

DRESIS: the first comprehensive landscape of drug resistance information

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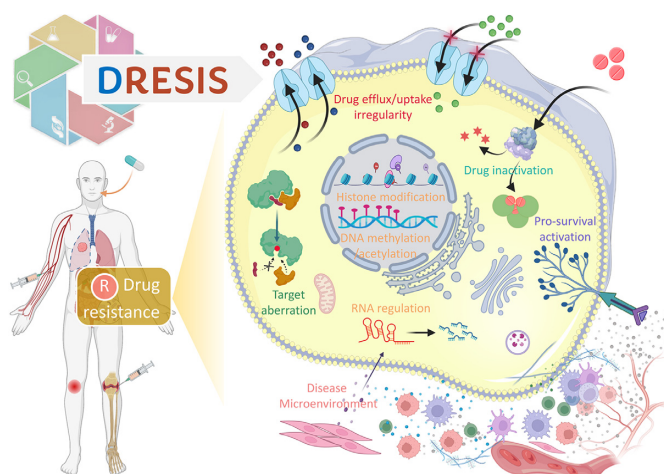
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ABSTRACT

Widespread drug resistance has become the key issue in global healthcare. Extensive efforts have been made to reveal not only diverse diseases experiencing drug resistance, but also the six distinct types of molecular mechanisms underlying this resistance. A database that describes a comprehensive list of diseases with drug resistance (not just cancers/infections) and all types of resistance mechanisms is now urgently needed. However, no such database has been available to date. In this study, a comprehensive database describing drug resistance information named ‘DRESIS’ was therefore developed. It was introduced to (i) systematically provide, for the first time, all existing types of molecular mechanisms underlying drug resistance, (ii) extensively cover the widest range of diseases among all existing databases and (iii) explicitly describe the clinically/experimentally verified resistance data for the largest number of drugs. Since drug resistance has become an ever-increasing clinical issue, DRESIS is expected to have great implications for future new drug discovery and clinical treatment optimization. It is now publicly accessible without any login requirement at: <https://idrblab.org/dresis/>

GRAPHICAL ABSTRACT



A Comprehensive Database for Drug Resistance information

INTRODUCTION

Widespread drug resistance has emerged as a key issue in local/global healthcare, and many regional/worldwide action plans have therefore been set up by both local governments and the World Health Organization (WHO; 1–3). To address such a critical issue, extensive efforts have been devoted to discovering new compounds (e.g. allosteric modulators) (4–7), proposing efficacious drug combinations (8–10) and developing new biotechnology (e.g. PROTAC) (11–13) which effectively overcome the corresponding resistance (14–16). As is known, the success of these efforts is extensively dependent on the thorough understanding of the molecular mechanisms underlying each type of resistance (17–22). Therefore, a large number of studies (>1000 papers per year recorded by PubMed) have been conducted and

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published in recent years to reveal those important mechanisms (23–28)

Among these studies, the aberration in a drug's therapeutic target (e.g. mutation) has been reported as one of the most important mechanisms underlying existing types of resistance (29–32), which inspires researchers to discover alternative therapies that can circumvent this type of mechanism (33,34). However, besides target aberration, additional types of mechanisms have been reported to play key roles (35–38), which, as shown in Figure 1, comprise (i) irregularity in drug uptake and efflux (39), (ii) drug inactivation due to enzymatic modifications (40,41), (iii) epigenetic alteration of DNA, RNA or protein (42–44), (iv) unusual activation of pro-survival pathways (45,46) and (v) regulation by the disease microenvironment (47,48). These five mechanisms are distinct from target aberration, and have thus attracted extensive interest from related research communities (44–50).

Moreover, a particular resistance has also been reported to be made up of multiple mechanism types, which further reminds us about the great complexity of the studied types of resistance (51–54). In other words, before responding to a drug's resistance, it is critical to acquire explicit knowledge of its mechanism(s), and a knowledge base providing all existing types (a total of six types) of mechanism underlying each drug's resistance is therefore greatly required (55–57).

So far, a variety of valuable knowledge bases have been developed to provide drug resistance-related information. These databases describe drug resistance information for certain disease classes, such as cancer [e.g. CancerDR (58), KinaseMD (59)], virus infection [e.g. Stanford HIV Database (60), HBVdb (61)], bacterial infection [e.g. CARD (62), MEGARes (63)] and fungal infection [MARDy (64)]. These databases have attracted widespread interest from research communities (58–71). However, as reported, there are far more diseases suffering from resistance than just cancer/infection (72–76). Moreover, existing databases mainly focus on the mechanisms of target aberration, and none of them describes the five additional types. Thus, a resistance-based database covering various disease classes and diverse types of mechanism is still urgently needed.

Herein, a comprehensive database for drug resistance information named 'DRESIS' was therefore developed. First, a comprehensive literature review was conducted by searching PubMed, which led to >20 000 drugs with clinically/experimentally validated resistance information. Second, the diseases corresponding to resistance to these drugs were manually retrieved from the literature, which, to the best of our knowledge, covered a much wider range of disease classes compared with other available databases. Finally, for all collected drugs, the molecular mechanisms underlying each type of resistance were systematically collected, and the disease- and tissue-specific abundance of the resistance-relevant molecules were analyzed and provided in the DRESIS database.

All in all, the DRESIS database was introduced to (i) systematically provide, for the first time, all existing types of molecular mechanisms underlying drug resistance, (ii) extensively cover the widest range of diseases among all available databases and (iii) explicitly describe

the clinically/experimentally verified resistance data for the largest number of drugs among existing databases. Since drug resistance has become an ever-increasing clinical issue, our DRESIS database (<https://idrblab.org/dresis/>) is expected to have great implications for the future of new drug discovery.

