In substance use disorder (SUD) and post-traumatic stress disorder (PTSD), previously neutral environmental stimulus (such as specific place or sound), via pairing with unconditional stimulus (such as cocaine or explosion-evoked injuries) acquires powerful motivational control over behavior. These conditional stimuli (CSs) induce pathologic behaviors such as drug seeking or overwhelming conditioned fear. Recent studies demonstrate that these specific CSs activate various brain structures including the ventral tegmental area (VTA) – the core brain region of the meso-cortico-limbic dopamine system involved in learning and memory as well as conditioned responses. Importantly, the role of specific receptor mechanisms within the VTA in CS-induced drug seeking or conditioned fear remain unknown.

Our aim is to identify the neurobiological mechanisms in the VTA that underlie the CS-dependent induction of drug seeking and conditioned fear. We hypothesize that CS-induced drug seeking and CS-induced fear depends on activation of partially similar and partially distinct adrenergic receptor mechanisms within the VTA. In addition, these receptor mechanisms are crucially linked to altered dopamine signaling in the forebrain, common feature in SUD and PTSD.

We will use an innovative combination of *in vivo* optogenetics targeting genetically-marked cells, fluorescent tracers, *in vivo* fast scan cyclic voltammetry (FSCV) and brain-region-specific behavioral pharmacology in rats after intravenous drug self-administration or fear conditioning. Receptor- and brain region-specific interrogation of the CS-induced drug seeking and CS-induced fear conditioning is likely the most useful avenue towards the identification of selective compounds or receptor mechanisms that modulate distinct circuitries involved in CS-induced behaviors.

Tha main goal of this project is to advance the research field by demonstration that CS-dependent drug seeking and stress-responses can be modulated via specific neuronal populations and receptor mechanisms in the VTA. We anticipate that by manipulating genetically-marked subpopulations of the VTA neurons as well as by modulating activity of specific receptors in the VTA, we will accomplish progress towards circuit specific control of CS-induced behaviors. In addition, the project may help tailor specific therapeutic interventions as well as new drug targets for the treatment of SUD or PTSD.