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Data-driven targetome discovery and database requirements: insights from the therapeutic target database

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Abstract

Target discovery is pivotal in cutting-edge drug development and impacts translational outcomes and efficacy, the current state of research depends heavily on empirical approaches that can be costly, while there is no publicly available database of drug-target for polypharmacological correlates incorporating relevant clinical data. In the present perspective, 3 Therapeutic Target Database (TTD) exports are utilized: (1) counts of unique target classes having at least one approved drug, (2) approved-drug counts per target class, and (3) the top 20 de-duplicated drug-driven target co-occurrence pairs. These data enabled development of a data-driven map of the targetome. Through comparison of class richness versus translational yield, rating of frequency of drug driven co-occurrence target pairs, we identified emerging, high-yield and biologically plausible but understudied target families, and guide rational combination therapies. The next generation of research should update drug-target databases with more clinical information, quantitative polypharmacology, and provenance metadata to advance combination therapy.

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TTD is a professional resource database integrated with therapeutic targets, related drugs, clinical data and various forms of associated information. The aim of TTD is to offer drug developers and researchers data required for target priority setting and drug development[1]. Inputs comprised three TTD-derived tables: target class counts (e.g., G-protein coupled receptor (GPCR) rhodopsin = 99 classes), approved drug counts by target class (e.g., GPCR rhodopsin = 585 approved drugs; kinase = 201), and a ranked list of the drug driven top 20 target co-occurrence pairs (Frequency = Number of distinct drugs annotated to both targets). Comparing class richness and approved drug density enabled identification of translation gaps, and ranking co-occurrence frequency identified robust co-target observations. Co-occurrence was treated as an empirical hypothesis generator but not proof of clinical synergism/safety.

From Supplementary Figs S1 and S2, it is observable that, GPCR Rhodopsin Family[2–5] (99 classes; 585 approved drugs) and kinases[6–10] (62 classes; 201 approved drugs) are dominant of the translational research. This reflects the comprehensive study of drug chemical space and target structure. Other drug-rich classes include peptidases[11–15], nuclear hormone receptors[16–19], paired-donor oxidoreductases[20], voltage-gated ion channels[21–25], cytokine receptors[26–30], and immunoglobulins[31–35]. mRNA targets[36–41] (21 classes; 25 approved drugs) indicate their ability for translation. This strengthen the value of sustained study in delivery technologies[37,42,43] and modification engineering[44–46]. Multiple oxidoreductase[47–49] subclasses, certain carbonic anhydrase isoforms[50–57], specialized transferases[58,59], and selected solute carriers[60–65] are consistently represented in the class catalog. However, they have relatively few approved drugs associated with them. These gaps likely owing to the challenges in target tractability[66,67], or inadequate probe development[68,69], rather than a lack of biological relevance.

Empirical co-occurrence targets

As shown in Fig. 1, target co-occurrence (is observed in several approved drugs) does not imply to be identical to direct biological synergy. Nevertheless, the targets of co-occurring that have been identified in the current perspective are not arbitrary coincidences; all potential co-occurrence pairs are based on the approved drug entries in TTD (all drugs have been through regulation process and shown to be clinically effective). In large groups of major co-occurrences, we also confirm its biological and clinical significance by referencing mechanistic research and combination therapies (as described in each subsection), to make sure that these co-occurrence pairs are of real therapeutic interest and not random associations.

The most common co-occurrence (shared by 10 drugs) is norepinephrine transporter (NET)-serotonin transporter (SERT)[70–74]. Dopamine transporter (DAT)-NET[70,72,75] and DAT-SERT[76–79] are also recurrently observed. Also, several pairs of serotonin/dopamine[80–83] receptors (e.g., 5-HT 2A receptor (HTR2A)-dopamine D2 receptor (D2R)[84–87]) overlap. These trends indicate the widespread polypharmacological strategy in central nervous system (CNS) studies and provide a perspective of rationally optimised multi-target therapy or controlled combinations in affective and cognitive illnesses with stringent safety recording.

Bacterial DNA gyrase[88–90] and *Staphylococcus* topoisomerase IV[91] co-occur frequently[92–96] (shared by nine drugs). This supports the development of dual-target strategies to surmount antibiotic drug resistance[97].

