Researchers target HIV-related brain difficulties

October 7 2010

(PhysOrg.com) -- During the last two decades, scientists and doctors have developed a potent mix of medications that nearly stops HIV in its tracks for most patients. This combination antiretroviral therapy, or cART, can knock down levels of the virus in the body to a thousandth or less of what it would otherwise be. That means more years of a healthy life for many HIV patients.

But that success does not extend fully to the brain, where an assault triggered by the virus continues despite treatment. About half of patients infected by HIV experience symptoms, such as difficulty thinking or concentrating, as a result of the effects of the virus on the brain. So far, nearly a dozen studies in people have failed to identify a drug useful for treating the condition, which is known as HIV-associated neurocognitive disorder.

At the University of Rochester Medical Center, neurologist Harris A. “Handy” Gelbard, M.D., Ph.D., leads a team of scientists intent on developing the world’s first treatment designed specifically to prevent or ease the neurological effects of HIV. This week, Gelbard – whose team has spent a decade exploring novel ways to treat the condition – received word that the project would continue for another five years, thanks to $6.7 million in new funding from the National Institute of Mental Health.

The commitment comes at a crucial juncture. The team, which includes the Rochester group as well as scientists from the University of

Nebraska and the biotech company Califia Bio Inc. has already created a compound that shows great promise in the laboratory. Scientists hope to begin a clinical trial in people within five years – a crucial step for a condition that currently has no approved treatment.

“Most patients are able to cope with the cognitive effects of HIV, but oftentimes their cognitive abilities are diminished. Their ability to take on new tasks, to really concentrate, or to juggle several tasks at once, may be reduced,” said Gelbard, who is director of the Center for Neural Development and Disease.

“HIV infects the brain early on and goes on to wreak havoc there despite our best treatments. It’s a serious problem for the more than 30 million people worldwide infected with HIV,” he added.

Just this week in a paper published online in the journal Neurotherapeutics, the team reviews its findings to date and lays out new strategies to treat the condition.

The problem for patients lies in the way the brain reacts to HIV. When the brain detects the virus, the body sends immune cells flooding in to fix the problem and eliminate the threat. But the response itself quickly becomes the problem, with immune cells attacking healthy brain cells. Sophisticated structures called synapses, which are central to the ability of brain cells to communicate with each other, are especially vulnerable.

“Synapses are the currency of neurologic function,” said Gelbard, who is professor of Neurology, Pediatrics, and Microbiology and Immunology. “The more damage to the synapses, the more symptoms patients will notice.”

While HIV’s effects on the brain are rapid, brain cells don’t outright die. Instead, brain cells called neurons sicken – they lose crucial structures

called dendrites, and they lose the ability to communicate with each other. The gradual process offers some hope for researchers, who have shown that such “sick” cells can be rescued and returned to health if the inflammatory assault is stopped.

The test compound is designed to slow or eliminate inflammation by knocking out an enzyme known as MLK3, which plays a key role in the inflammatory process. Scientists believe that when MLK3 is abnormally active, it becomes a crucial switch, turning cells that normally nourish the brain’s neurons and prompting those cells to instead attack the neurons and synapses.

In its hunt for a compound to stop MLK3, the team took advantage of other researchers’ work with an experimental drug that was designed to stop the enzyme in patients with Parkinson’s disease. The compound didn’t end up helping patients, and the study was halted. But the compound – and its futility to treat Parkinson’s – provided the team with crucial clues about how to better target MLK3.

The team took advantage of those clues and screened thousands of compounds, using the findings to build a better compound to stop MLK3. The team has shown that its lead compound is successful getting into the brain and staying there at levels necessary to knock out MLK3. In tests the compound has reduced inflammation dramatically and has preserved the structure of synapses.

Gelbard’s team plans to apply to the National Institutes of Health for funding to fast-track the development of the compound into a drug that can be tested in patients.

Gelbard is quick to point out that progress against HIV-related dementia is likely to pay off for other conditions as well. He notes that inflammation and MLK3 both play a large role in Alzheimer’s and

Parkinson's diseases. And he notes that the compound under development shows very early promise for treating heart failure.

Provided by University of Rochester Medical Center