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Database issue

DrugMAP 2.0: molecular atlas and pharma-information of all drugs

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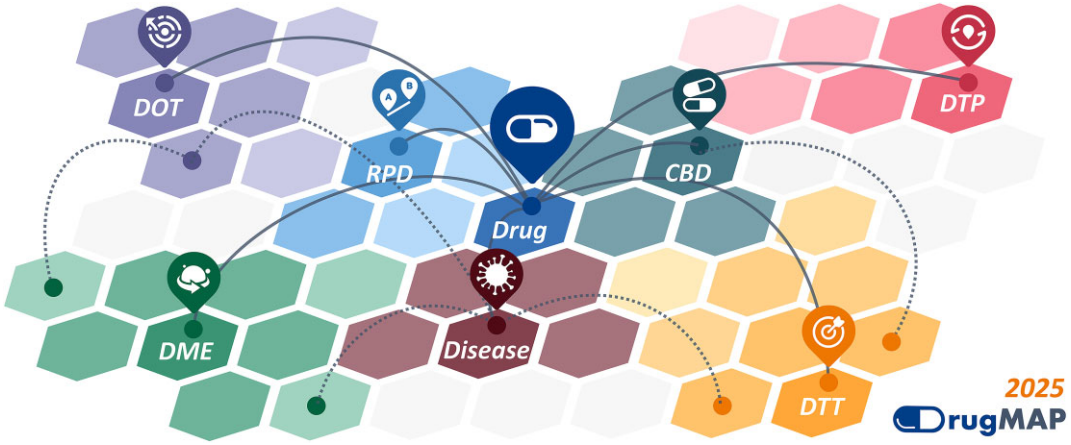
Abstract

The escalating costs and high failure rates have decelerated the pace of drug development, which amplifies the research interests in developing combinatorial/repurposed drugs and understanding off-target adverse drug reaction (ADR). In other words, it is demanded to delineate the molecular atlas and pharma-information for the combinatorial/repurposed drugs and off-target interactions. However, such invaluable data were inadequately covered by existing databases. In this study, a major update was thus conducted to the *DrugMAP*, which accumulated (a) 20831 combinatorial drugs and their interacting atlas involving 1583 pharmacologically important molecules; (b) 842 repurposed drugs and their interacting atlas with 795 molecules; (c) 3260 off-targets relevant to the ADRs of 2731 drugs and (d) various types of pharmaceutical information, including diverse ADMET properties, versatile diseases, and various ADRs/off-targets. With the growing demands for discovering combinatorial/repurposed therapies and the rapidly emerging interest in AI-based drug discovery, DrugMAP was highly expected to act as an indispensable supplement to existing databases facilitating drug discovery, which was accessible at: https://idrblab.org/drugmap/.

Graphical abstract



Introduction

The efficacy and safety of a drug are substantially determined by its pharmaceutical properties and interactions with various pharmacologically important molecules (1–3). *DrugMAP* database was therefore constructed to describe the molecular atlas and pharma-information for >30 000 unique

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molecular entities (4). The emergence of acquired drug resistance has amplified the need for new therapeutics, which is challenged by the rising costs and failure rates in drug discovery (5–7). In this context, there are great research interests in the discovery of combinatorial therapies (8–10), realization of drug repurposing (11–13), and explanation of off-target adverse drug reactions (14–16), which highlights the demands for the invaluable molecular atlas and pharma-information of drug combinations, repurposed drugs and ADR-associated off-targets (17–19). Furthermore, with the booming applications of artificial intelligence (AI) in biomedical research (20–23), it is essential to have a knowledge base accumulating a large number of the precious data discussed above to facilitate cutting-edge academic/clinical studies in precision medicine, drug discovery, and so on (24–26).

Till now, several reputable data repositories related to the aforementioned topic have been developed. Some describe the general information and the high-throughput cell line screening result for drug combination, including CDCDB (27), DCDB (28), DrugCombDB (29), SYNERGxDB (30), etc. Some others demonstrate the information on various adverse drug reactions (ADRs) together with their frequency in patients, including DrugCentral (31), SIDER (32), FAERS (33), etc. However, none of the existing databases provides the interacting atlas of either combinatorial or repurposed drugs at the molecular level, and the detailed pharma-information of these drugs is largely absent from these databases. Moreover, the molecular mechanism (especially, the off-target information of the studied drug) underlying each ADR has not been described by any of those available databases (including the original version of *DrugMAP*). Therefore, it is highly demanded to have a database providing the molecular biological data for the combinatorial/repurposed drugs and ADR-related off-targets, which can promote the discovery of efficacious combinatorial/repurposed drugs (34–36) and the understanding of the off-target mechanism underlying studied ADRs (37–39).

