

PI Name: Richard Crist

PI email: crist@penmedicine.upenn.edu

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**Single nucleus transcriptomic analysis of the nucleus accumbens reveals distinct cell type-specific patterns of gene expression associated with the escalation of morphine intake in male rats**

Benjamin C. Reiner<sup>1</sup>, Yafang Zhang<sup>1,2</sup>, Lauren M. Stein<sup>1</sup>, Emilie Dávila Perea<sup>1</sup>, Gabriella Arauco-Shapiro<sup>1</sup>, Jennifer Ben Nathan<sup>1,2</sup>, Kael Ragnini<sup>1,2</sup>, Matthew R. Hayes<sup>1</sup>, Thomas N. Ferraro<sup>3</sup>, Wade H. Berrettini<sup>1</sup>, Heath D. Schmidt<sup>1,2</sup>, and Richard C. Crist<sup>1</sup>

<sup>1</sup> Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania,

<sup>2</sup> Department of Biobehavioral Health Sciences, School of Nursing, University of Pennsylvania,

<sup>3</sup> Department of Biomedical Sciences, Cooper Medical School of Rowan University

Opioid exposure is known to cause transcriptomic changes in the nucleus accumbens (NAc). However, no studies to date have investigated cell type-specific transcriptomic changes associated with the escalation of opioid taking. Here, we use single nucleus RNA sequencing (snRNAseq) to comprehensively characterize longitudinal cell type-specific alterations of the NAc transcriptome in rats self-administering morphine. One cohort of male Brown Norway rats was injected with acute morphine (10 mg/kg, i.p.) or saline. A second cohort of rats was allowed to self-administer intravenous morphine (1.0 mg/kg/infusion) for ten consecutive days. Each morphine-experienced rat was paired to a yoked saline control rat. snRNAseq libraries were generated from NAc punches. 1,106 differentially expressed genes (DEGs) were observed in the acute morphine group across 27 cell clusters, compared to 2,453 DEGs in the morphine self-administration group. Importantly, we identified 1,329 DEGs that were specific to the escalation of morphine taking, including *Rgs9* and *Celf5*, which were validated in an independent cohort of animals by RNAscope. DEGs were identified in novel clusters of astrocytes, oligodendrocytes, and medium spiny neurons in the NAc. Bioinformatic analyses identified cell type-specific upstream regulatory mechanisms of the observed transcriptome alterations and downstream signaling pathways. These results indicate that escalation of morphine taking is associated with distinct cell type-specific transcriptomic changes in the rat NAc. These findings highlight specific striatal cell populations and novel molecular substrates that could be targeted to reduce compulsive opioid taking.