MedicalXpress

Study identifies potential drug for treatment of debilitating inherited neurological disease

March 15 2018

St. Jude Children's Research Hospital scientists have demonstrated in mouse studies that the neurological disease spinal bulbar muscular atrophy (SBMA) can be successfully treated with drugs. The finding paves the way for clinical trials for treating the disease and even preventing its progression in individuals who have inherited the disease mutation.

The researchers, led by J. Paul Taylor, M.D., Ph.D., a Howard Hughes Medical Institute (HHMI) investigator and chair of the St. Jude Department of Cell and Molecular Biology, published their findings March 5 in the journal *Nature Medicine*.

SBMA, or Kennedy's disease, affects only men, causing loss of muscle-controlling motor neurons, leading to muscle wasting and impaired ability to talk and swallow. As the disorder progresses, men with the disorder often become wheelchair bound and require help with such tasks as eating.

The disease is caused by a mutation in the androgen receptor, which is activated by the male hormone testosterone. The mutation causes a malfunction of the receptor that triggers toxicity in motor neurons, killing them. The mutation also causes the receptor to become less sensitive to testosterone, which can lead to feminization, testicular atrophy and infertility. SBMA affects about 1 in every 40,000 men worldwide, a number that is likely underestimated because of its misdiagnosis as another disorder.

Taylor and his colleagues were led to seek drugs to treat SBMA because of findings from a previous study in his laboratory. The study pinpointed a molecular niche in the mutant androgen receptor protein that appeared to be a key to driving SBMA symptoms. However, that niche did not seem to be essential to the normal function of the androgen receptor. The study started with fruit flies genetically engineered to have the human androgen receptor, giving the scientists a living "test tube" to explore the effects of mutating the receptor.

"This identification of a small patch of this protein that appeared to be functionally important for driving the disease, but is not essential for most androgen receptor functions, gave us a potential drug target," Taylor said.

Pharmaceutical companies have been developing drugs to target this small patch, called the "activator function-2" or "AF2" domain. The companies were testing the drugs as possible treatments for prostate cancer, which also involves the androgen receptor. Taylor obtained a collection of the test drugs to evaluate for use with SBMA.

Using the genetically engineered flies, the researchers identified two drugs—whose long chemical names are abbreviated TA and MEPB—that alleviated SBMA symptoms. Then, using mice, the scientists determined that MEPB more effectively reached target tissues in the brain and spinal cord.

For their trials of TA and MEPB as potential SBMA treatments, the researchers developed a new genetically engineered mouse model to more accurately mimic the mutation found in men with SBMA. The transgenic mice showed many of the symptoms of humans with the disease.

Researchers found that MEPB effectively alleviated symptoms of

SBMA in the mice. "Treating the mice with MEPB forestalled muscle atrophy and prevented loss of their motor neurons, with recovery of their testicles to normal size," Taylor said. "The treatment also protected their ability to walk and their muscle strength and endurance."

Taylor said drugs to treat SBMA would be useful in restoring function in adult men with the disease and preventing it in children who inherit the mutation for SBMA.

"At this point, while we do have an accurate genetic test for the disease, we must warn people with a family history that if that test reveals the disease mutation, we do not have a therapy available," he said. "However, if we did have a drug therapy, we could start treating children before puberty, when the disease manifests, so they either don't get the disease, or we can at least dramatically mitigate it."

Taylor is seeking to partner with pharmaceutical companies to further test the drugs as treatments for SBMA. "Our proof-of-concept study demonstrates that this class of compounds can be effective," he said. "And we can offer predictive cell culture and fly models that can quickly identify the most viable candidates for further development and clinical trials."

More information: Nisha M Badders et al. Selective modulation of the androgen receptor AF2 domain rescues degeneration in spinal bulbar muscular atrophy, *Nature Medicine* (2018). DOI: 10.1038/nm.4500

Provided by St. Jude Children's Research Hospital