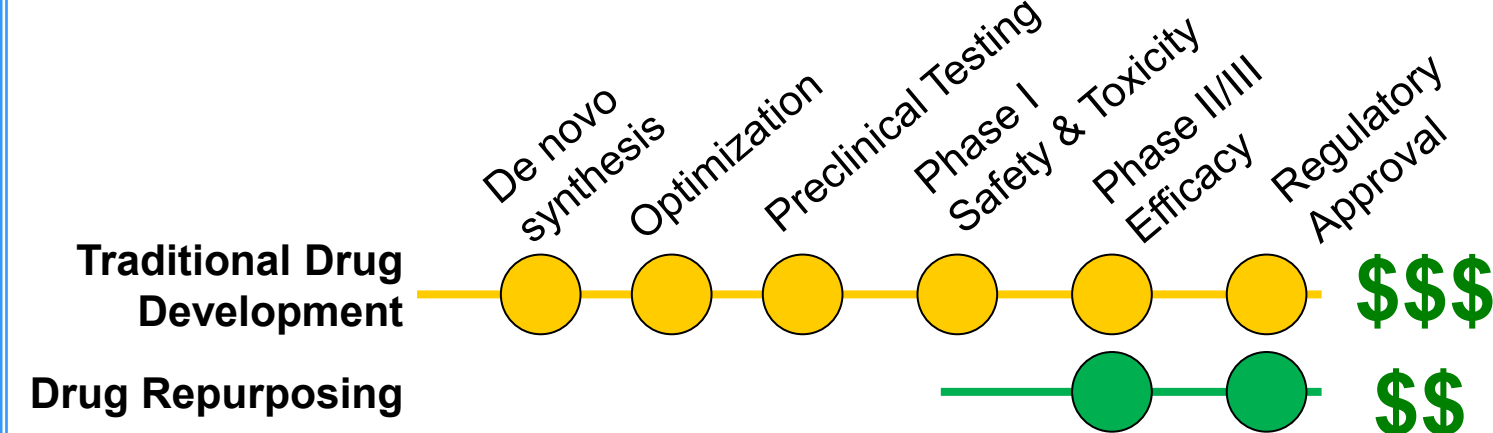


INTRODUCTION

- Methamphetamine use disorder (MUD) remains a major public health challenge,¹ with no FDA-approved pharmacotherapies and limited success from traditional single-target drug discovery approaches.
- Publicly available multi-omic datasets—including genetic, transcriptomic, epigenomic, and proteomic profiles—can be leveraged to identify disease-associated genes that may serve as targets for pharmacotherapy development.
- Integrating these complementary lines of evidence can reveal convergent biology, enabling prioritization of more robust targets for drug repurposing.

OBJECTIVE

Traditional drug discovery and development timelines are long and resource intensive. Drug repurposing accelerates the process by leveraging optimized compounds with established human safety and toxicity profiles.^{2,3}

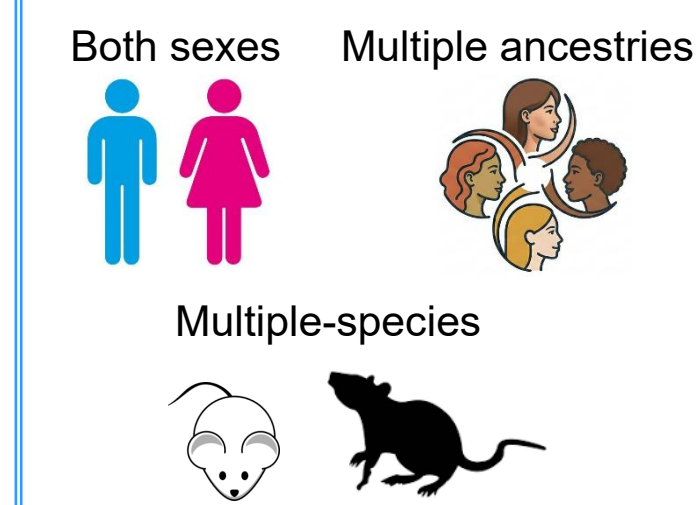


Objective: Develop an integrated translational drug-repurposing pipeline that leverages large-scale molecular and clinical data to efficiently bridge gene discovery and clinical validation.