Herein, a major update to *DrugMAP* was therefore conducted, which is described in Figure 1. First, a total of 22039 combinatorial drugs (CBDs), including 583 approved, 4817 clinical trials, and 16639 investigative ones, were collected, and their interacting atlases with 1583 molecules of clinical importance were provided. Second, a total of 842 repurposed drugs (RPDs) that were approved for treating one disease and then repurposed (approved/clinical trial/investigative) for dealing with other disease(s) were accumulated, and their interacting atlases with 795 molecules were also offered. Third, a total of 3260 off-targets (DOTs) of literature-reported ADR for 2731 drugs, including 1437 approved, 410 clinical trial, and 884 investigative ones, were also covered, and their corresponding molecular atlas was described. Finally, diverse pharma-information was added during this update, which included: (a) diverse ADMET(absorption, distribution, metabolism, excretion, and toxicity) properties, such as bioavailability, *Lipinski* Role of 5 (RO5) violation, half-life, clearance, elimination, and distribution; (b) versatile disease webpages illustrating disease hierarchy based on ICD of *World Health Organization*, and MONDO of *U.S. National Institute of Health* and (c) comprehensive data on the ADR and ADR-related off-targets for each drug. The latest version of *DrugMAP* can be freely accessed without any login requirement by all users at: https://idrblab.org/drugmap/.

Factual content and data retrieval

Describing the molecular atlas and pharma-information for combinatorial drugs

The use of combinatorial drug, which involves the co-administration of multiple agents targeting different pathways, can extensively elevate therapeutic efficacy (40), reduce dosage requirement (41), and delay the onset of resistance (42). This approach has become a standard clinical strategy for treating multifactorial disease that involves multiple pathways, like cancer (43), autoimmune (44) and cardiovascular conditions (45). However, the large space of possible drug combinations and the high costs and resources required to test these therapeutic strategies in clinical trial, make it impractical to experimentally assess all possible combinations (46). Moreover, the overlapping toxicity of drug combinations and drug-drug interactions were common problems currently faced in discovering combinatorial therapies (47,48). Therefore, there was an urgent need to depict the molecular interaction networks between different component drugs in a drug combination to systematically evaluate the pharmacokinetic/pharmacodynamic process (49–51) and balance the toxicity and synergistic benefits (52–54). To bridge the gaps, various combinatorial drugs as well as their interacting atlas were collected and normalized based on different data resources.

Systematic collection of approved and clinical trial drug combinations

The drug combinations approved by the U.S. FDA are definitely supported by successful clinical trial data (55), while those that have been or are currently being tested in clinical trials must also have enough experimental evidence to justify their applications. These drug combinations were systematically curated for *DrugMAP* using the following procedures. First, a comprehensive list of approved drug products was obtained from the FDA Orange Book. All drug combinations were filtered according to the types of ingredients, dosage forms, routes of administration, and strengths, finally resulting in a total of 583 approved combinations. Second, the search for combinatorial drugs in clinical trial was performed based on ClinicalTrials.gov by systematically screening the fields of '*official title of study*', '*intervention*', and '*condition/disease*', leading to the retrievals of 5236 combinatorial drugs and their NCT IDs. Third, the retrieved combinations were refined based on the names of the components as well as the disease indications, leading to 583 approved and 4817 clinical trial combinations.

Investigative drug combinations identified by comprehensive literature review

In addition to those drug combinations catalogued by the U.S. Food and Drug Administration (U.S. FDA) and ClinicalTrials.gov, numerous investigational combinations identified using high/low-throughput biochemical assays have been reported in scientific literature (56–60). To further expand the coverage of drug combinations in *DrugMAP*, investigative combinations were systematically collected by the following procedure. First, a systematic literature review was conducted using diverse keywords such as 'combinatorial drug', 'drug combination' and 'combinatorial therapy'. Second, the drug combinations of clearly reported therapeutic effects were

