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CRISPR Epigenome Editing for Interrogating the Role of DNA Methylation at the *Fosb* Locus

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There are currently no FDA-approved treatments for stimulant use disorders (SUD), in particular cocaine abuse. Therefore, elucidating and modulating the genetic and epigenetic drivers of cocaine SUD could further enhance the understanding of cocaine SUD and leading novel therapies.

Elevated levels of the transcription factor Δ FosB are a common molecular hallmark induced by drugs of abuse, most prominently in dopamine receptor 1 expressing medium spiny neurons (D1-MSNs) within the nucleus accumbens (NAc). Importantly, changes to Δ Fosb expression levels have been established as one mechanism that contributes to the stability of altered neuronal states and patient symptoms in cocaine SUD and multiple other SUDs.

We hypothesize epigenome editing technologies can be leveraged to functionally interrogate the epigenetic control of *Fosb* isoforms levels (including Δ FosB), as well as uncover new therapeutic opportunities to enable sustained improvement of neuropathology in cocaine SUD. By analyzing publicly available sequencing data sets, we report that repeated cocaine exposure leads to increased levels of DNA methylation at the *Fosb* gene in mice and human post-mortem brains. Therefore, we tested an array of CRISPR/dCas9-based epigenome editors at the *Fosb* promoter in murine primary MSNs from the NAc and observed transcriptional repression of *Fosb* and Δ Fosb transcripts. These results indicate that CRISPR/dCas9-based epigenome editors are an opportune platform for perturbation of a key cocaine SUD gene. Future research will further engineer these platforms for neuron specificity and test their efficacy *in vivo* for both repressing *Fosb* isoforms and reducing cocaine-associated behaviors in mice.