MOLECULAR PROFILE DATA

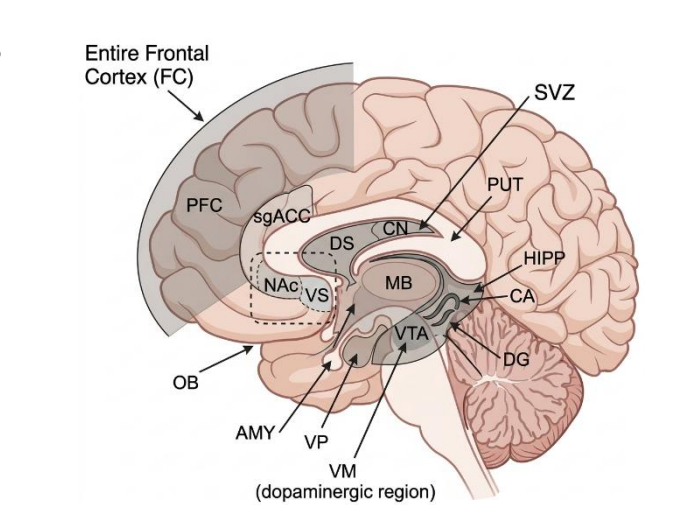
A. “Participant” Selection

To create robust and generalizable findings we include:



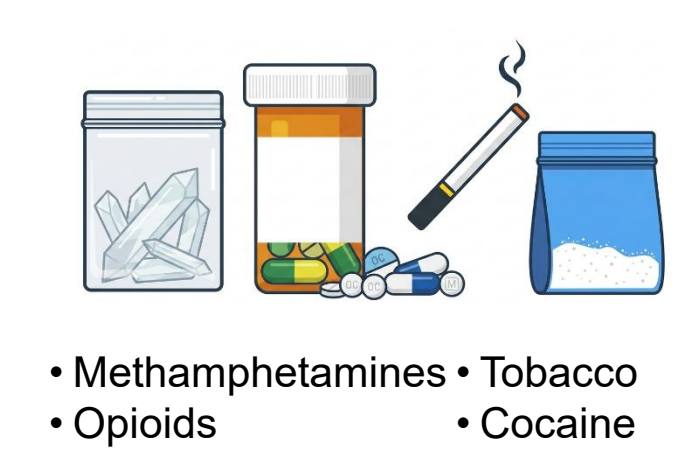
B. Biospecimen Collection

Looking at multiple brain regions to identify systemic changes



C. Diverse Phenotypes

Enhance signal from sparse MUD data with shared addiction biology across substances



D. Data Collection

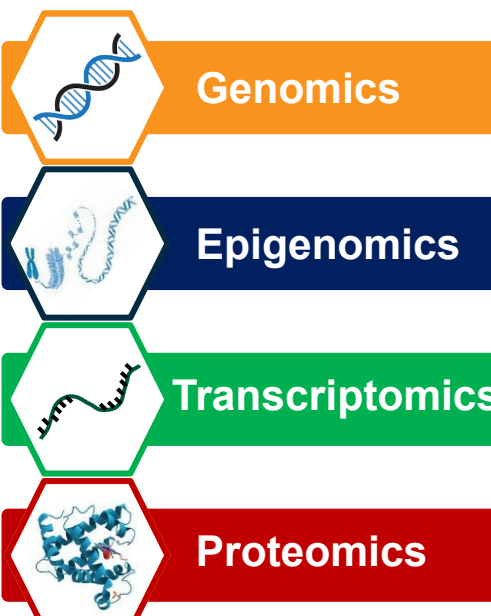


Figure 1. Data selection for drug repurposing. To create a robust and generalizable finding we identified **A.** human postmortem brain samples across both sex and ancestry as well as brain tissue from rodent mechanistic studies. **B.** Multiple brain regions were sampled to give a wholistic view of biology underlying substance use disorder. **C.** Molecular profiling of human brain samples related to MUD is sparse. Datasets from multiple SUDs were used to enhance the signal associated with common mechanism of addiction. **D.** Extant data was identified for multiple omic approaches and used as inputs for this effort.

