

ISRIB Reverses Age-Related Mental Decline in Mouse Model

Inhibition of the integrated stress response by ISRIB restores neuronal and immune dysfunction and alleviates memory deficits in aged mice.
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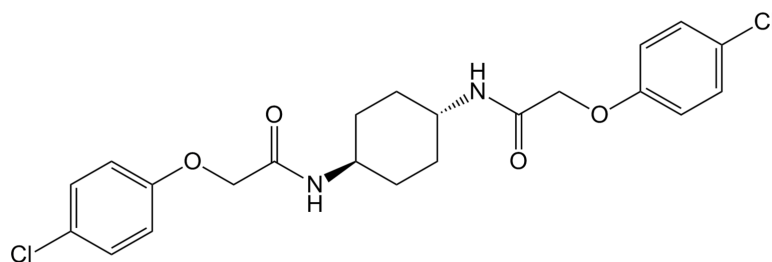
PASADENA, CALIFORNIA, UNITED STATES, December 10, 2020 /EINPresswire.com/ -- In the [new study](#), published December 1, 2020, in the open-access journal eLife, researchers from UC San Francisco showed rapid restoration of youthful cognitive abilities in aged mice after a small, daily dose of an experimental drug, accompanied by a rejuvenation of brain and immune cells that could help explain improvements in brain function.

The drug, called [ISRIB](#) (integrated stress response [inhibitor](#)) was discovered by the Walter lab at UCSF through a semi-automated screening of a large library of small molecules. It has already been shown in laboratory studies to restore memory function months after traumatic brain injury (TBI), reverse cognitive impairments in Down Syndrome, prevent noise-related hearing loss, fight certain types of prostate cancer, and even enhance cognition in healthy animals.

The research team at UC San Francisco have spent years investigating the effects of what's known as integrated stress response, or ISR. Generally speaking, this is a healthy function of the human body that identifies signs of infection or cellular mutation and shuts down the protein production machinery in the cells to clear away any that might cause trouble. It was its connection to traumatic brain injury that inspired the team's latest line of research, with earlier studies finding that cognitive decline brought on by these injuries has similarities to premature aging. Given that ISRIB had previously been shown to reboot protein production and bring improvements to memory function following traumatic brain injury. Given the parallels, the team



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ISRIB

set out to explore its effects on aging.

They demonstrate that treatment with the drug-like small molecule ISR inhibitor ISRIB reverses ISR activation in the brain, as indicated by decreased activating transcription factor 4 (ATF4) protein levels. ISRIB treatment also reverses spatial memory deficits and ameliorates working memory in old mice. Observations of brain cells in the mice's hippocampus after the first dose of ISRIB was delivered revealed that typical signatures of aging disappeared virtually overnight. Electrical activity in the neurons became lively and responsive to stimulation, while connectivity between the cells become more robust, reminiscent of that seen in younger mice.

"We've seen how ISRIB restores cognition in animals with traumatic brain injury, which in many ways is like a sped-up version of age-related cognitive decline," said Rosi, who is director of neurocognitive research in the UCSF Brain and Spinal Injury Center and a member of the UCSF Weill Institute for Neurosciences. "It may seem like a crazy idea but asking whether the drug could reverse symptoms of aging itself was just a logical next step."

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