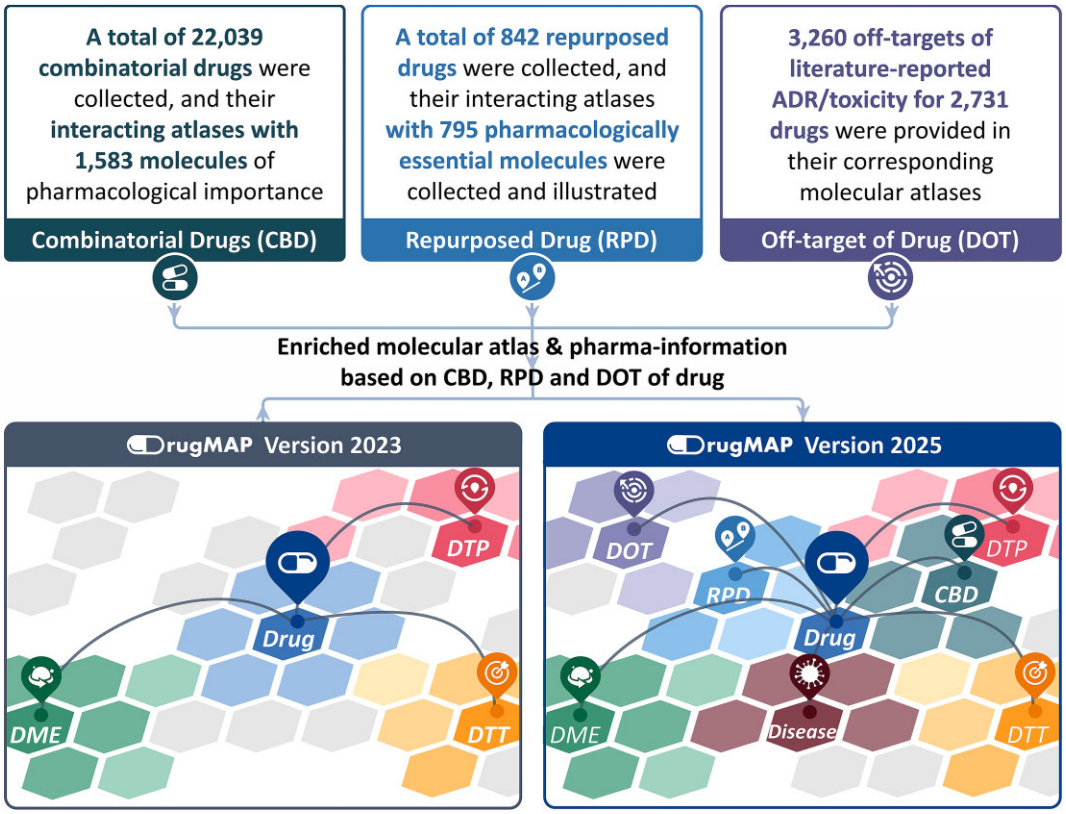

Figure 1. An overview of this update of *DrugMAP*. In previous version, the molecular atlas was primarily composed of the pharmacokinetic data of medications (*blue*) and their interactions with three types of molecules: drug therapeutic target (DTT, *orange*), drug transporter (DTP, *red*), and drug-metabolizing enzyme (DME, *green*). In current version, *DrugMAP* was integrated with the combinatorial drug (CBD, *strongblue*), repurposed drug (RPD, *skyblue*), off-target effect of drug (DOT, *purple*) and disease (*brown*) information for all drugs.

manually collected from the literature, and the biochemical assays were recorded. Third, based on the dose-response landscapes of biochemical assays, quantitative synergy scores were calculated using a variety of models, including the *Highest Single Agent*, *Loewe additivity*, *Bliss independence* and *Zero Interaction Potency* (61). The synergy score was normalized using Min-Max Scaling and visualized with unified heatmaps (as illustrated in Figure 2B). Finally, the interacting atlas of all CBDs were mapped and provided based on the molecular interactions of component drugs (as shown in Figure 2C).

Describing the molecular atlas and pharma-information for repurposed drugs

Drug repurposing that identifies new therapeutic use for existing drugs, holds significant promise in accelerating the drug developments process and reducing associated costs and timeframes (62). This strategy leverages the known safety profile and pharmacokinetic property of approved drugs (63,64), thus circumventing the initial stages of drug development that involve substantial time and financial resources (65). However, the discovery of repurposed drugs is greatly challenged by various potential therapeutic targets and unclear disease mechanisms (66–68). Moreover, the repurposed drugs must be comprehensively evaluated using interaction networks among multiple diseases (69), to mitigate the risks of unforeseen ADRs and interactions (70). Thus, the molecular atlas of existing repurposed drugs can facilitate the discovery of new ones.

Confirming and collecting the information of repurposed drugs and diseases

The information on repurposed drugs and their disease was collected and confirmed through the following steps. First, drug indications in *DrugMAP* are comprehensively reviewed, and the list of drugs treating multiple diseases was collected. Second, these drugs were then strictly screened and de-emphasized based on the disease class and the ICD-11 code (the first two digits) to ensure that the remaining drugs were the repurposed ones. Third, keyword combination of 'drug reposition', 'drug repurposing', and 'repurposed drug' was adopted in literature review, to fill the vacancy of repurposed drugs that were not covered by *DrugMAP*. Finally, the repositioning profiles of 842 approved drugs were collected and shown, and a total of 3272 drugs that were tested for multiple diseases in clinical trial were also described. A list of repurposed diseases and the molecular atlas of studied repurposed drugs were provided on a separate webpage (as shown in Figure 3A).

