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Novel compound has promise for treatment of Huntington's disease

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A major, multi-institutional study based at Massachusetts General Hospital (MGH) has identified a promising treatment strategy for Huntington's disease (HD). In their report receiving online publication in *Cell Chemical Biology*, the team describes finding that their novel compound appears to protect against neurodegeneration in cellular and animal models of HD by means of two separate mechanisms - inhibiting the regulatory enzyme SIRT2 and activating the antioxidant pathway controlled by the NRF2 transcription factor.

"Based on numerous studies, it has become evident that the pathologies of neurodegenerative diseases, including Huntington's disease, are very complex, so targeting multiple pathways may help us achieve maximum therapeutic benefit," says Aleksey Kazantsev, PhD, who led the study as an investigator at the MassGeneral Institute for Neurodegenerative Disorders (MIND). "The lead compound identified in the current study has two distinct mechanisms, both of which are shown to be potentially neuroprotective and which we expect will have synergistic benefits."

Previous work from Kazantsev's MIND team identified SIRT2, which regulates many important cellular functions, as a promising treatment target for HD as well as for Parkinson's disease. Building on those findings, he and his collaborators from 12 research institutions in 5 countries began searching for a scaffold - a group of molecules with similar chemical structures - that could be the basis of more potent and selective SIRT2 inhibitors. Starting with the most powerful SIRT2-inhibiting compound they identified, which they called MIND4,

they assembled a group of structurally similar compounds with varying levels of SIRT2 inhibition.

To investigate how MIND4 acted to inhibit SIRT2, the researchers investigated its effects on gene expression in cellular models of HD and in unaltered neurons. They were surprised to find that the top seven pathways activated by treatment with MIND4 were related to the oxidative stress response mediated by NRF2, which regulates the expression of protective, antioxidant proteins. Additional experiments indicated that cellular responses to MIND4 were indicative of SIRT2 inhibition, that it protected against HD-related neurodegeneration in rat brain tissue and in a Drosophia model of the disease, and that its activation of NRF2-mediated pathways did not depend on SIRT2 inhibition. In fact, one of the related compounds they investigated, called MIND4-17, stimulate NRF2 activity even though it did not inhibit SIRT2.

"Finding that MIND4's SIRT2 and NRF2 activities are independent of each other is a critical step for further drug development, which indicates that work to improve the potency of each activity should proceed separately," says Kazantsev. "We still don't know whether the neuroprotective results we observed in this study depend more on one activity or the other, but since MIND4, which produces both activities, was a better protectant than MIND4-17, which only activates NRF2, I speculate that both activities will be necessary."

He adds, "MIND4 is a great starting template for drug development, and we have promising preliminary results in two mouse models. We also need to optimize the pharmacology to meet FDA requirement for a version we can test in human patients. Right now, we expect to have results regarding the mechanism behind NRF2 activation ready for submission soon." Kazantsev recently joined the Cambridge, Mass.-based startup company Effective Therapeutics, LLC, but continues to

collaborate with his colleagues at MGH and other institutions.

Anne B. Young MD, PhD, former MGH chief of Neurology, founder of MIND and also of Effective Therapeutics, says, "These multidisciplinary studies highlight new pathways that can be targeted for HD therapy but also very likely for other neurodegenerative diseases too."

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