Neuron Navigator 1 (Nav1) Regulates Learning, Memory and the Response to Multiple Drugs of Abuse (DOA)

Yalun Tan1,*, Jared R. Bagley2,*, Wan Zhu1, Zhuanfen Cheng1, Saori Takeda1, Ahmed Arslan1, Yuan Guan1, J. David Jentsch2, and Gary Peltz1

1Department of Anesthesiology, Stanford University Medical School; 2Department of Psychology, Binghamton University; *Both authors made unique but equal contributions to this work

Genetics has a major effect on addiction susceptibility and on learning and memory capability. Consistent with the effect that genetic factors have on addiction susceptibility, inbred mouse strains exhibit substantial differences in the extent of voluntary cocaine self-administration (CSA). Computational genetic analysis identified Nav1, a member of the neuron navigator family that regulates dendrite formation and axonal guidance, as a candidate gene affecting CSA. The Nav1 mRNA expression level in striatum is cis-regulated and inversely correlated with striatal Drd2 mRNA expression. We hypothesized that Nav1 alleles affect memory, learning, and DOA responses. To test this hypothesis, CRISPR engineering was used to produce a Nav1 KO in C57BL/6 embryos. Nav1 KO mice exhibited a reduced sensitivity to the psychomotor activating effects of cocaine and reduced susceptibility to opiate dependence. They also exhibited normal motor coordination but impaired spatial learning and recognition. On the cellular level, our preliminary data indicates that inhibitory synaptic transmission in the Nav1 KO cortex was reduced. Collectively, our results suggest that Nav1 alleles regulate learning, memory and the response to multiple DOA. We are now using scRNA-Seq to molecularly characterize Nav1 effects on DOA responses, and are investigating whether a Nav1-associated protein complex provides a new therapeutic target for prevention of drug addiction.