Ontology mapping and enriched molecule atlas of repurposed disease

Disease was undoubtedly a crucial part of drug repositioning (71). Therefore, diseases were added as one of the key nodes into *DrugMAP*, which substantially enriched the molecular atlas together with disease-molecule association. First, disease ontologies were mapped to available databases, such as Orphanet (72), MedGen (73), and HPO (74), through text mining and keyword matching. Second, the literature-reported

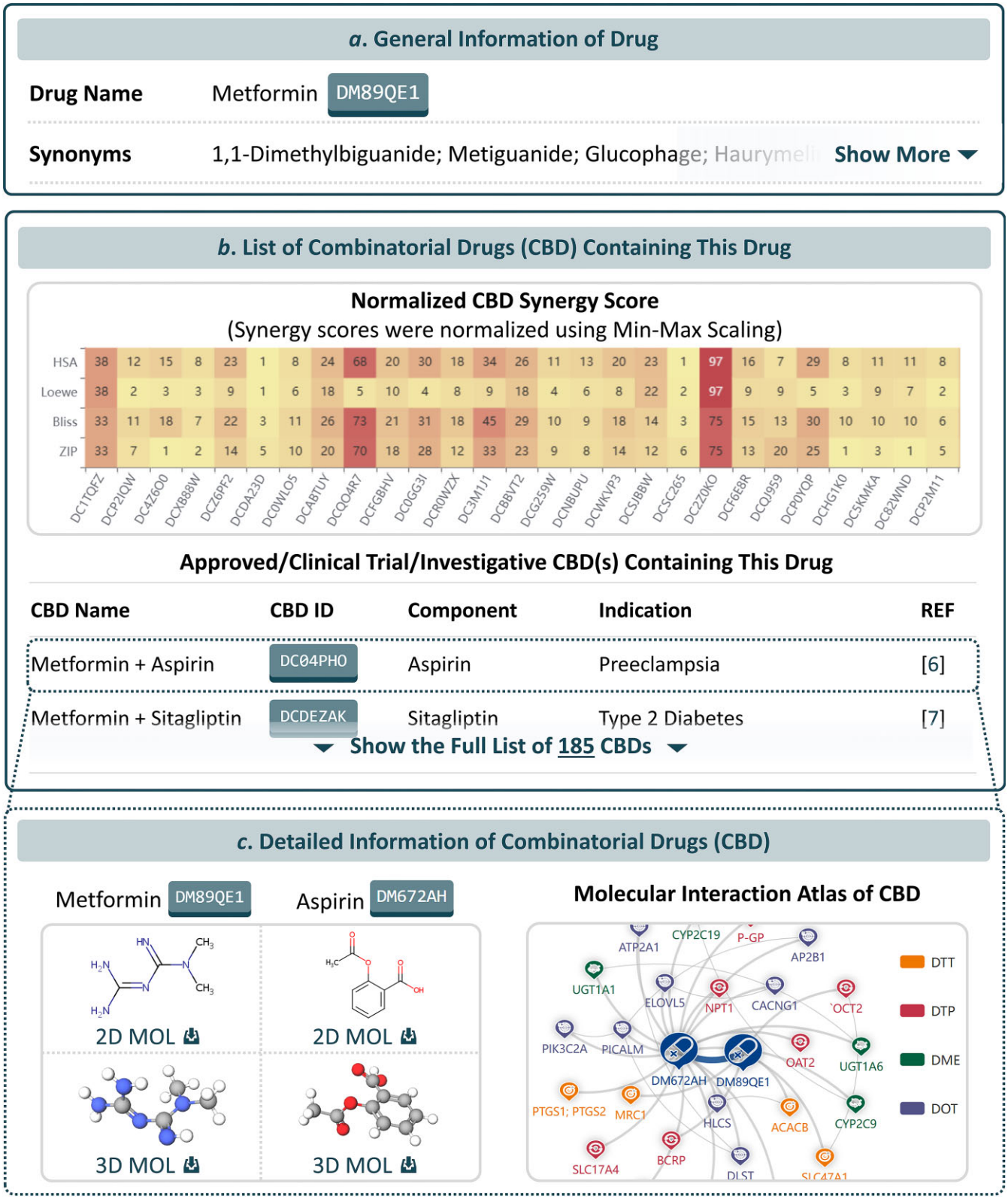

Figure 2. A typical CBD page showing combinatorial drug in *DrugMAP*. (**A**) general information of drug, such as drug name, synonyms and therapeutic class; (**B**) the list of CBDs containing this drug, at the top of this module, a heatmap of the normalized CBD synergy score is provided, the color of which was determined by the synergy score calculated from the HSA, Loewe, Bliss and ZIP models normalized via Min-Max Scaling; (**C**) detailed CBD page, opened by clicking on the CBD ID, provided details on the molecular atlas and the structures of the constituent drugs.

