Name: Michael C. Saul
PI Name: Elissa J. Chesler
Presentation preference: oral or poster

Email: Michael C. Saul
PI email: elissa.chesler@jax.org

Common genetic and genomic underpinnings of learned and unlearned addiction-related behaviors

Michael C. Saul[1,2], Price E. Dickson[1,3], Udita Datta[1,2], Robyn Ball[1], Hao He[1], Troy Wilcox[1,2], Tyler Roy[1,2], Leona Gagnon[1,2], Jason Bubier[1,2], Vivek M. Philip[1,2], J. David Jentsch[2,4], Lisa M. Tarantino[2,5], and Elissa J. Chesler[1,2].

[1]The Jackson Laboratory, Bar Harbor, ME USA, [2]Center for Systems Neurogenetics of Addiction, [3]Marshall University, Huntington, WV USA, [4]Binghamton University, Binghamton, NY USA, [5]UNC-Chapel Hill, Chapel Hill, NC USA

Genetic variation in mechanisms responsible for individual differences in addiction may jointly influence multiple aspects of addiction-related behaviors. However, confounding of risk and the effects of drug exposure often complicates the search for shared genetic regulators. To discover joint drivers of addiction and addiction risk behaviors, we deployed Reference Traits Analysis, our multivariate statistical method for integrating independently assayed cohorts. Multiple exploratory, novelty response, and locomotor behavioral phenotypes were assayed in Diversity Outbred mice (J:DO). These standard behavioral assays can be measured straightforwardly and non-invasively in mice without substance exposure history. Mice were then either tested on learned cocaine self-administration behaviors or unlearned cocaine sensitization and saline sensitization phenotypes in Diversity Outbred mice. Mapping the resultant indices, we identified multiple significant quantitative trait loci for learned and unlearned addiction-related behaviors. Using formal pleiotropy analysis, we discovered a locus on Chr *M.m.* 7 that jointly regulates unlearned sensitization responses and learned self-administration responses, not solely driven by locomotor activity effects. Mediation analysis with expression data implicated the gene *Me3* as a positional candidate. These results indicate that genetic drivers of addiction risk-related behaviors have pleiotropic effects on learned and unlearned addiction-related behavior. By correlating derived behavior indices with drug-naïve striatum gene expression, we can identify molecular mechanisms associated with cocaine related behaviors. One such cocaine self-administration related co-expression network includes an ortholog of a previous human GWAS hit also implicated in prior mouse studies. Together, these approaches reveal shared and distinct mechanisms of multiple aspects and phases of addiction-related behavior. Supported by P50 DA039841; R01 DA037927