FACTUAL CONTENT AND DATA RETRIEVAL

Systematic collection of the drug resistance information

The drug resistance data provided in DRESIS were collected using the following procedure. First, a large number of drugs were collected from different well-established pharmaceutical databases, which resulted in >2000 approved drugs [collected from the website of the US Food and Drug Administration (FDA)], >9000 drugs in clinical trials [from ClinicalTrial.gov (77) and TTD (78)] and >32 000 pre-clinical/investigative agents [from DrugBank (79), CCNSC (80) and TTD (78)]. Second, the resistance information of these drugs was systematically identified based on a comprehensive literature review in PubMed using the keyword combinations of 'Drug Name + drug resistance', 'Drug Name + susceptibility', 'Drug Name + drug sensitivity', 'Drug Name + drug response', and so on. As a result, a total of 816 FDA-approved, 336 pre-clinical/clinical trials and 19 675 investigative drugs were identified with either clinically reported or *in vivo*/cell line-validated resistance data. Third, the additional information on the corresponding disease for each type of resistance was systematically retrieved from the original publications. All diseases were standardized using the latest WHO International Classification of Diseases [ICD-11 (81)], which resulted in a total of 395 disease classes defined by ICD-11. Moreover, 232 (58.7%) out of the 395 disease classes covered by DRESIS belonged to either cancer or infection, and this result was consistent with our previous understanding that the disease indications suffering from resistance were more extensive than just cancer/infection (72–76). Some of the typical DRESIS diseases (other than cancers and infections) included: Alzheimer's disease, diabetes mellitus, hypertension and Parkinson disease. To the best of our knowledge, the systematic resistance data of these diseases (beyond both cancers and infections) were provided, for the first time, among all existing pharmaceutical knowledge bases.

In the online database, detailed descriptions of the resistance information for each drug were systematically provided. In the webpage of a typical drug 'doxorubicin' (as illustrated in Figure 2), its general pharmaceutical information is described in the upper section, which included: Drug Name, Drug Synonyms, Disease Indications (together with the corresponding Clinical Status of the drug), Drug Structures (downloadable in both 2D and 3D formats), Drug Target and External Linkage to other well-established molecular biological databases such as PubChem (82), DrugBank (79), TTD (83), VARIDT (84) and INTEDE (85). Moreover, the resistance information of the studied drug is explicitly illustrated in the lower section of Figure 2, which describes a list of diseases with reported resistance for the studied drug. For each drug, multiple diseases were usually found with reported resistance, and these diseases were classified according to their types of resistance