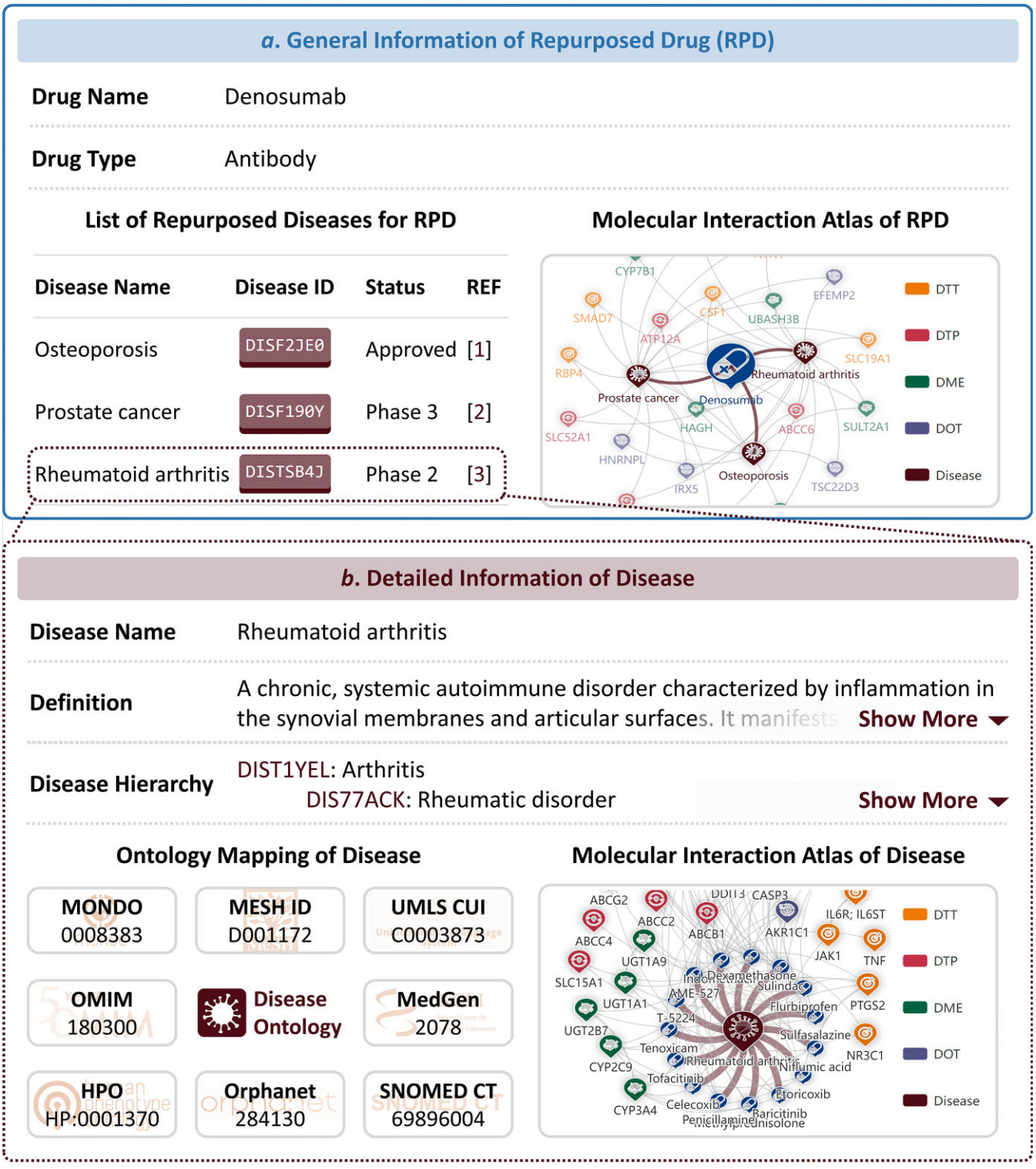

Figure 3. A schematic illustration of repurposed drugs (RPD) and disease page in *DrugMAP*. (**A**) a typical RPD page provided the general information of drugs, and illustrated a list of repurposed diseases as well as the molecular atlas of RPD consisting of repurposed drugs; (**B**) a disease page, accessed by clicking on disease ID, which not only provided the name, definitions, and hierarchy of disease, but also described information about the mapping of the disease ontology to reputable existing databases. The molecular interaction atlas of the disease was also provided.

associations between disease and proteins were also curated from multiple resources, such as GenCC (44), DisGeNET (75) and KEGG (76), and further integrated into the molecular atlas of repurposed drug. Each association between diseases and proteins was determined by considering multiple factors, including data sources, expert assessment, the quantity and quality of supporting literature, and the presence of conflicting results. These factors work together to help researchers assess the credibility and clinical relevance of gene-disease associations. Third, the protein-protein interactions related to the *DrugMAP* molecules were collected to enrich the molecule atlas of repurposed drug. The disease information (such as disease name, definition, hierarchy, ontology mapping, and interacting atlas) was also provided on a separate webpage for disease (as illustrated in Figure 3B).

