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Advancing Programmable Human Digital Twins for Substance Use Disorder Drug Discovery

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In the quest for effective, safe, and personalized treatment for Substance Use Disorder, traditional one-drug-one-gene approach often falls short due to its inability to fully capture the complexity of human pathology and fill in the translational gap from early drug discovery to clinic. We propose a paradigm shift towards a system pharmacology framework, leveraging the rich data from patient and perturbation omics profiling. This approach aims to transform disease states into healthy ones by identifying key biomarkers and system-wide modulators through multi-scale predictive modeling of drug actions in the human body. However, there are challenges ranging from the integration of diverse omics data types to the exploration of uncharted chemical, target, and functional genomics spaces. To address these challenges, we leverage advanced AI techniques for their power in data-driven feature extraction, harmonizing heterogeneous data sets, and multi-level modeling of complex biological systems. Our recent efforts include 1) harnessing the vast volumes of unlabeled data to illuminate the dark corners of chemical and biological knowledge, 2) cell type-specific phenotype compound screening across biological levels, and 3) Transfer learning to bridge disease models and human physiology. Put together, the AI-powered systems pharmacology approach has been successfully applied to personalized Alzheimer's disease drug repurposing and Opioid Use Disorder drug discovery.