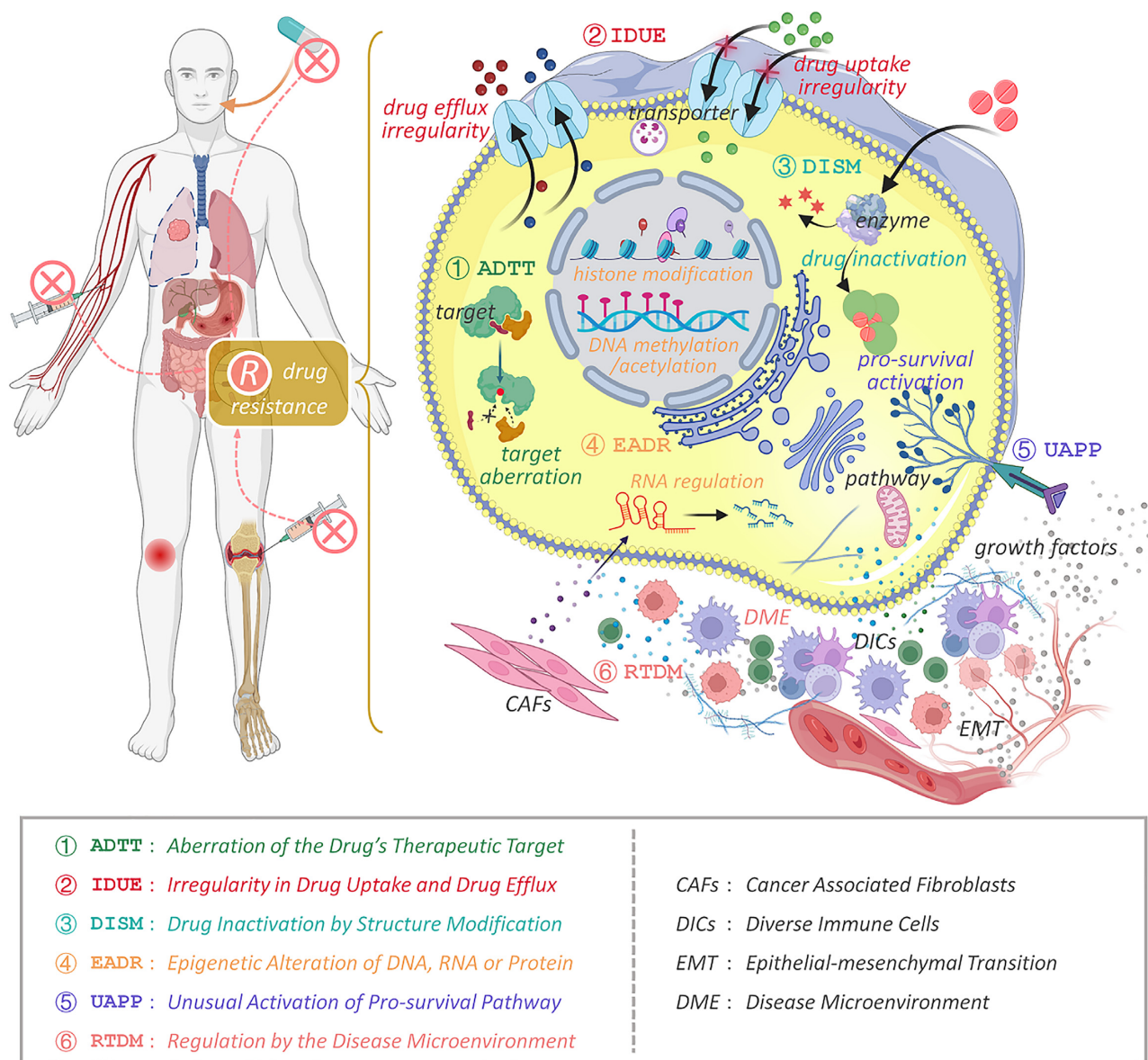


Figure 1. Schematic illustration of the six types of mechanism that are reported to play an essential role in the determination of a drug's resistance. These six mechanism types are: aberration of the drug's therapeutic target (ADTT), irregularity in drug uptake and drug efflux (IDUE), drug inactivation by structure modification (DISM), epigenetic alteration of DNA, RNA and protein (EADR), unusual activation of the pro-survival pathway (UAPP) and regulation by the disease microenvironment (RTDM). The six types of key resistance molecule (indicated using black italic font, i.e. therapeutic target, drug transporter, drug-metabolizing enzyme, epigenetics-related molecule, pathway activator/suppressor and microenvironment regulator) were considered as essential for the mechanisms of ADTT, IDUE, DISM, EADR, UAPP and RTDM, respectively. (The figure was created with Biorender.com.)

evidence (clinically reported, validated by an *in vivo* model or identified using a cell line experiment). All in all, the resistance-based relationships between drugs and diseases were established in DRESIS, and the resulting data were well organized for access and downloading by users.

Diverse types of mechanism underlying drug resistance

Six types of mechanism have been reported to play crucial roles in determining the resistance of drugs (33–36,49). As shown in Figure 1, these six mechanism types are aberration of the drug's therapeutic target (ADTT), irregularity in drug uptake and drug efflux (IDUE), drug inactivation by struc-

ture modification (DISM), epigenetic alteration of DNA, RNA and protein (EADR), unusual activation of the pro-survival pathway (UAPP) and regulation by the disease microenvironment (RTDM). Moreover, the resistance factors key in the six mechanisms were also highlighted in Figure 1 (in black italic font). In particular, six types of key resistance molecules (therapeutic target, drug transporter, drug-metabolizing enzyme, epigenetics-relevant molecule, pathway activator/suppressor and microenvironment regulator) were shown in DRESIS as essential for the mechanisms of ADTT, IDUE, DISM, EADR, UAPP and RTDM, respectively. Based on these mechanisms, new therapeutic strategies were proposed to counteract the existing types of resis-

Drug (ID: DG00109) and It's Reported Resistant Information

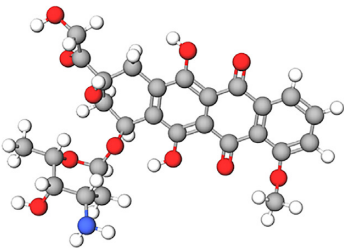
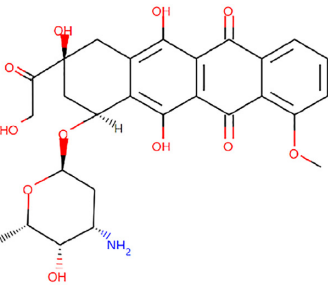
Name	Doxorubicin		
	▼ In total 3 Indication(s)		
Indication	Solid tumour/cancer [ICD-11: 2A00-2F9Z]	Approved	[1]
	Liver cancer [ICD-11: 2C12]	Phase 3	[1]
	Breast cancer [ICD-11: 2C60]	Phase 2	[1]
Structure	 		
	▼ Disease(s) with Clinically Reported Resistance for This Drug (4 diseases)		
Drug Resistance Disease(s)	Brain cancer [ICD-11: 2A00]		[4]
	Acute myeloid leukemia [ICD-11: 2A60]		[5]
	Acute lymphocytic leukemia [ICD-11: 2B33]		[12]
	Pneumonia [ICD-11: CA40]		[29]
	▼ Disease(s) with Resistance Information Discovered by Cell Line Test for This Drug (4 diseases)		
	Gastric cancer [ICD-11: 2B72]		[38]
	Liver cancer [ICD-11: 2C12]		[41]
	Kidney cancer [ICD-11: 2C90]		[47]
Target	DNA topoisomerase II (TOP2)	TOP2A_HUMAN ↗ ; TOP2B_HUMAN ↗	[1]
▶ Click to Show/Hide the Molecular Information and External Link(s) of This Drug			

Figure 2. Detailed descriptions on the resistance information of each drug (using doxorubicin as an example). General pharmaceutical data are provided in the upper section, which includes Drug Name, Drug Synonyms, Disease Indications (together with the corresponding Clinical Status of the drug), Drug Structures (downloadable in both 2D and 3D formats), Drug Target and External Linkage to other molecular biological databases. The resistance information of the studied drug is illustrated in the lower section, which describes a list of diseases with reported resistance for the drug. For a drug, multiple diseases were usually found with reported resistances, and the diseases were classified here according to their types of resistance evidence (clinically reported, validated by an *in vivo* model or identified using a cell line experiment).

tance or to optimize the available regimens for disease treatment (33,35,52,86).

It is known that the resistance of a drug may be extremely complicated, involving multiple mechanism types (87–89). Taking the anticancer drug ‘doxorubicin’ as an example, its resistance in breast cancer was reported to not only originate from the irregularity of its transporter *ABCB1*, but to also stem from the unusual activation of the pro-survival pathway *PI3K/AKT* (90). In other words, the resistance of a drug may be collectively generated by multiple types of mechanisms. Therefore, DRESIS was constructed to provide a unique function of describing multiple types

of resistance mechanism for each of the approved/clinical trial/pre-clinical/investigative drugs.

