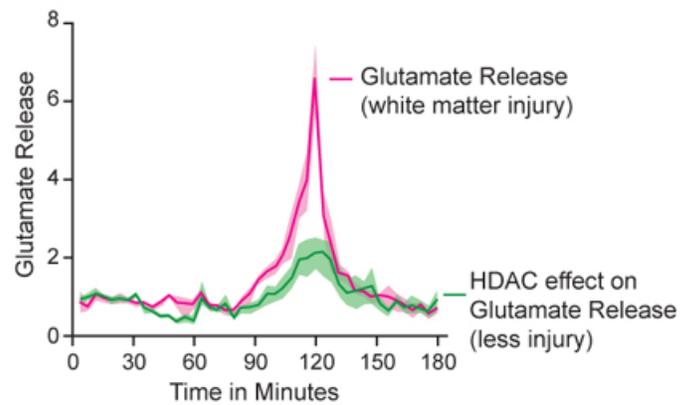
White matter consists of bundles of nerve processes (axons) that connect and transmit impulses between neurons in the brain's gray matter and supporting cells called glia. Axons can be likened to the telephone land-line wires that connect one phone to other telephones. Glial cells provide and enable axons to transmit signals with high fidelity. Previous research previously did not focus on injury to the axons or to the supporting cells, although it is now shown that white is injured in most strokes and contributes to clinical deficits following strokes. The new research did, using white matter from the optic nerves of two different strains of mice, and mimicked stroke by depriving those cells of oxygen and glucose. When this happened cells lost their functionality.

The researchers found the administration of HDAC inhibitors before or after oxygen and glucose deprivation reduced the amount of white matter cell death and preserved the electrical functionality of the axons. "One of the things that happens after a stroke is the level of glutamate (a neurotransmitter) rises and this causes a massive amount of cell death. It overwhelms cells and they swell and pop. The HDAC inhibitors reduced and delayed the accumulation of glutamate," said Morrison. The HDAC inhibitors also appeared to be working on other areas including mitochondria, the so-called power plants that generate most of Adenosine triphosphate that power cells. Mitochondrial functionality was well preserved after the induced stroke when given one of the inhibitors. In addition, the HDAC inhibitors also appeared to help prevent glial cell death to restore optimal axon function. It also appears that HDAC inhibitors not only are protective against DNA and ischemic damage, but they also promote development of neural progenitor cells into neurons. Morrison thinks there is a possibility that these progenitor cells can be developed into neurons to replace other neurons killed in a stroke.

"There is a lot of work to be done before we can make a neuroprotective cocktail," he said. "HDAC inhibitors may have multiple effects on different cell types and we have to know which specific HDAC enzymes (there are more than dozen) are expressed in the different cell populations in the brain and which ones are activated by damage. And there is a chance we can promote recovery with it." While the drugs have U.S. Food and Drug Administration approval in treating cancer, Morrison noted that the dosages may be different when used as a therapy in dealing with stroke and other brain injuries.

The research is important because medicine has few therapies to prevent or treat stroke. "We don't have a lot of drugs that will effectively block injury in the nervous system or promote recovery. The HDAC inhibitors seem to do both and achieve it before and after injury. Because they also restored functional properties in two different strains of mice, it showed that it is not just a unique response by one strain. It was a general response to the HDAC inhibitors because the two strains were genetically and biologically different," Morrison said.

Other members of the research team investigating the potential of HDAC inhibitors as neurorestoratives include Sean Murphy, Ph.D., a UW professor of neurological surgery and a CHDD research affiliate; Selva Baltan, M.D., Ph.D., associate professor of neurology; Camelia Danilov, Ph.D. and a senior fellow in the department of neurological surgery; and Amelia Bachleda, B.S., in the department of neurology. The next step for the UW researchers is to test the efficacy of the enzymes in a live mouse model.



HDAC inhibitor reduces glutamate release following a stroke. In the graph, the red line indicates the amount of glutamate released after a stroke was induced while the green line shows a significantly lower level of glutamate when an HDAC inhibitor was introduced before a stroke.

CHDD is an interdisciplinary center dedicated to the prevention and amelioration of developmental disabilities through research, training, clinical service, and community outreach. CHDD includes the University Center of Excellence in Developmental Disabilities and the Eunice Kennedy Shriver Intellectual and Developmental Disabilities Research Center.

#### CHDD Outlook

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