DRUG REPURPOSING DATABASES

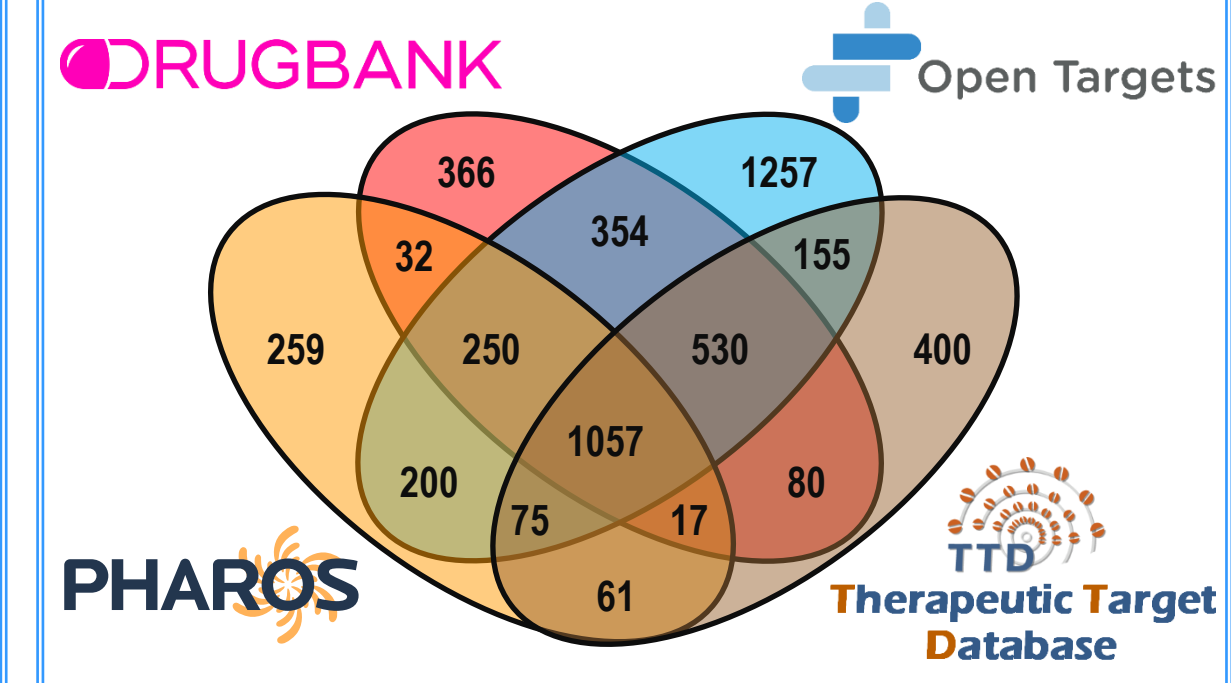


Figure 2. Overlap in the count of approved drugs that are in the four drug repurposing databases: Pharos⁴ (orange, n=1,956), DrugBank⁵ (red, n=2,688), Open Targets⁶ (blue, n=3,878), and TTD⁷ (brown, n=2,375).