Describing multiple types of resistance mechanisms for each drug. As shown in Figure 3, an interactive graph was plotted in DRESIS to describe multiple types of resistance mechanisms for each drug, and such data were organized by both mechanism types and disease classes. Taking ‘doxorubicin’ as an example, it has six resistance mechanisms indicated by different colors in the interactive graph. The corresponding resistance diseases are shown under each mechanism, and key resistance molecules are provided for the cor-

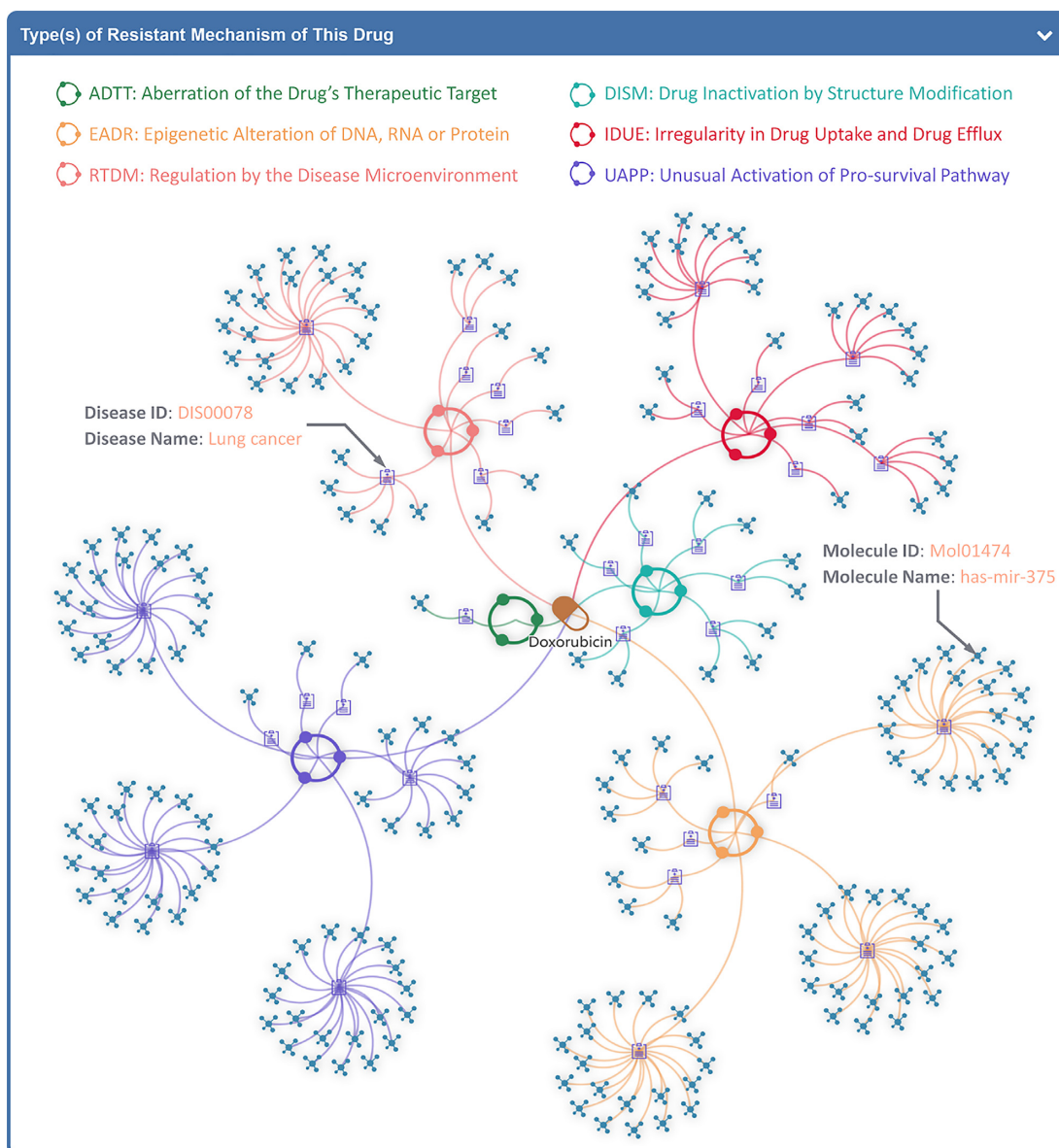


Figure 3. Illustrating the multiple types of resistance mechanisms for the drug doxorubicin using an interactive diagram. The drug is placed in the middle and surrounded by various types of mechanisms (as illustrated on the top of this diagram). Various disease classes were linked to each mechanism type, which were further connected to key resistance molecules (illustrated in outermost leaves). Doxorubicin has six types of resistance mechanisms shown by various colors in the interactive diagram. Resistance diseases are shown under each mechanism, and key resistance molecules are given for the corresponding disease. A comprehensive illustration of resistance mechanisms and resistance diseases is provided for each drug, which can be interactively accessed online.

responding disease. In other words, a comprehensive illustration of both resistance mechanisms and resistance diseases are provided for each drug, which can be interactively accessed online.