Prostaglandin G/H synthase 1 (COX-1) and prostaglandin G/H synthase 2 (COX-2) co-occur frequently[98–101], reflecting the polypharmacology of nonsteroidal anti-inflammatory drugs (NSAIDs) in the prostanoid signaling pathway. Furthermore, recurrent Janus kinase (JAK) pairings (e.g., JAK1-JAK2)[102–105] have been identified as empirically validated combinations for immunomodulation. Building on this observation, we hypothesize that potential

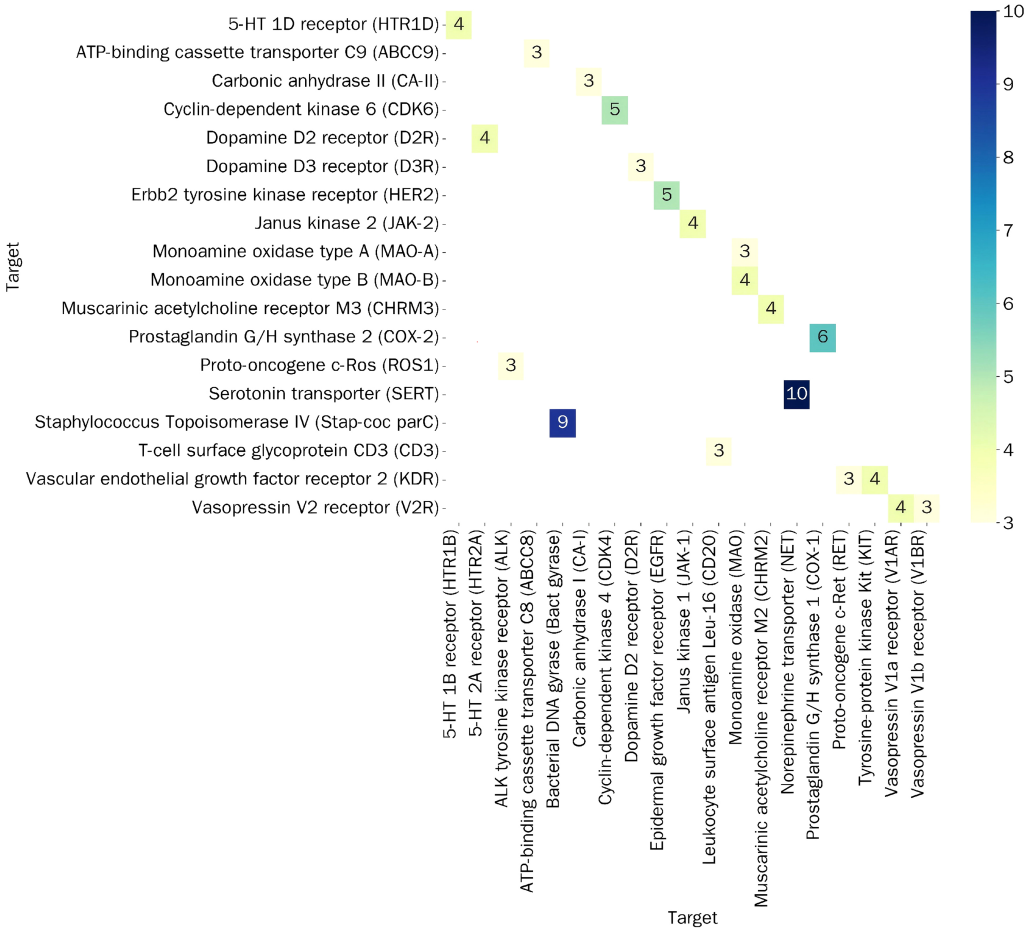

Fig. 1 Top 20 de-duplicated drug-driven target co-occurrence pairs. The relation between targets is represented by the number of shared drugs.

co-occurrences linking JAKs to broader categories, such as cytokine receptors[106] and immune surface markers[107], could further expand the immunomodulatory combination therapies. Collectively, these empirically observed JAK pairings and the apparent JAK-associated co-occurrences (with cytokine receptors or immune surface markers), constitute inflammation-related JAK-centric combinations[108–110]. This mapping facilitates the identification of synergistic immunomodulatory windows, while immune-related adverse events should be carefully profilied.

