Submitter Name: Marsida Kallupi
Submitted email: mkallupi@health.ucsd.edu
PI Name: Olivier George
PI email: olgeorge@health.ucsd.edu

**Characterization of addiction-like behaviors to oxycodone in Heterogenous Stock rats**

Marsida Kallupi[1], Lani Tieu[1], McKenzie Pavlich[1], Lisa Maturin[1], Fred Malaton[1], Dyar Othman[1], Leah Solberg-Woods[2], Abraham Palmer[1], Giordano de Guglielmo[1], and Olivier George[1]

[1]Department of Psychiatry, University of California, San Diego, La Jolla CA 92093, USA.
[2]Wake Forest University Health Sciences, Winston-Salem, NC 27157, USA.

Identifying the mechanisms that underlie compulsive oxycodone use is a major goal for understanding the genetic risk factors for oxycodone use disorder and facilitating the identification of novel druggable targets. One major impediment to studies of oxycodone use disorder is the complexity of the phenotype and the lack of control of environmental variables. To address this issue, we used a unique outbred strain of rats (Heterogeneous Stock) that mimics the behavioral and genetic diversity found in humans and characterized by individual differences in addiction-like behaviors. Rats were allowed to self-administered oxycodone 12h/daily for 14 days. The animals were screened for their addiction-like behaviors using an addiction index that incorporates the key criteria of oxycodone-use disorder: escalated intake, compulsive-like responding and motivation for oxycodone. We detected withdrawal severity by measuring hyperalgesia and the development of tolerance. The measures were analyzed across sexes and experimental subgroups. The addiction index, averaging the z-scores for escalation, motivation, and hyperalgesia allowed identification of individuals that are vulnerable (high addiction-like behavior, HA) with positive addiction index values vs. resistant (low addiction-like behavior, LA) with negative values. The results showed significant interindividual variability of oxycodone intake, compulsivity, and motivation. We found significant sex differences in all measures of oxycodone-use disorder. Future studies, will allow to identify genetic variants that predict the characteristics of oxycodone use disorder, including 1) escalation of intake, 2) compulsive-like intake, and 3) motivation for oxycodone. Such data will have considerable translational value for designing pharmacogenetic studies in humans.