Moreover, the detailed resistance mechanisms were also explicitly described in DRESIS (shown in Figure 4). Under a particular mechanism type for a specific disease, the data of key resistance molecules, type of resistance evidence and experimental details were systematically provided and organized in the drug page. A total of 2197 key resistance molecules were identified, and their specific alterations in drug resistance disease were described. Moreover, different types of resistance evidence (such as clinically reported, val-

idated by an *in vivo* model and identified by a cell line experiment) were identified from the literature. A variety of experimental details were also provided, which included diverse experimental techniques [such as MTT assays, flow cytometry assays, disk diffusion methods, quantitative polymerase chain reaction (qPCR), western blotting and luciferase activity assays], hundreds of disease cell lines (such as A459, CaOV3, K562, MCF7 and SNU1) and infectious strains (such as *Klebsiella pneumoniae* KPLA-9, hepatitis C virus H77, *Staphylococcus aureus* RN4565 and *Vibrio cholerae* PG149a), and hundreds of *in vivo* models (such as Sur1 knockout rats, C57/BL6 mice, tumor xenograft mouse and CB17 SCID^{-/-} mouse xenografts). Moreover, the signaling

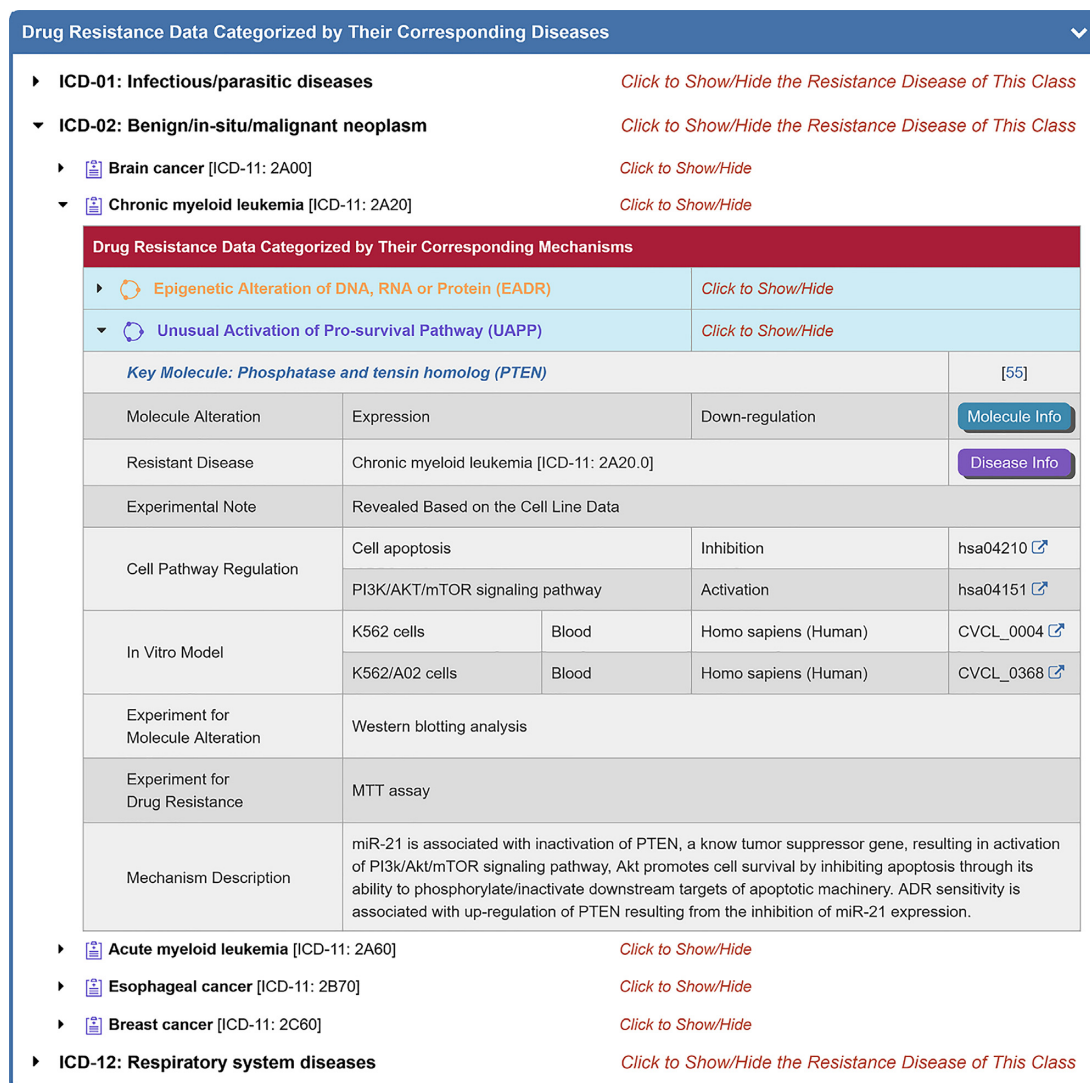


Figure 4. Detailed resistance mechanisms of drug that were categorized according to the disease classes. Under a mechanism type for a specific disease, the data of key resistance molecules, type of resistance evidence and experimental details are systematically shown in a typical drug page. For key resistance molecules, their alterations in resistance disease are described, and different types of resistance evidence (clinically reported, validated by an *in vivo* model or identified by a cell line experiment) were discovered. Various experimental details were described, which included: diverse experimental techniques, hundreds of disease cell lines and infectious strains, hundreds of *in vivo* models and a variety of signaling pathways regulated in the resistance diseases.

pathways (such as MAPK signaling, PI3K/AKT/mTOR, PTEN signaling and cell apoptosis) that were regulated in the resistance diseases were also identified and provided online.

The panorama of resistant drugs for a particular disease

For a specific disease, the resistance of some drugs is, on the one hand, collectively determined by multiple types of mechanisms (87–90). On the other hand, some molecules can also be key for the resistance of multiple drugs (83,91). Therefore, it is of extensive interest to have an overview of the comprehensive lists of both drugs and key resistance molecules for a specific disease. In this study, a panorama of resistant drugs for each disease was collected and systematically described in DRESIS. As illustrated in Figure 5, for the disease ‘breast cancer’, a full list of resistant drugs

was provided using their drug IDs on the vertical axis, and another list of key resistance molecules was shown using the corresponding molecule IDs on the horizontal axis. Due to the huge amount of both drugs and key molecules involved in breast cancer (and also in many other diseases), DRESIS enabled the visualization of the entire panorama through dragging the sliders on both bottom and right sides of the interactive diagram shown in Figure 5. Different types of resistance mechanisms were indicated in the diagram using circles (with the letter ‘R’ in the middle) of different colors. By placing the mouse on any of the circles, the detailed information on mechanism type, resistant drug and key molecule could be interactively viewed. All in all, DRESIS is unique in providing a panorama that enables a full visualization of all drugs and all key molecules in the development of resistance in a disease. Such panorama diagrams are valuable for the audience to have a quick and global under-

