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Human-First Drug Repurposing for Addiction: From AI-Informed Multi-Omics Systems Biology Through Candidate Drug Validation and Trial Emulation

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The fight against addiction demands innovative methodologies to address the intricacies of developing new therapies for substance use disorders, including personalized treatment approaches for improved patient outcomes. We present a transformative approach using large (cell-type-specific) multiplex networks to provide a mechanistic understanding of addiction. Through the application of the MENTOR algorithm, we harness human multi-omics data to unravel the biological underpinnings of substance use disorders, generating insights into both cellular and system-level dynamics. Additionally, the mechanistic interpretation of MENTOR results is augmented by leveraging large language foundation models, trained on a wealth of biological data, including scientific literature, biological databases, and networks with tens of millions of edges. This computational synergy provides an unprecedented capability for generating hypotheses and elucidating pathways linked to addiction. To enhance therapeutic discovery, we utilize advanced protein AI technologies to discover new binding pockets for drug repurposing opportunities. Our approach further integrates massive multiplex networks to function as a digital twin, enabling in silico perturbation testing of potential drugs, thereby accelerating the identification of novel therapeutic interventions. These drug candidates are then further validated through cross-species testing, including high-throughput functional validation of of both molecular and behavioral phenotypes in Drosophila and mice. Moreover, we leverage large-scale Electronic Health Records to perform retrospective clinical trial emulations, assessing the real-world efficacy of prioritized drug candidates. This integrative framework, blending cutting-edge AI, multiplex networks, multi-omic and clinical data, lays the groundwork for a paradigm shift in understanding and treating addiction, paving the way for targeted, mechanistically informed therapies.