

Name: Julia Winter, Ph.D.

Email: julia.winter@pennmedicine.upenn.edu

Epigenetic editing of Cartpt promotes acquisition and extinction of cocaine memory

Despite the high numbers of cocaine dependent individuals in the US, effective and targeted therapies are missing. In classic disease models, removing a pathological insult restores homeostasis. Yet, addiction persists far beyond the period of active drug use. Cocaine abstinence induces changes in gene expression and neuronal signaling in reward-related brain regions that limit recovery during abstinence. We found that 2 weeks of abstinence increased Cartpt (cocaine- and amphetamineregulated transcript) in the mouse nucleus accumbens and decreased repressive H3K27me3 at the Cartpt locus. While endogenous CART peptide is best described for its anorexigenic function, it is also implicated in human addiction and dopamine homeostasis. To test the causal relevance of Cartpt chromatin remodeling, we used CRISPR-based epigenetic editing tools, dCas9-FOG1 and dCas9-JMJC-ZF, to manipulate H3K27me3 at Cartpt in vivo. Enriching H3K27me3 in D1 neurons repressed Cartpt expression and augmented acquisition and extinction of cocaine preference. These results show that CRISPR epigenetic editing can recapitulate endogenous chromatin states to modulate addiction-related behavior, highlighting broad therapeutic potential of both Cartpt and epigenetic editing.

Authors:

Submitter: Julia Winter, Postdoc, University of Regensburg, Philadelphia