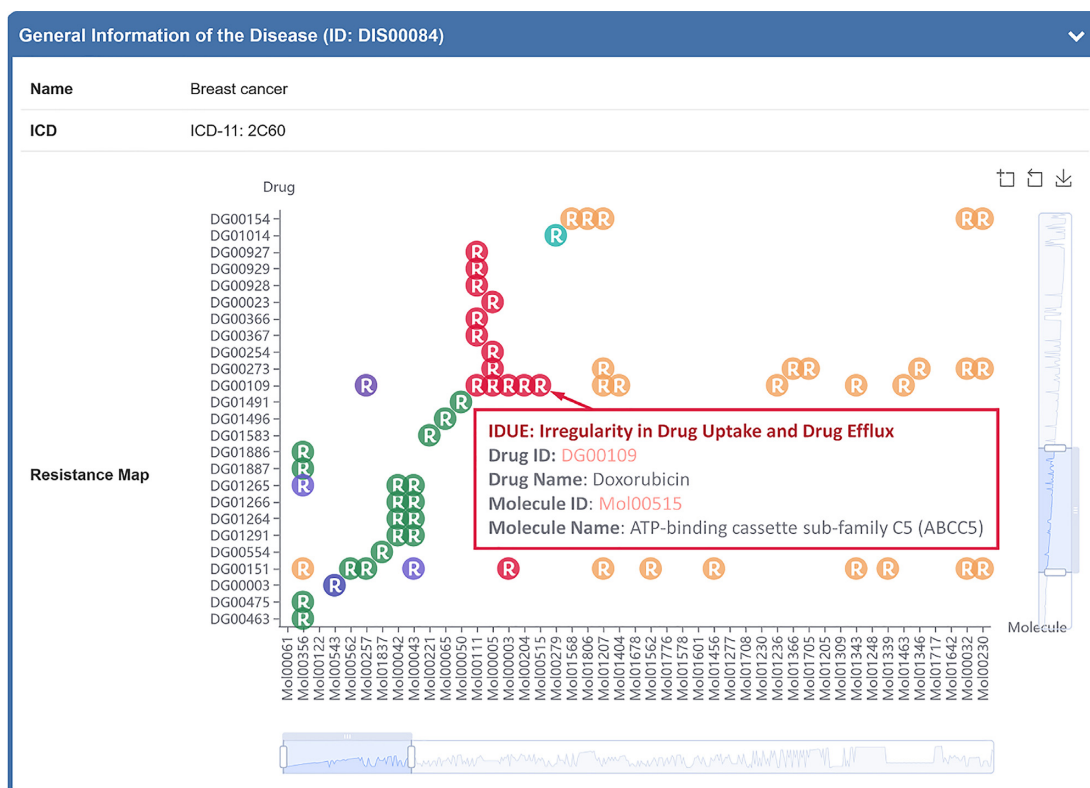


Figure 5. A panorama diagram of resistant drugs for the disease breast cancer in DRESIS. A full list of resistant drugs is provided using the drug IDs on the vertical axis, and another list of key resistance molecules is shown by the molecule IDs on the horizontal axis. Due to the huge amount of both drugs and key molecules involved in breast cancer (also in many other diseases), DRESIS enabled the visualization of the entire panorama through dragging the sliders on both the bottom and right sides of the interactive diagram. Different types of resistance mechanisms are indicated in this diagram using circles (with the letter 'R' in the middle) of different colors. By placing the mouse on any of the circles, the detailed information on mechanism type, resistant drug and key molecule can be interactively viewed. This panorama diagram is valuable for the audience to have a quick and global understanding of the resistance profile for any disease of research interest.

standing on the resistance profile for any disease of research interest.

Besides the panorama diagram, detailed resistance mechanisms were also explicitly described in the disease webpage of DRESIS (illustrated in Figure 6). For any mechanism type of a drug, the data of the key molecule, type of resistance evidence and experimental details were also provided and organized in disease pages. The alterations of key resistance molecules in drug resistance disease and different types of resistance evidence were also provided. Moreover, the experimental details of the applied experimental techniques, disease cell lines, infectious strains, *in vivo* models and the pathways regulating the resistance disease were also collected and provided.

Disease/tissue-specific abundances of resistant molecules

Disease/tissue-specific abundances of different molecules have frequently been reported to determine drug pharmacokinetics (92,93), mitigate adverse drug reactions (94) and greatly affect drug efficacy (95). Since such disease/tissue-specific variations in the newly identified key resistant molecules were expected to inspire new therapeutic strategies (96–100), these data needed to be collected for future analysis. In the latest version of DRESIS, the disease/tissue-dependent abundance data of these key resistance molecules

were therefore systematically collected and illustrated online.

Disease-specific differential expression of the key resistance molecules. For those key resistance proteins, a total of 5535 series records of the raw expression data based on the Affymetrix Human Genome U133 Plus 2.0 Array from the GEO (101) were first collected, and the corresponding tissue and disease information for each series were also identified. Second, by matching with the disease classes provided in DRESIS, a total of 516 series records (covering 63 DRESIS disease classes) were identified for retrieving disease-specific differential expression. Third, all series record data were processed using the well-established R package *affy* (102), and a baseline of the median intensities of protein expression were chosen for conduct normalization. Fourth, Student's *t*-test, fold change and Z-score were adopted to quantify the level of differential expression among sample groups, which included: the samples from the patients' diseased tissue, samples from the normal tissue of healthy people, samples from normal tissue adjacent to disease tissue and samples from tissue other than diseased tissue of patients.

