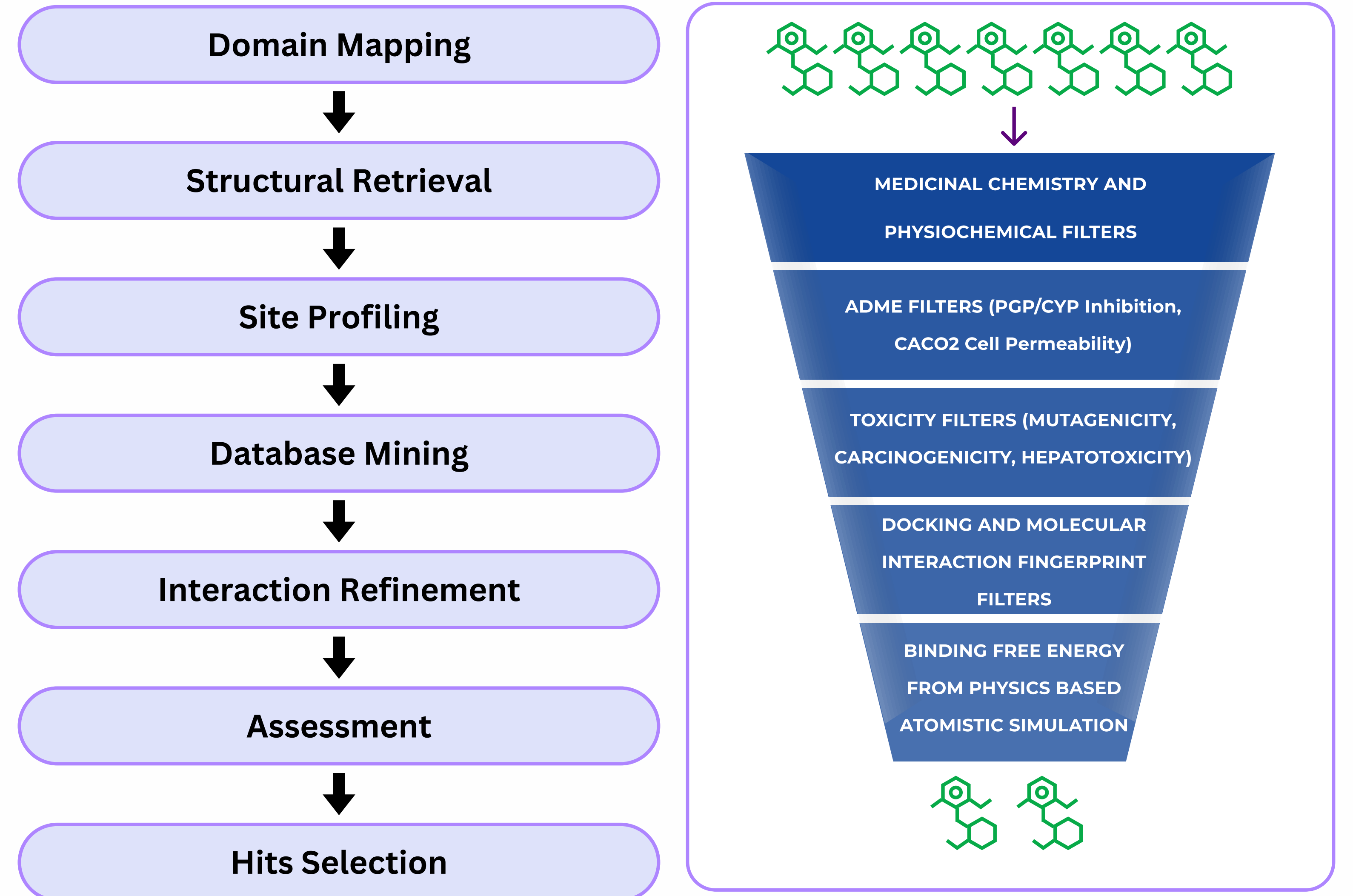## Targeted Drug Repurposing

- **Therapeutic Area**: Cardiovascular system (CVS) + Oncology
- **Context**: Repurpose existing molecule for exploring new indications in oncology and enhancing cardiac tolerability
- **Objective**: Repurpose existing approved and clinical stage drugs and compounds for new medical indications with pharmacology, formulation, and toxicity data

Method

- Utilized advanced **NLP/ML** technology customized for specific datasets to build a list of possible clinically approved drugs for a given therapeutic area/disease condition (**genomics/proteomics big data analysis**)

- Screened the shortlisted compounds using **AI/ML** with domain-enriched computational screening and analysis to check small molecule interactions with Target ID

- Optimized leads for activity and specificity

Flow

Domain Mapping → Structural Retrieval → Site Profiling → Database Mining → Interaction Refinement → Assessment → Hits Selection

MEDICINAL CHEMISTRY AND PHYSIOCHEMICAL FILTERS

ADME FILTERS (PGP/CYP Inhibition, CACO2 Cell Permeability)

TOXICITY FILTERS (MUTAGENICITY, CARCINOGENICITY, HEPATOTOXICITY)

DOCKING AND MOLECULAR INTERACTION FINGERPRINT FILTERS

BINDING FREE ENERGY FROM PHYSICS BASED ATOMISTIC SIMULATION

Solution

1. Built comprehensive database of disease-associated genetic variants (SNPs, CNVs, InDels, translocations, etc) curated for over **160** attributes resulting in **40,652** variants mapped to **7022** genes and **2053** phenotypes. Our databases have not only aptured attributes common to several databases available today but the differentiator was the expansion of the core database to include domain-enriched novel metadata as described below:
   a. Cellular level data such as linkage of significant genetic epidemiological data and molecular data from *in vivo* and *in vitro* experiments. We captured data on gene regulation, post-translational protein modifications, and cell behavior such as apoptosis, growth, motility, and adhesion that is missed in conventional variant-disease databases but is critical to understanding the etiology of the disease. We also helped incorporate data from platforms such as **KEGG**, **Ingenuity**, and **MAGENTA** pathway analysis, **eQTL** analysis, and Microarrays
   b. Proprietary Protein mutagenesis database of mutagenesis experiments on proteins from disease-related genes was used to extract meaningful and significant data for complex descriptions of protein-protein interactions, protein-complex formation, cis/trans interacting domains, and binding sites using in-house built structured vocabulary. We consolidated data/metadata from diverse experimental models and mapped it to phenotypes at different levels of biological organizations

Results

- Captured **data on gene regulation, post-translational modifications**, and cell behaviour which are missed in traditional variant-disease databases
- Several compounds were identified with a **high binding affinity** for a PPI domain in a target involved in DNA repair pathways identified for the indication of interest
- The compounds demonstrated enhanced interaction profiles, with several **surpassing benchmark** metrics
- Selected compounds showed compatibility with desirable **ADMET** properties, predicting a favourable in vivo response
- **Consolidated data from multiple experiment models** to map new indications