Researchers Race to Design the First Treatments Specifically for NeuroAIDS

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Experimental drugs are showing promise against neuroAIDS, the nerve damage caused by HIV infection that lessens many patients' ability to think and move. As evidence of the progress, researchers at the University of Rochester Medical Center today received a $7 million grant to confirm that two new drug classes can protect the brain from HIV-related nerve damage. Driving their approach is the realization that antiviral drugs that work against AIDS do not cure neuroAIDS.

As many as 900,000 Americans are infected with the human immunodeficiency virus (HIV), which attacks immune cells and leaves patients vulnerable to infection. Before the arrival of modern antiviral therapies in 1996, HIV also had a devastating effect on the brain known as HIV-associated dementia (HAD) or neuroAIDs. The current, standard combination of treatments has extended the lives of most U.S. AIDS patients, but has not cured neuroAIDS, despite early reports to the contrary. Antiviral combinations only slow the onset of HIV-related nerve damage that is becoming more common the longer HIV patients live.

Where patients suffered rapid, severe neurological damage before combination therapy, they now gradually lose attention span, memory, speaking ability and decision-making skills despite the best available treatment. The realization that anti-viral drugs do not cure HAD led researchers to ask whether there is something else about HIV besides its attack on immune cells that causes disease in the brain. The emerging answer is that the indirect effects of infection, like proteins released by

the virus and chemicals released by human cells reacting to them, are toxic in themselves.

As a result, labs nationwide are urgently searching for compounds that counter such toxins, with several now in human trials. These include antioxidant medications, calcium channel antagonists, NMDA antagonists like the Alzheimer's drug Memantine, platelet activating factor (PAF) inhibitors, and in the case of the new grant, drugs that inhibit glycogen synthase kinase 3 beta (GSK-3b) and mixed lineage kinase (MLK).

"The number of HIV patients that suffer brain damage is usually estimated at one in five, but I believe that nearly all of them, if they live long enough, will be affected," said Harris A. Gelbard, M.D., Ph.D. professor in the Department of Neurology at the Medical Center, and principal investigator on the new grant. "As the sensitivity of our measurements improves, so does number of people known to have more subtle cases of HAD. With HIV patients living long enough to re-engage in life and return to work, a condition that often reduces mental function by about 25 percent, and for which there is no approved treatment, deserves attention."

A Better Understanding

Researchers believe that the virus itself secretes toxins that signal too many human nerve cells to begin programmed cell death (apoptosis), a normally healthy process where old or damaged cells chose to die and be recycled. Furthermore, nerve cells exposed to HIV may lose their ability to pass on nerve signals long before the virus causes them to self-destruct. To protect themselves from infection, exposed nerve cells pull in their branches (dendrites), which would normally connect them to other nerve cells. Such disconnected nerve cells, if protected by the right drug, have the potential to be "reconnected," researchers said.

HIV also “activates” immune cells that reside in the brain. In response, those cells set off chain reactions that bring other immune cells rushing into the brain to fight infection. The same reactions cause inflammation (swelling) that presses on brain tissue, reducing function. Thus, researchers believe a successful therapy for neuroAIDS will need to combine standard antiviral combination therapy with new drugs that both protect nerve cells from toxins and reduce inflammation.

The new grant, from the National Institute of Mental Health, is a competitive renewal of a previous grant, but with a shift in focus. In the original grant cycle, Gelbard and Sanjay Maggirwar, Ph.D., assistant professor in the Department of Microbiology and Immunology at the Medical Center, identified an enzyme, GSK-3b, that when over-activated by HIV signals for nerve cell suicide. Maggirwar was the first to theorize that interfering with this pathway could protect against neuroAIDS, and to prove his theory using sodium valproate and lithium, existing epilepsy drugs that turned out to be GSK-3b inhibitors. Gelbard and Maggirwar; along with received in 1999 one of the first grants from the National Institutes of Mental Health designed to convert basic neuroscience into new neuroAIDS drugs.

Based on their work, Stephen Dewhurst, Ph.D., dean’s professor of Microbiology and Immunology at the Medical Center, recognized that a second molecular target, an enzyme called mixed lineage kinase 3 (MLK3) may be “of equal or greater importance” than GSK-3b. HIV exposure throws off the ability of MLK3 to regulate enzymes that maintain the balance between cell survival and cell death, shifting it toward death. MLK also regulates p38, an enzyme that encourages inflammation. Thus, MLK inhibitors could conceivably shut down affected immune cells before they trigger inflammation and prevent cell suicide.

The new grant is a partnership between the University of Rochester

Medical Center and the Center for Neurovirology and Neurodegenerative Disorders (CNND) at the University of Nebraska Medical Center. Researchers in Rochester will confirm that MLK and GSK-3b inhibitors are can indeed reverse nerve damage in cell cultures. CNND researchers will test the compounds in mice with HAD to determine that they work in a living system genetically similar to humans. If these tests are successful, human studies will proceed with an existing MLK3 inhibitor, CEP-1347, developed by Pennsylvania-based biotech Cephalon.

Ira Shoulson, M.D., professor of Neurology at the University of Rochester Medical Center, had served as an auditor of Cephalon's PRECEPT trial, where CEP-1347 was tested as a treatment for Parkinson's disease. He proposed that Cephalon make the drug available for the study of the drug's effect on neuroAIDs. CEP-1347 has already proven capable of reversing the neurotoxic effects of HIV proteins in living cells, according to research published in the July 1, 2006, edition of the Journal of Immunology.

"We really don't know yet whether MLK or GSK-3b inhibitors will be superior to other treatment approaches," Dewhurst said. "We do know that new directions are needed because, despite ten years of trying, no research effort has yielded an approved HAD drug."

Source: University of Rochester Medical Center