For the key resistance non-coding RNAs (ncRNAs), RNA sequencing data of 9421 tumor and 8589 normal samples were **first** collected from two existing databases, i.e.

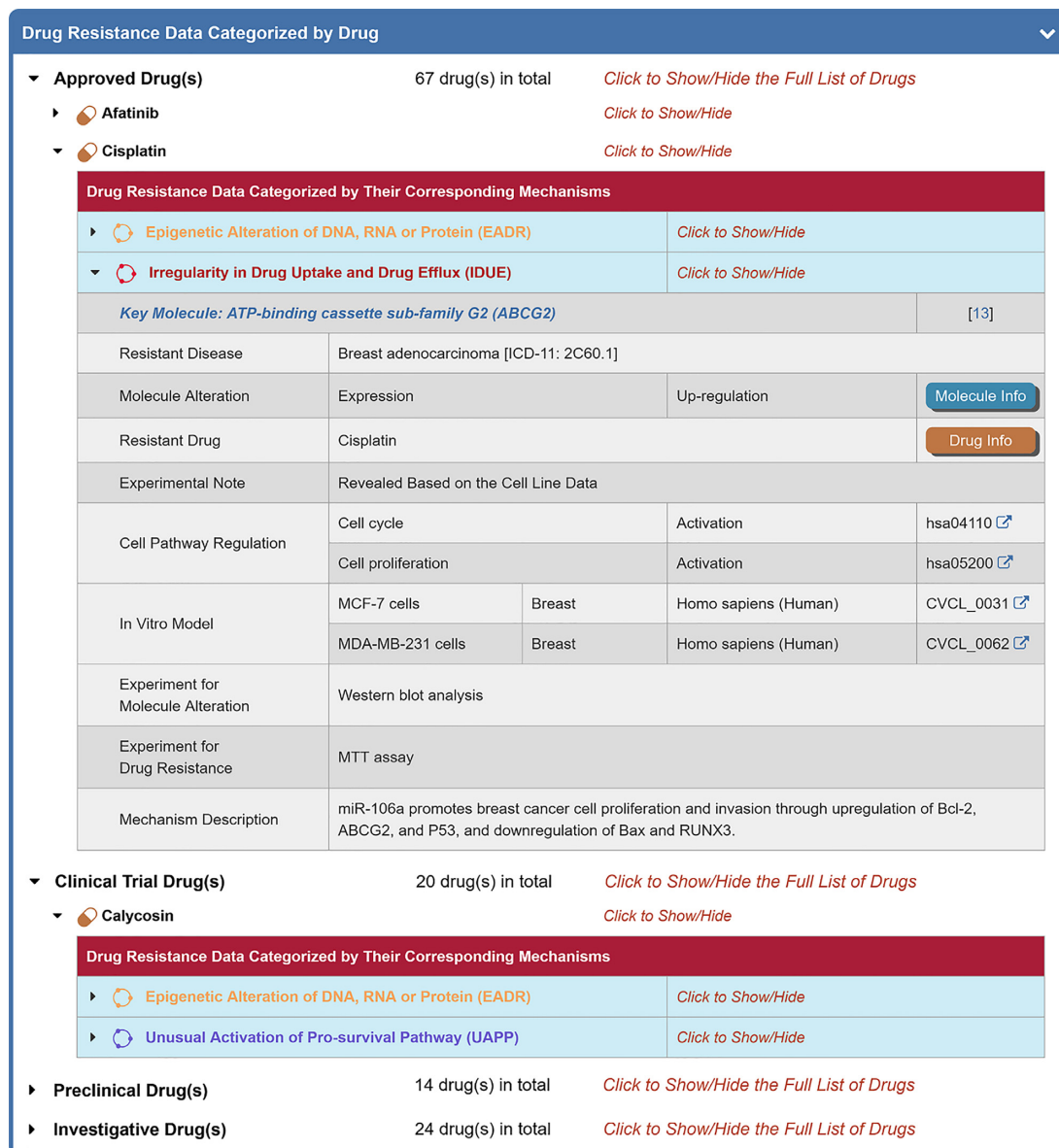


Figure 6. Detailed resistance mechanisms of disease that were categorized according to the drug names. Under each mechanism type for specific drugs, the data of key resistance molecules, type of resistance evidence and experimental details are systematically shown in a typical disease page. For key resistance molecules, their alterations in resistance disease were described, and different types of resistance evidence (clinically reported, validated by an *in vivo* model or identified by a cell line experiment) were discovered. Various experimental details are described, which included: diverse experimental techniques, hundreds of disease cell lines and infectious strains, hundreds of *in vivo* models and a variety of signaling pathways regulated in the resistance diseases.

TCGA (103) and Genotype-Tissue Expression (104). Second, these RNA sequencing data were analyzed using the uniform pipeline from the UCSC Xena project to minimize the variations induced by different sources (105). Third, the abundance variations of those key resistance ncRNAs between patients with the disease and healthy individuals were analyzed using Student's *t*-test, fold change and Z-scores. The differential expression pattern was finally provided in the format of the violin plots in the latest DRESIS (as shown in Figure 7).

Tissue-specific expression variations of the key resistance molecules. For the key resistance proteins, a benchmark (106) was first collected from GEO which contained the

samples across 36 human tissues. Second, for a particular protein, the median of the abundances from multiple samples within the same tissue was calculated and the resulting values were scaled based on a logarithm to the base of two. Finally, bar plots were drawn to illustrate the expression variations of those key resistance proteins among various tissues. For the key resistance ncRNAs, their tissue-specific abundances were also collected. First, a benchmark (105) was first collected from the Genotype-Tissue Expression database which provided 7862 healthy samples across 31 human tissues. Second, for an ncRNA, the median of the RNA abundances from multiple samples of the same tissue was calculated and the resulting values were scaled based on the logarithm to the base of two. Finally, a bar



Figure 7. A typical page in DRESIS that provides the disease-specific expression abundances of the key resistance molecules. The violin plot in the upper part of this diagram shows the disease-specific abundances of a key molecule, and the abundance profiles of a total of 63 disease classes are provided for each key resistance molecule. The abundance variation, Z-score and fold change between groups are described. Red group, key molecules expressed in disease tissue of patients; green group, key molecule expressed in normal tissue of healthy individuals.

plot was drawn to show the tissue-specific abundance variations of those key resistance ncRNAs among various tissues (as shown in Figure 8).