Specific oncology oncogenes clusters, including epidermal growth factor receptor (EGFR)-ErbB2 tyrosine kinase receptor (HER2)[111–114], cyclin-dependent kinase 4 (CDK4)-cyclin-dependent kinase 6 (CDK6)[115–117], tyrosine-protein kinase kit (KIT), and vascular endothelial growth factor receptor 2 (KDR)[118–121], as well as multiple intra-family receptor tyrosine kinase links[122–124], recur among top co-occurrences. This indicates the common multi-inhibition of the kinase[125–130]. It is worth noting that SynLethDB[131,132] is a mechanistic database of experimentally confirmed synthetic lethality (SL) interactions. Unlike the drug-driven co-occurrence targetets shown in our analysis of TTD database, the SL target combinations listed in the SynLethDB database are carefully assembled including specific annotations of their underlying molecular mechanisms. Moreover, the database adds a parameter of Statistic Score which quantifies the reliability of a certain genetic interaction, with the help of which the positive SL pairs can be distinguished in comparison with negative pairs. It is important to underline that SL pairs offer sound evidence of a synergistic effect of two different targets that is strictly genetically validated, and its lethal activity depends on a co-effect between two different targets, therefore, giving high therapeutic specificity. Here are examples of this: the DNA damage response associated kinase group PARP1-BRCA2[133], is one of the core SL interactions of DNA damage response pathways, and is widely annotated in SynLethDB. The relevance of oncology kinase clusters in translation research is emphasised from both our drug-driven co-occurrence targets and the SL-validated genetic interactions. Such results warrant the design of selective multi-kinase inhibitors, or biomarker-directed combination, which overcome acquired chemoresistance. A specialized database with drug combinations, namely DrugCombDB[134] is also important in targetome research. It is a database of pairings of clinically applied drug combinations, a large part of which applies to cancer treatment wherein combination therapy has become a clinical practice. It is worth noting that at present DrugCombDB pays much attention to drug-drug combination without recording the associations between such combinations and their corresponding targets (genes/proteins). It is hoped that more can be done to update drug-target databases with cross databases in the future. For example, combining DrugCombDB's clinical combination data with TTD's drug-target associations, SynLethDB's synthetic lethality gene pairs, and functional genomics data (e.g., CRISPR analysis) will enable the construction of a comprehensive "genetic interaction-target-drug-combination therapy" network. In addition to increasing the identification of target combinations by anchoring them to clinically validated therapies, this cross combined platform will support the rational design of biomarkers-directed combinations therapies, which ultimately will advance the targetome-precision combination therapies.

Additional intra-family pairs (e.g., carbonic anhydrase isoforms[135–137], vasopressin receptor subfamilies[138–140], muscarinic

receptor subfamilies[141–144]) and immune surface marker pairings[145–148] show mechanistic plausibility across diverse therapeutic areas, both in malignant and non-malignant disorders.

Future perspective

Underinvested but biologically plausible classes should be studied through structural biology, ligand activity measurements and the development of probes. To further justify the notion that these targets are underinvested and yet biologically plausible, three essential strategies might be considered in future research and database integration that include: bibliometric measurements to compare levels of published studies, citations and distribution of research institution of these targets against dominant classes (e.g. GPCRs and kinases) by PubMed or Web of science; clinical pipelines measures can be used to measure distribution of drugs across preclinical and clinical development; and database derived measures can combine measures of target druggability, probe quality and preclinical efficacy (e.g., *in vivo* tumor growth inhibition rates) to confirm that these targets which lack sufficient translational support have actual comparable biological potential to well-invested classes. Such attempts should use fragment-based screening[149,150], DNA-encoded libraries[151,152], cryo-EM[153,154], Alpha Fold, and phenotypic assays[155,156]. The excellent quality of the probes[157] will reduce the risk of downstream research programs and validate therapeutic hypotheses. There is a high translational potential of the mRNA/oligonucleotide targets, the tissue-targeted delivery[158–160] systems, chemistry to reduce the immunogenicity[161–163], and the evaluation of the safety of the chronic administration[164,165] should be studied. Design of CNS multi-target single-molecule agents[166–169], combinations that can regulate the activity of NET/SERT/DAT[70–79] and HTR2A-D2R[84–87] are possible. Selective multi-kinase inhibitors or biomarker-directed combinations based on EGFR/HER2/KIT/KDR[111–114,118–121] clusters can be engineered which can overcome anticancer resistance in tumors[170,171]. Dual-target antibiotics[92–96] (e.g., bacterial DNA gyrase and *Staphylococcus* topoisomerase IV) has been adopted as a combination practice to overcome antibiotic resistance. JAK-centric combinations[108–110] in preclinical stages could be investigated to show the regions of synergy and safety of immunomodulation. Initiating clinical combination regimens can be done with high-frequency co-occurrence pairs combining preclinical screening, and combinations with already well-established safety profiles can be considered first, which ultimately can reduce the time and cost of clinical translation.

