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"Dissecting the molecular mechanisms by which Lim-Only 4 regulates alcohol consumption and reward"

Previous work in the laboratory has demonstrated a role for the transcription co-factor Lim-Only 4 (LMO4) in the basolateral amygdala (BLA) in regulating alcohol consumption and reward. Knockdown of LMO4 knockdown in all BLA neurons leads to reduced alcohol consumption and reward. Unbiased whole genome sequencing has identified the Kappa Opioid Receptor (KOR) as a transcriptional target of LMO4 in the BLA. KOR expression is reduced by 50% in the BLA of mice with LMO4 knockdown and LMO4 directly binds to KOR promoter elements. KOR is an intriguing target because it has previously been shown to regulate excessive alcohol use and is thought to mediate the dysphoric effects caused by chronic alcohol abuse.

KOR and LMO4 are expression are colocalized in approximately 50% of the neurons in the BLA. An interesting question that stems from this finding is whether restricting LMO4 knockdown to KOR expressing cells in the BLA also reduces alcohol consumption and reward. We will achieve this by using an intersectional strategy involving Cre-dependent shRNA's against LMO4 and recombinant mice that express Cre-recombinase under the control of the KOR promoter (KOR-Cre mice). Specifically, my project will involve designing and validating Cre-dependent small hairpin RNAs (shRNAs) against LMO4. The best shRNA candidate will then be packaged into lentiviral particles. I will then stereotaxically infuse these viral particles into the BLA of KOR-Cre mice and validate the Cre-dependent expression of the shRNA as well as LMO4 knockdown in vivo. I will then measure the effects of this selective manipulation on alcohol consumption and reward.