

Project 1: INIA - Robust Systems Genetics of Alcohol and Stress Effects on CNS

Robert Williams, Ph.D., Principal Investigator

University of Tennessee, Health Sciences Center, Memphis, TN

Environmental factors interact with gene variants to influence patterns of alcohol use, abuse, adaptation, addiction, withdrawal, and relapse. Ethanol is a highly soluble small molecule that has subtle effects on many molecular processes. Individual differences in how humans handle ethanol are complex and is not well understood. In common with other components of INIA-Stress, this project explores and tests genetic, molecular, synaptic, cellular, and behavioral causes and correlates of alcohol consumption and the covariation between ethanol use and stress. Our focus is on exploiting new high-resolution genomic resources to model networks of molecular and synaptic interactions in basal forebrain regions that have important roles in addiction and alcoholism. To ensure relevance and robust results we use several large genetic reference populations and apply sophisticated statistical methods to generate hypotheses that are then subjected to rigorous tests. Data from molecular and functional studies are combined using a systems genetics approach to define shared and unique genetic and synaptic factors that modulate ethanol use and convergent effects of stress on ethanol addiction.

In Aim 1 (Data Acquisition) we generate normative expression data and networks for key forebrain regions from three genetic reference populations with very different genetic structures (inbred and outbred, mouse and rat). Our goal is to extract robust networks that are cross-validated and that have strong prospects of generalizing to human populations. In Aim 2 (Model Construction) we develop open source programs and standard operating procedures that will produce well defined and testable hypotheses. The INIA *Models Work Group* is responsible for developing, testing, and using custom statistical software with which they will construct explicit process diagrams and statistical models. These models are integrated into the INIA GeneNetwork web site for use and critique by all INIA and NIAAA researchers. In Aim 3 (Predictive Validation), we experimentally manipulate sets of isogenic lines which we predict will be high or low responders using a battery of INIA protocols. The synergy among genetic, transcriptome, electrophysiological, and experimental studies will allow us to test the role of complex interactions in the mesocorticolimbic system that contribute to alcoholism in a subset of genetically and environmentally vulnerable humans.