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# Life at the Extremes: Leveraging Phenotypic Diversity to Identify Mechanisms of Substance Use Disorders

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Mice are widely used in preclinical research to study genetic and biological mechanisms of substance use disorders. Historically, studies have focused on only a few inbred mouse strains, thereby limiting the generalizability and translational value of the work. More recent work has leveraged the expanded genetic and phenotypic diversity present in a unique experimental mouse population; the Collaborative Cross (CC). The contribution of eight diverse founder strains results in allelic combinations in the CC that are not present in traditional rodent populations. Phenotypic outcomes resulting from this genetic heterogeneity, paired with genetic and genomic tools that have been developed to support these populations, accelerates the discovery of mechanisms underlying risk for substance use disorders. The Center for Systems Neurogenetics of Addiction (CSNA) has amassed data in 50 CC strains for an unprecedented number of addiction-relevant traits including impulsivity, initial locomotor sensitivity to cocaine, behavioral and incentive sensitization and intravenous cocaine self-administration. Our data reveal multiple behaviorally extreme CC strains that offer an excellent opportunity for studying mechanisms that could impact susceptibility or resilience to developing cocaine use disorder (CUD). We will discuss specific CC strains that exhibit behaviors at the extreme ends of the phenotypic distribution for one or more CSNA assays. We will demonstrate how genomic data and mechanistic assays that consider neurobiological correlates of drug response and reward can be used to generate novel hypotheses. Our work has the potential to aid in the development of pharmacological and behavioral strategies to decrease risk and more effectively treat CUD.