Name: Desmond J. Smith Email: DSmith@mednet.ucla.edu

Cocaine and cannabis: a joint dependence revealed by a longitudinal genetic study in mice

Arshad H. Khan[1,6], Jared R. Bagley[2], Nathan LaPierre[3,7], Carlos Gonzalez-Figueroa[4], Tadeo C. Spencer[4], Mudra Choudhury[4], Xinshu Xiao[4], Eleazar Eskin[5], James D. Jentsch[2], Desmond J. Smith[1]

[1]Department of Molecular and Medical Pharmacology, Geffen School of Medicine, UCLA; [2]Department of Psychology, Binghamton University, Binghamton, New York; [3]Department of Computer Science, UCLA; [4]Department of Integrative Biology and Physiology, UCLA; [5]Department of Computational Medicine, UCLA; [6]Cedars-Sinai Medical Center, 8700 Beverly Blvd, Los Angeles; [7]Department of Human Genetics, University of Chicago

Background/Rationale/Significance. To identify genetic pathways for addiction, we analyzed intravenous self-administration of cocaine or saline in a panel of 84 inbred and recombinant inbred mouse strains over 10 days. We integrated the behavior data with RNA-Seq data from the medial frontal cortex and nucleus accumbens from 41 strains.

Hypothesis. The self-administration of cocaine and saline showed distinct genetic bases. We maximized power to map loci for cocaine intake by using a linear mixed model to account for this longitudinal phenotype while correcting for population structure.

Results. A total of 15 unique significant loci were identified in the genome-wide association study (GWAS). A transcriptome-wide association study (TWAS) highlighted the *Trpv2* ion channel as a key locus for cocaine self-administration from the GWAS. In addition, 17 genes supplementary to the GWAS were identified including *Arhgef26, Slc18b1* and *Slco5a1.* We found numerous instances where alternate splice site selection or RNA editing altered transcript abundance.

Discussion. Our work emphasizes the importance of *Trpv2,* a known cannabinoid receptor, for the response to cocaine as well as identifying further relevant loci.