Selective PDE4D inhibitor shows potential to treat Fragile X autism spectrum disorder

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New preclinical research suggests the potential utility of BPN14770, a selective PDE4D inhibitor currently under development by Tetra Discovery Partners as a prospective treatment for memory and cognitive problems associated with Alzheimer's disease, in the treatment of Fragile X Syndrome (FXS) and possibly other autism spectrum disorders.

Daily treatment of adult male fmr1 C57B16 knockout mice (a standard FXS animal model) for 14 days reduced hyperarousal, and improved social interactions and increased natural behaviors such as nesting and marble burying compared to control FXS mice that received a placebo. At the same time, there was no deleterious effect on behavioral scores in normal wild-type mice treated with BPN14770. The behavioral benefits of BPN14770 in the FXS mice endured for two weeks after drug washout. Microscopic analysis of neurons in the prefrontal cortex from the treated FXS mice showed an improvement in dendritic spine morphology; this finding, combined with the 11 hour half-life of BPN14770 in mice, suggests that the enduring treatment benefits of BPN14770 were not due to slow washout of the drug.

The new research was published online today in *Scientific Reports*, an online, open-access primary research publication from the publishers of *Nature* by Tetra Discovery Partners and the company's research collaborators.

"This preclinical study strongly supports PDE4D as a therapeutic target for the treatment of FXS," said Mark E. Gurney, Ph.D., Chairman and Chief Executive Officer of Tetra Discovery Partners. "We have already demonstrated evidence of human safety and tolerability for BPN14770 in a Phase 1 study in healthy young and elderly volunteers. This research suggests BPN14770 may also have utility in the treatment of FXS, which is associated with a spectrum of neuropsychiatric symptoms, mild to severe cognitive impairment and intellectual disability, and potentially also find use in the treatment of other conditions on the autism spectrum."

"The results from these studies are very promising," commented Michael Tranfaglia, M.D., Medical Director and Chief Scientific Officer of the FRAXA Research Foundation. "Inhibition of PDE4 has been validated as a treatment strategy by many research groups in the Fragile X field. However, the current study demonstrates the enhanced therapeutic potential of PDE4D inhibition with BPN14770, which shows the ability to rescue major Fragile X phenotypes not only in acute dosing, but in chronic dosing as well.

"Furthermore, the significant carryover of BPN14770 effects, even two weeks after treatment suggests this drug candidate has genuine long-term beneficial effects on Fragile X pathology," Dr. Tranfaglia continued. "Additionally, tolerance has been a major problem with other drug classes studied as potential treatments for Fragile X syndrome, such as mGluR5 NAMs and GABA-B agonists, but no tolerance was been seen in studies with BPN14770. The selective nature of this compound, which targets only PDE4D, also greatly improves the tolerability of the drug over past-studied, general PDE4 inhibitors, which should facilitate clinical trials in this difficult-to-treat population."

More information: Mark E. Gurney et al, Multiple Behavior Phenotypes of the Fragile-X Syndrome Mouse Model Respond to Chronic Inhibition of Phosphodiesterase-4D (PDE4D), *Scientific Reports* (2017). DOI: 10.1038/s41598-017-15028-x

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