Associating off-targets with the literature-reported ADRs for all drugs

The primary factors contributing to the failure/withdrawal of drug were low drug availability and undesirable off-target toxicity (77–80). Surprisingly, recent research has illuminated the facts that part of 'unintended' off-targets could actually hold great potential to be unexplored disease target (81). This highlighted the necessity of capitalizing on the broad target selectivity of drugs and harnessing beneficial off-target effects (82). In other words, the valuable information on the ADRs of drugs and their associated off-targets would provide strong support for the discovery of novel therapeutic targets and the avoidance of undesirable adverse drug reactions (83–85).

The data of ADR-related off-targets for drugs in *DrugMAP* was collected and confirmed through the following steps. First, literature was retrieved from PubMed using keyword combinations of 'drug name' + toxicity, 'drug name' + off-target, 'drug name' + ADR, 'drug name' + adverse reaction, 'drug name' + side effect, etc. Second, the newly identified studies were systematically validated, and reliable interactions were extracted. Primary off-targets responsible for literature-reported ADRs were then collected into *DrugMAP* as drug off-targets (DOTs). Third, off-targets influencing their own post-translational modification, biochemical pathway, and cellular process through interactions with drugs were also collected. As a result, a total of 3260 DOTs associated with literature-reported ADR for 2731 drugs (including 1437 approved, 410 in clinical trials and 884 investigative) were compiled. Moreover, 15 126 DOTs with a clearly defined mode of action were included. Comprehensive information on these DOTs, including their functions, structures, and associated pathways, was provided on a separate webpage for DOTs (as illustrated in Figure 4A). The corresponding molecular atlases are also presented (as shown in Figure 4B).

Systematical and in-depth update of the pharma-information for all drugs

A variety of emerging drugs were systematically integrated into the latest *DrugMAP*. First, drugs approved during the past two years (*DrugMAP* was first released in 2023) were manually curated from recent official reports (86,87). Second, the latest information on clinical trial drugs together with their clinical status was gathered and updated using timely data from *ClinicalTrials.gov* and official *drug pipeline reports* from numerous pharmaceutical companies, such as Pfizer, AbbVie, and Novartis. Third, for each drug, detailed information on its interacting molecules was further compiled. As a result, the number of drugs collected to *DrugMAP* had expanded from 32487 to 42909, and the number of drug-interacting molecules had increased from 5788 to 9172.

Furthermore, the additional pharma-information of drug was significantly enriched in this update. Specifically, the RO5 violations for drugs were confirmed using the PubChem (88) database and visualized using a radar chart to facilitate quick overview. The ADMET (absorption, distribution, metabolism, excretion and toxicity) characteristics of drugs had also been substantially enriched (89). Particularly, a total of 15 ADME characteristics (bioavailability, metabolism, clearance, elimination, half-life, etc.) had been made available in *DrugMAP*, encompassing a total of 12 729 ADMET data for drugs. Additionally, comprehensive information on ADRs and ADR-associated off-targets had been integrated into the enriched drug pharma-information. Detailed descriptions of the general and pharma-information of drugs in *DrugMAP* were illustrated in Figure 5.

Conclusion and Perspectives

The *DrugMAP* has been previously developed to provide comprehensive and accurate molecular atlas for all drugs. With the growing research interest in drug combinations and repurposing and the exponential growth of AI techniques in the field of drug discovery, the molecular atlas of combinatorial/repurposed drugs provided in the latest *DrugMAP* offered valuable 'interacting network' data resources for researchers to explore potential drug combinations and identify repurposing opportunities at the molecular and network levels, and the integration of drug-centred molecular interaction networks offered by DrugMAP could also enable researchers to gain insights into the complex interactions between drugs, diseases and molecular entities. By leveraging this extensive network, AI algorithms and models can more effectively analyze and predict the interactions, synergistic effects and potential repurposing opportunities of drugs, ultimately enhancing the efficiency and success rates of drug discovery endeavors. For instance, some studies have successfully applied the executable signaling network model to predict novel combinatorial drugs for treating COVID-19 (90), and some others have constructed AI tools to discover potential repurposing and combinatorial drug for Alzheimer's disease (91). Due to the great demand for interacting networks in drug combination and repositioning (92–94), the *DrugMAP* further expanded the richness and availability of the molecular atlas by introducing various additional nodes of CBDs, RPDs, DOTs and diseases, which was expected to provide insights for the development of novel combinatorial therapeutics and drug repositioning strategies at the molecular and network level (95–97).

