Name: Soren Emerson PI Name: Erin Calipari

## **Molecular Determinants of Ensemble Recruitment**

Soren Emerson<sup>1,3</sup>, Alberto Lopez<sup>2</sup>, Rishik Bethi<sup>2</sup>, Ainoa Konomi-Pilkati<sup>1,2</sup>, Danielle Adank<sup>3</sup>, Brooke Christensen<sup>1,3</sup>, Julian Delgado<sup>2</sup>, Suzanne O. Nolan<sup>1,2</sup>, Allison Morris<sup>2</sup>, Amy R. Johnson<sup>1,2</sup>, Kristie Rose<sup>4</sup>, and Erin S. Calipari<sup>1,5</sup>

 <sup>1</sup>Department of Pharmacology, Vanderbilt University; <sup>2</sup>Vanderbilt Center for Addiction Research, Vanderbilt University; <sup>3</sup>Vanderbilt Brain institute, Vanderbilt University;
<sup>4</sup>Department of Biochemistry, Vanderbilt University; <sup>5</sup>Department of Psychiatry and Behavioral Sciences, Vanderbilt University Medical Center

Cocaine use disorder (CUD) imposes a large burden on public health, particularly because there are no FDA-approved pharmacotherapies for the disorder. The onset and maintenance of CUD are driven by physiological and transcriptional changes within the brain that lead to maladaptive cocaine taking and seeking; however, the precise underlying molecular mechanisms remain opaque. We have identified lysine acetyltransferase 2a (KAT2A) as a novel cocaine-recruited epigenetic regulator within the nucleus accumbens (NAc). In vivo, cocaine self-administration increases the KAT2A-recruiting covalent mark on histone H3 (H3S10P), directly increases KAT2A:H3 associations, and increases canonical KAT2A -associated acetylation of H3 (H3K9Ac), which is permissive to gene expression. Further, KAT2A and KAT2A-associated phosphoacetylation have increased occupancy at the key cocaine response genes cFos, Homer3, Oprk1, and Sigmar1 following cocaine administration. Using in vitro and in vivo pharmacology and biochemistry, we characterize the influence of dopaminergic signaling and cellular depolarization on KAT2A recruitment to H3. We show that manipulation of KAT2A in vivo, induced using systematic pharmacology or in a region- and cell type-specific manner, prevents drugassociated learning assessed via cocaine locomotor sensitization and self-administration. Finally, using snRNA sequencing we characterize the relationship between KAT2a expression, and the formation of transcriptionally active cell populations induced following cocaine administration. Together, these results highlight a novel cocaine-induced transcriptional regulator and its role in the formation of transcriptionally active neuronal ensembles, as a potential future therapeutic target to alleviate the devasting impact of CUD on public health.