

## ***Connecting Gene Networks to Drug Discovery for Alcohol use Disorders***

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Novel computational strategies and drug databases now allow researchers to integrate gene expression signatures associated with disease with those induced by drug treatments (Lamb et al, 2006). While these integrated analyses have uncovered new drugs for cancer and other complex diseases, they have not yet been applied to psychiatric illnesses. Pharmacotherapies for alcohol use disorder (AUD), a complex psychiatric disease with strong genetic and environmental risk factors, are limited in number and efficacy.

**Methods:** High Drinking In the Dark (HDID-1) mice are a genetic animal model of AUD risk that have been selectively bred (from the genetically diverse HS/Npt line) to achieve intoxicating blood alcohol levels (BALs) after a short, binge-like drinking session. We compared gene expression from 8 key brain regions in HDID-1 and HS/Npt mice to determine a molecular signature for high intensity, binge-like drinking that may impact risk for AUD. Using multiple computational methods, we queried LINCS-L1000 (Library of Integrated Cellular Signatures), a database populated with the gene expression signatures of thousands of compounds, to predict and prioritize drugs with the greatest potential to target the HDID molecular signature and decrease excessive alcohol consumption and/or reduce BALs.

**Results:** Our analysis successfully uncovered novel compounds for testing, and we validated 2 of the top candidates in vivo. Pergolide (a dopamine and serotonin receptor agonist) and terreic acid (a Bruton's tyrosine kinase inhibitor) robustly reduced alcohol intake and blood alcohol levels in HDID-1 mice.

**Discussion:** These findings provide the first evidence that brain gene expression data can be integrated with informatics tools, such as LINCS-L1000, to successfully predict drugs that decrease drinking in animal models of AUD. Effective drug treatments for many psychiatric diseases are lacking, and the emerging tools and approaches outlined here give researchers studying complex diseases renewed opportunities to discover or repurpose existing compounds and expedite treatment options.

**Reference:** Lamb, J., et al., The Connectivity Map: using gene-expression signatures to connect small molecules, genes, and disease. *Science*, 2006. 313: p. 1929-35.

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