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KMH-0046, A Novel Nr4a1 Agonist, Increases Expression of Downstream Target Genes Over Multiple Doses and Time in-vivo

Cocaine Use Disorder is a significant public health challenge lacking any FDA approved therapeutics. Few molecular targets have been identified, suggesting the disorder may driven by epigenetic changes. One such driver of epigenetic changes to cocaine associated genes is Nr4a1. Activating Nr4a1 with small molecule agonists has been shown to decrease cocaine conditioned place preference (1). Existing agonists, such as Cytosporone-B (Csn-B) lack target specificity and tend to activate multiple genes in the same family. Following development of the novel Nr4a1 activator we then tested the compound in-vivo. Here we show that KMH-0046, a novel Nr4a1 agonist increases expression of Nr4a1 and increases the downstream target, Cartpt. Furthermore, we demonstrate that KMH-0046 is well tolerated and observed no signs of toxicity, demonstrating its potential as a therapeutic.

1. Carpenter, M.D., Hu, Q., Bond, A.M. et al. Nr4a1 suppresses cocaine-induced behavior via epigenetic regulation of homeostatic target genes. Nat Commun 11, 504 (2020). <https://doi.org/10.1038/s41467-020-14331-y>

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