TARGET IDENTIFICATION

A. Molecular Profiles B. Multiplex Network Layers C. Hierarchal Clustering D. Mechanistic Modules

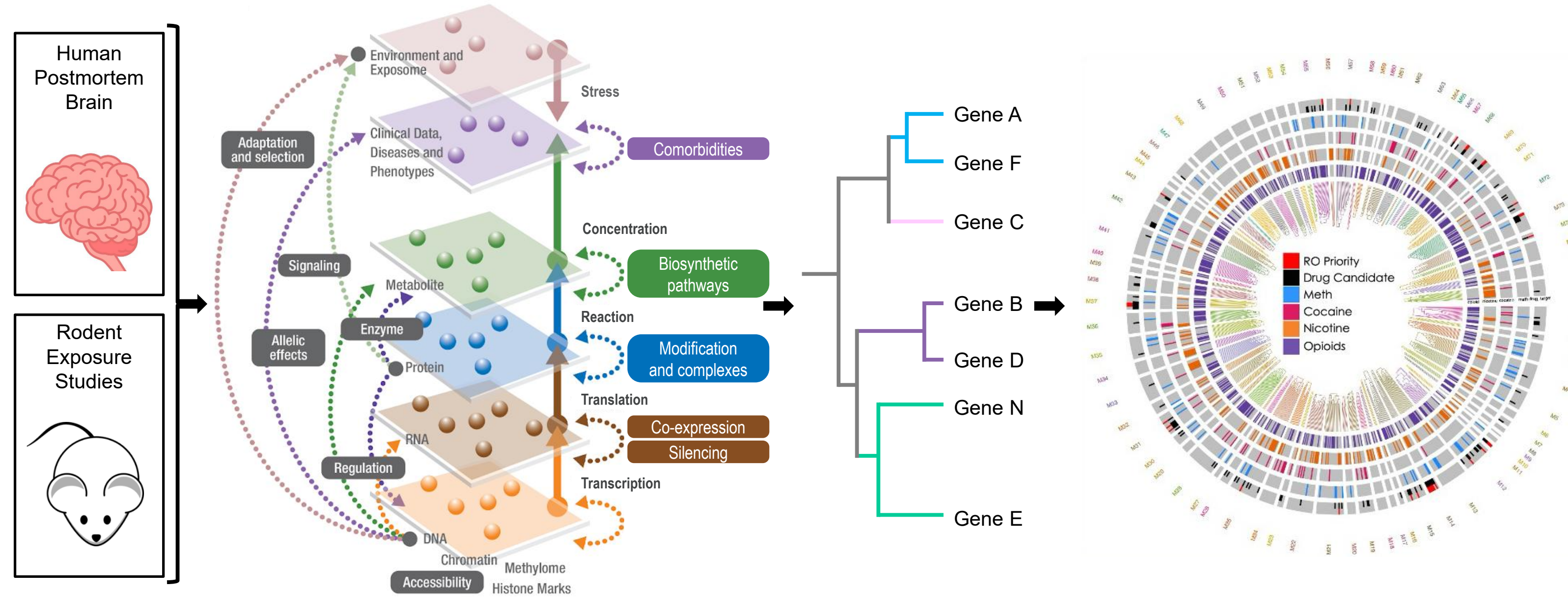


Figure 3. MENTOR[®] framework for identifying mechanistic modules for drug repurposing. **A.** Gene sets derived from omic data from both human and rodent brain samples were used as inputs. **B.** MENTOR's multi-layered approach allows it to maintain the unique topology of each data type while facilitating cross-layer information flow, critical for accurately capturing the complex nature of biological systems. **C.** Hierarchically clustered Euclidean distance represents gene connectivity for each queried gene. **D.** Mechanistic modules identified from the clustering are displayed as a dendrogram. The dendrogram is divided into discrete mechanistic modules containing closely interconnected genes in the multi-layered approach.