Standardization, access and retrieval of the DRESIS data

To make the access and analysis of DRESIS data convenient for all readers, the collected raw data were carefully cleaned up and then systematically standardized. These standardizations included: (i) all diseases were standardized based on the latest International Classification of Disease that was officially released by the WHO (81); (ii) drugs, proteins, ncRNAs, cell lines, pathways, species and diseases in DRESIS were cross-linked to well-established databases. Second, a user-friendly interface was provided in DRESIS to conveniently browse and search data. DRESIS provides a quick search utility so that users can search the entire DRESIS textual component for drug resistance data in the main search frame or in a pull-down menu. Addition-

ally, ‘Drug structure similarity search’ and ‘Molecule sequence similarity search’ were provided in DRESIS. Users can input the drug structure in the format of SMILES or draw structure to discover the drugs with the same or similar structures that are collected in DRESIS. In the section ‘Molecule sequence similarity search’, users can input the protein/RNA sequence in FASTA format. Finally, all drug resistance data can be viewed, accessed and downloaded from DRESIS, which is freely accessible without a login requirement by all users at: <https://idrblab.org/dresis/>.

CONCLUSION AND PROSPECT

In this study, a database named ‘DRESIS’ was introduced to provide comprehensive resistance information of a large number of drugs. It is unique in systematically providing, for the first time, all existing types of molecular mechanisms underlying drug resistance, extensively covering the widest range of diseases among the existing databases and

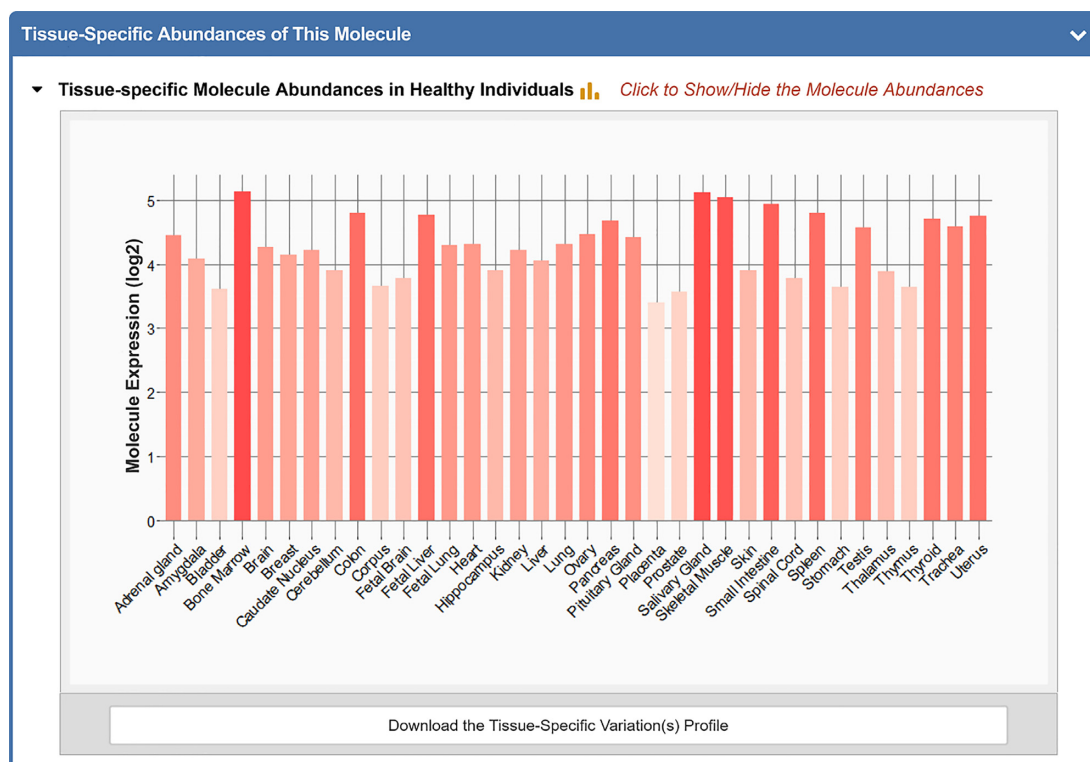


Figure 8. A typical page in DRESIS that provides the tissue-specific expression abundances for key resistance molecules, which was drawn to describe the tissue-specific abundance variations of the key resistance molecules among different tissues. The corresponding expression data were retrieved from two benchmarks previously published in two reputable studies (105,106).

explicitly describing the clinically or experimentally verified resistance data for the largest number of drugs. Since drug resistance has become an ever-increasing clinical issue, there will be an exponentially increasing amount of new drug resistance data derived from patients with different diseases in the future. So, the drug resistance data in DRESIS will be updated in a timely fashion and the web-pages will be regularly improved. Furthermore, more annotation information and practical analysis tools will be added to keep pace with ongoing research. Therefore, this newly constructed database is expected to serve as a timely and valuable resource for understanding of the molecular mechanisms of drug resistance in diverse diseases, which will have great implications for the future practice of new drug discovery.

DATA AVAILABILITY

All drug resistance data can be viewed, accessed and downloaded from DRESIS, which is freely accessible without a login requirement by all users at: <https://idrblab.org/dresis/>.

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