The pharma-information for all drugs in *DrugMAP* was crucial for drug developments. Therefore, *DrugMAP* was committed to keep updating and enriching its pharma-information. In this update, some of the key enhancements included the visualization of RO5 violation and ADMET property of drugs. Newly implemented features explicitly described ADR and ADR-associated off-targets. Furthermore, drug disease information had also been incorporated, providing invaluable insights into target discovery and drug repurposing, which encompassed disease synonyms, classification, definitions, hierarchies, ontology mappings and protein associations and so on so forth.

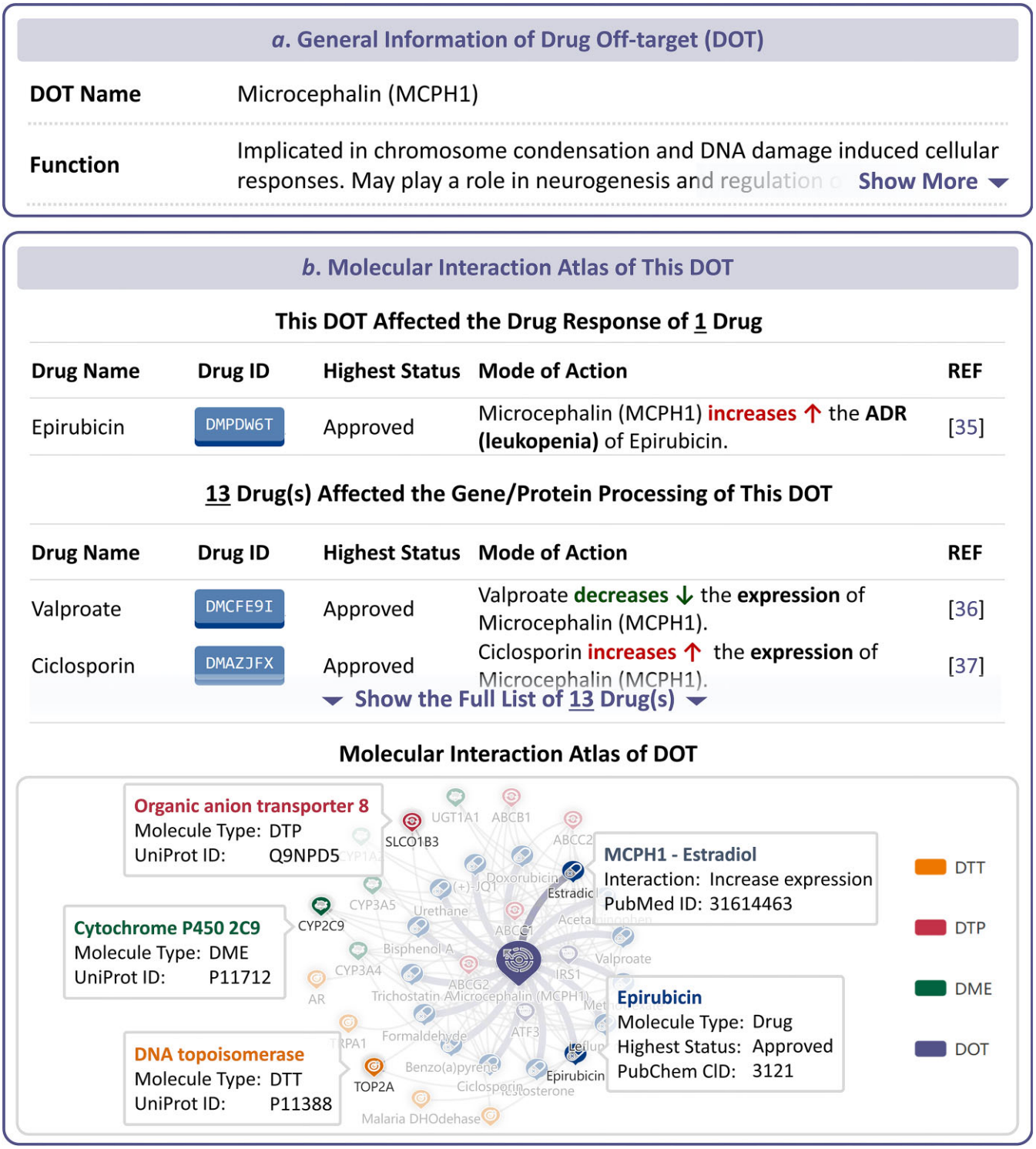

Figure 4. A typical page of the drug's off-target (DOT) in *DrugMAP*. (**A**) the general information of each DOT; (**B**) the molecular atlas module of DOT, which not only provided a detailed list of drugs affected by the DOT and those drugs affecting the DOT and their modes of action, but also provided an interactive interaction network where the user could hover the mouse over the nodes and the interactions to view detailed information about the molecules and interactions.