DRUG REPURPOSING

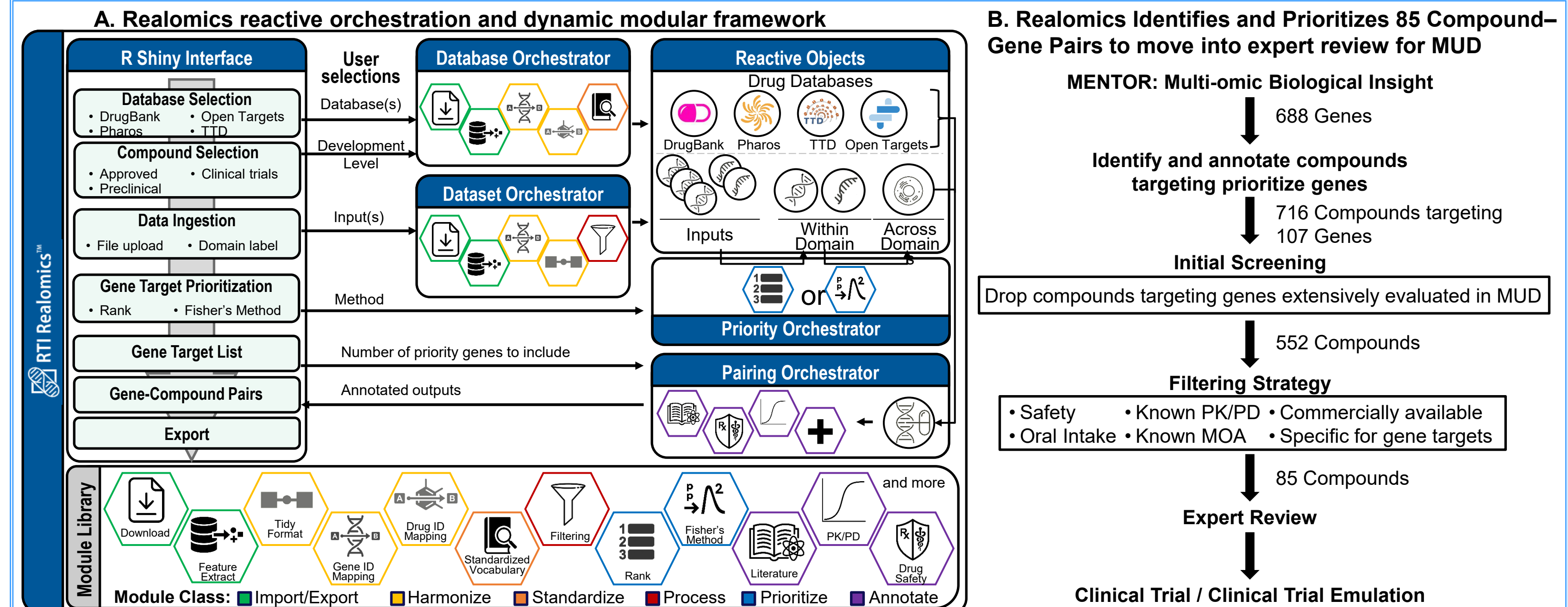


Figure 4. Realomics drug repurposing framework[®]. **A.** Realomics provides an interactive R Shiny environment where users define app settings and parameters that are passed to functional orchestrators. These orchestrators use the inputs to dynamically select which modules from a library are used to construct a customized data processing and analysis pipeline that generate reactive objects. Reactive objects of ingested user supplied inputs are first integrated within individual evidence domains and subsequently across domains to prioritize targets and generate drug-gene pairs, which are then systematically annotated to support downstream expert review. **B.** MENTOR identified 688 genes that Realomics used to generate 716 gene-compound pairs. A filtering strategy prioritized 85 genes for expert review for further evaluation.

FUTURE DIRECTIONS

- Integrate additional biological evidence domains including epigenetics, metabolomics and metagenomics.
- Incorporate preclinical evidence via cross-species homology modeling.
- Multiplex network modeling and mechanistic interpretation to identify actionable targets in biological context.
- Enhanced annotations for revised prioritization of gene-compound pairs.

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