Although TTD is significant, the research community needs more interactive, interoperable targetome data resource with indication level mappings (e.g., line of therapy and patient subgroup); quantitative polypharmacology metadata (e.g., potency and exposure-adjusted potency such as Ki, IC_{50} values, engagement ratio of each target and combination target selectivity); annotations of clinical outcome and safety data (e.g., trial endpoints, phase transitions, reasons why some treatments can fail); metadata on chemical/probe quality and structure-activity relationship (e.g., GWAS findings, somatic mutation prevalence, RNA expression levels, CRISPR results); curated records of negative or failed combination therapies including specific failure cases (such as side effects of antidepressant drugs which are associated with their blockade of the SERT, NET, and DAT[172]); and open data sharing. Notably, future drug-target databases ought to incorporate the capability of resources by target synergy i.e. SynLethDB[131,132]. which provides a Statistic Score which differentiates positive SL interactions over negative pairs, a crucial gap in the current drug-target database in terms of genetic understanding. This complements the drug-driven co-occurrence data analyzed in our perspective. Integrating SL data ensures a comprehensive representation of drug combinations. Modernized databases can provide a more comprehensive risk-benefit assessment framework for researchers through incorporating parameters like Statistic Score in SynLethDB[131,132], thereby reducing translational failure rates and accelerating the development of safe and effective drug combinations. And efforts should be put into the curation and sustainability of dynamic targetome databases[173–175].

In dealing with gap in the technology of database construction, there is a need to consider the incorporation of superior data integration modalities and standard mapping of terminologies in the elegization of targetome-related databases[176–178]. Intersection of heterogeneity in the context of multi-source data (e.g. clinical records, omics data and drug information) can be addressed by leveraging semantic interoperability protocols (e.g., Unified Medical Language System (UMLS)[179] to cross-align terms) and privacy-preserving record linkage (PPRL) methods[180,181]. Automated data validation pipelines (e.g. rule-based cheques to maintain consistency of coding, e.g. MedDRA to classify adverse events) can reduce manual curation errors, and improve data quality[182,183]. Also, using modular database structures, with dynamic schema designs (e.g. graph databases to capture target-drug-pathway relationships), enables updates of new data (e.g. SL pairs, polypharmacology profiles) and ensure complex querying to answer polypharmacology studies[184]. Incorporation of these technical features will enhance the efficiency, scalability as well as utility of targetome databases, allowing more accurate combination therapy to be designed[185].

This perspective analysis is based on the number of classes, approved drug density, and co-occurrence frequency trends. These measures should be validated experimentally and they cannot be substituted with genetic evidence, intensive efficacy data and safety profiles.

Our current TTD-driven targetome analysis confirms GPCRs and kinases as dominant translational classes, mRNA modalities as high-yield emerging therapies, and oxidoreductases, carbonic anhydrase isoforms, and specific transporters as underinvested, but biologically plausible opportunities, and we also show common drug driven co-occurrence targets which offer potential combination translation. To translate these insights into precision medicine, future databases must prioritize integration of multi-dimensional data (specific clinical details, quantitative polypharmacology

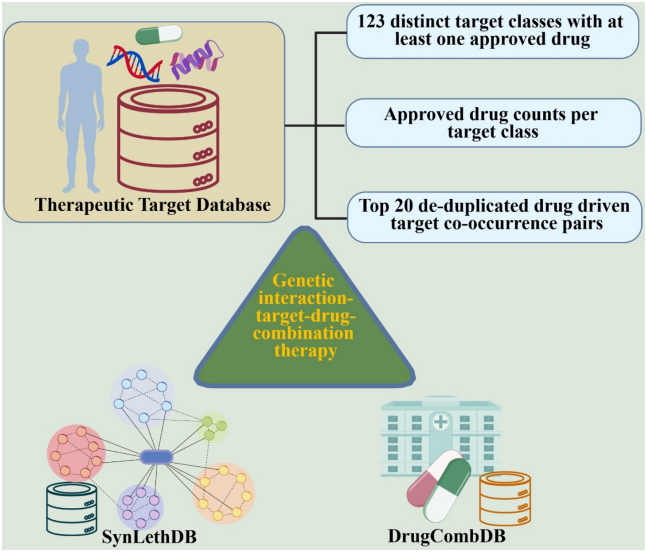

Fig. 2 Data-driven targetome discovery and databases.

metrics, functional genomics data, and curated negative/failure records), achieving cross-database interoperability (linking TTD's drug-target associations with SynLethDB's synthetic lethality pairs and DrugCombDB's clinical combinations via "drug-gene" metadata), and implementing provenance tracking and realizing open data sharing, and ultimately creating a comprehensive "genetic interaction-target-drug-combination therapy" network, as shown in Fig. 2, that facilitates combination therapies and reduces translational risk.

Ethical statements

Not applicable.

Author contributions

The authors confirm contributions to the paper as follows: study conception and design: Shan W, Xu J, Assaraf YG; draft manuscript preparation: Shan W, Xu J, Assaraf YG; manuscript revision: Xu J, Assaraf YG. All authors reviewed the results and approved the final version of the manuscript.

Data availability

All datasets in this perspective can be downloaded from https://zenodo.org/records/17453242.

Acknowledgments

Not applicable.

Conflict of interest

The authors declare that they have no conflict of interest.

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