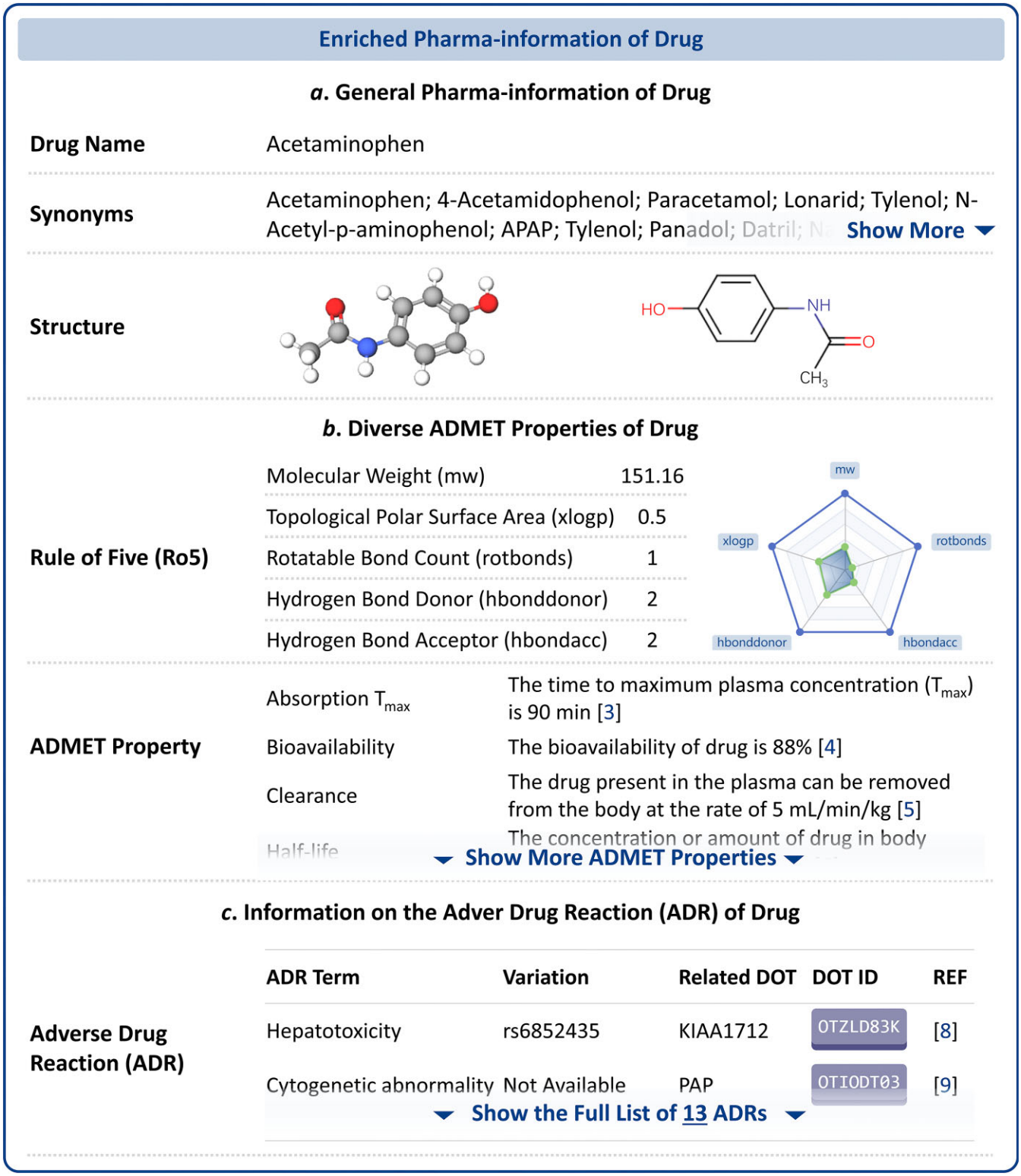

Figure 5. The schematic representation of the enriched pharma-information of drug in *DrugMAP*. (**A**) the general information of a medication, which included drug name, synonym, structure and so on; (**B**) a comprehensive list of diverse ADMET features of the drugs, providing an exhaustive description of the drug's 15 ADMET attributes such as absorption, bioavailability, clearance and so on, along with the corresponding literatures; (**C**) detailed information regarding the ADRs and ADR-associated DOTs of this particular drug.

All in all, considering the growing demand for the discovery of combinatorial therapies and drug repurposing, as well as the rapid developments of AI-assisted drug discovery technologies, drug-centered multimolecular interaction network promised to be an indispensable and important data source. Therefore, *DrugMAP* was expected to continually emerge as a popular data resource, and to serve as an essential supplement to existing pharmaceutical databases. *DrugMAP* is now freely accessible to all users without any login requirement at: https://idrblab.org/drugmap/.

Data availability

DrugMAP is freely accessible to all users without any login requirement at https://idrblab.org/drugmap/.

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Conflict of interest statement

None declared.

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