Name: Matthew Lane Email: lanemj@ornl.gov
PI Name: Daniel Jacobson PI Email: jacobsonda@ornl.gov

Binding Pathways to Break Addiction: Multiomic Insights into GLP-1R Agonist Therapeutics for Cigarette Smoking and Opioid Addiction.

Matthew Lane[1,2], Erica Prates[2], Kyle Sullivan[2], Alice Townsend[1,2], Jean Merlet[1,2], P. Doug Hyatt[2], Richard Morgan[2], Manesh Shah[2], Suzan Asmar[2], Tyler Walker[2], Christiane M. Alvarez[2], Alana Wells[2], Bryan C. Quach[3], Caryn Willis[3], Greg Keele[3], Eric O. Johnson[3,4], Dana B. Hancock[3], Daniel Jacobson[2]

[1]The Bredesen Center for Interdisciplinary Research and Graduate Education, University of Tennessee Knoxville, Knoxville, TN, USA;
[2]Computational and Predictive Biology Group, Oak Ridge National Laboratory, Oak Ridge, TN, USA;
[3]GenOmics and Translational Research Center, RTI International, Research Triangle Park, NC, USA;
[4]Fellow Program, RTI International, Research Triangle Park, NC, USA

GLP-1R agonists have recently shown potential for addiction treatment, opening new avenues for therapeutic development. In this study, we employed deep learning protein-folding approaches to identify a novel binding interaction between GLP-1 and gamma-aminobutyric acid receptor involved in neurotransmission.

To explore the effects of GLP-1R agonists on addiction-related genes, we developed a 25-layer multiplex network model targeting the prefrontal cortex. This model integrates multi-omic single-cell and bulk RNA sequencing data, supplemented with database and literature-derived information. Using RWRtoolkit's RWR_LOE functionality, we examined the statistically significant neighborhood of the GABA receptor, isolating the top 345 genes with scores above the histogram's inflection point.

We further analyzed these genes for genetic associations with nicotine and opioid addiction, identifying 19 genes linked to opioid addiction and 4 linked to nicotine addiction. Subsequent clustering using MENTOR revealed 17 distinct clusters. Notably, one cluster included RASGRF1, a gene implicated in both opioid and nicotine addiction and a key regulator of the MAP kinase cascade with another gene of interest, KCNMA1, associated with opioid addiction via chromatin mapping, influences cellular excitability. This cluster also enriches for terms related to chemical synaptic transmission, synapse signaling, neuron development, and protein glycosylation, highlighting roles in synaptic modulation and neuron structure.

This multi-omic framework enables us to identify GLP-1R agonist binding pockets, explore additional therapeutic targets, and support drug repurposing efforts. By leveraging multiplex networks and deep learning, our approach can help to significantly reduce the timeline for therapeutic application, offering promising insights into addiction biology and precision treatment strategies.