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### **Chromatin-directed alternative splicing in brain reward regions**

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Regulation of gene expression via stably altered chromatin is a compelling area of study for chronic neuropsychiatric diseases, such as addiction. Furthermore, regulation of alternative splicing is implicated in neurological disease in humans and cocaine exposure in mice. Recently, a small but compelling literature has described chromatin-regulated alternative splicing, suggesting a novel function for drug-induced neuroepigenetic remodeling. Of particular interest are genes that show both cocaine-regulated enrichment of histone H3 lysine 36 methylation (H3K36me3) and alternative exon expression, in light of novel data that H3K36me3 enrichment is linked to alternative exon selection via recruitment of splicing factors. The current proposal aims to test the hypothesis that alternative splicing is functionally coupled to cocaine-induced H3K36me3 enrichment at specific genes. We found that both cocaine self-administration and overexpression of the histone methyltransferase, SET2, regulate H3K36me3 and alternative splicing at a subset of alternatively spliced exons. We have validated these splicing events using quantitative radioactive PCR methods and identified *Bin1* as putatively regulated by this mechanism. We can then apply highly innovative methods of CRISPR-based, locus-specific epigenome editing using dCas9-SET2 targeted to *Bin1* in vivo to elucidate the direct causal relevance of H3K36me3 to skipped exon inclusion in this gene. Broadly, using this approach we will gain insights into a novel role of HPTMs in addiction, which will have widespread applications throughout drug abuse research as well as other fields.