ADCdb: the database of antibody–drug conjugates

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Abstract

Antibody-drug conjugates (ADCs) are a class of innovative biopharmaceutical drugs, which, via their antibody (mAb) component, deliver and release their potent warhead (*a.k.a.* payload) at the disease site, thereby simultaneously improving the efficacy of delivered therapy and reducing its off-target toxicity. To design ADCs of promising efficacy, it is crucial to have the critical data of pharma-information and biological activities for each ADC. However, no such database has been constructed yet. In this study, a database named ADCdb focusing on providing ADC information (especially its pharma-information and biological activities) from multiple perspectives was thus developed. Particularly, a total of 6572 ADCs (359 approved by FDA or in clinical trial pipeline, 501 in preclinical test, 819 with *in-vivo* testing data, 1868 with cell line/target testing data, 3025 without *in-vivo*/cell line/target testing data) together with their explicit pharma-information was collected and provided. Moreover, a total of 9171 literature-reported activities were discovered, which were identified from diverse clinical trial pipelines, model organisms, patient/cell-derived xenograft models, *etc.* Due to the significance of ADCs and their relevant data, this new database was expected to attract broad interests from diverse research fields of current biopharmaceutical drug discovery. The ADCdb is now publicly accessible at: https://idrblab.org/adcdb/.

Graphical abstract
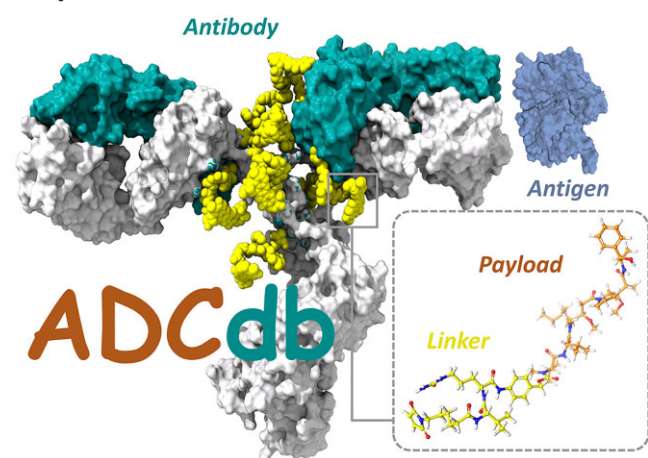
Introduction

Antibody-drug conjugates (ADCs) are a class of innovative biopharmaceutical drugs, which, via their antibody (mAb) component, deliver and release their potent warhead (*a.k.a.* payload) at the disease site, thereby simultaneously improving the efficacy of delivered therapy and reducing its off-target

toxicity (1). ADCs are recently known as 'magic biological missiles' that are expected to open a new era of therapeutic revolution for the targeted anti-cancer therapies (2). As reported, a typical ADC is based on the combination of a **mAb** that is selective to tumor-associated antigen (with the distinctively good biological activity), a **linker** that is stable in blood circulation yet is readily cleavable at the target site, and a **payload** with good biological activity inducing the death of disease cells (3). Moreover, detailed pharma-information of ADCs and their main components (mAb, linker and payload) are of great importance for the modern discovery of biopharmaceutical drugs, which include structures, conjugating type, targeted antigens, therapeutic targets, druglike properties of payload and so on (4). To design the ADC of clinical therapeutic potential, it is key to have those valuable data of biological activity and pharma-information for each ADC.

So far, a variety of knowledgebases have been developed to provide the ADC-related information. Some of them offer the general data of interacting network, disease indication, therapy types for very limited number (<60) of ADCs as part of a broader collection of biological/chemical information, such as Drugs@FDA (5), NCATS Inxights Drugs (6), DrugMAP (7), ChEMBL (8), DrugBank (9) and so on; some others aim at describing the particular components of each ADC, which include (a) those offering mAb moiety, such as: IMGT/mAb-DB (10), Thera-SAbDab (11) and PDB (12), and (b) those showing the physicochemical properties of either linkers or payloads, such as: PubChem (13) and DrugCentral (14). These databases above have attracted considerable attention from the related research communities. However, none of them specializes in providing the biological activity and detailed pharma-information of ADCs, and a knowledgebase that can comprehensively describe such valuable data is therefore highly demanded.

Herein, a database, named 'ADCdb', focusing on describing the biological activities and detailed pharma-information of ADC was therefore developed. *First*, the biological activity of each ADC was collected using a systematic literature review in PubMed, which led to a total of 6572 ADCs (359 approved by FDA or in clinical trial pipelines, 501 in the preclinical tests, 819 with *in-vivo* testing data, 1868 with only cell line/target testing data and 3025 with no *in-vivo*/cell line/target testing information). *Second*, subsequent analyses on the identified ADCs further discovered that, apart from the most popular ADC therapeutic area *cancer*, the ADCs collected to ADCdb covered many additional therapeutic areas, including arthritis, atherosclerosis, bacteremia, HIV infection, *etc.* Moreover, the collected ADCs covered a total of 1168 antibodies, 511 linkers, 447 payloads, 327 antigens and 54 targets. *Third*, a total of 9171 literature-published biological activities were discovered. Particularly, 739 biological activities were identified from 447 clinical trial pipelines; 587 activities were reported based on 270 patient-derived xenograft models; 2013 activities were acquired from 311 cell line-derived xenograft models; 5725 activities were revealed by 737 cell line data; and 107 activities from diverse model organisms. *Finally*, all the ADC data were fully cross-linked to a variety of well-established molecular biology databases, such as DrugMAP (10), ChEMBL (8), DrugBank (9), PubChem (13), TTD (15) and so on. To the best of our knowledge, ADCdb is the first ADC knowledgebase that had ever been developed. Due to the importance of the biological activity and pharma-information of ADC and the severe lack of such valuable data

in existing databases, this new database is highly expected to attract broad research interests from diverse cutting-edge directions of current biopharmaceutical drug discovery. ADCdb is now free and open to all users without login requirement at: https://idrblab.org/adcdb/

Factual content and data retrieval

Systematic collection of antibody–drug conjugate (ADC) information

Explicit pharma-information of antibody–drug conjugates (ADCs) together with their biological activity data were collected by the following procedures. *First*, a comprehensive literature review in diverse official patent organizations (such as *World Intellectual Property Organization*, *United States Patent and Trademark Office*, *European Patent Office* and so on), various R&D pipelines of hundreds of pharmaceutical companies and many literature databases (such as PubMed) was conducted by searching such keywords as 'antibody–drug conjugate', 'ADC', etc. This literature review identified a total of 6572 ADCs (which comprised 359 approved by FDA/in clinical trials, 501 in preclinical tests and 5712 investigative agents). Particularly, a full list of approved ADCs was explicitly described in Table 1. *Second*, the pharma-information of the ADCs, together with their three main components (mAb, linker, payload), were systematically extracted from diverse publications identified based on literature reviews. Such information contained therapeutic class & disease indication (together with the corresponding clinical status), structure, conjugating type, targeted antigen, drug-like properties of payload, etc. *Third*, the biological activity of these ADCs was further retrieved using comprehensive literature review in diverse literature knowledgebases (such as PubMed) based on such keyword combinations as 'antibody–drug conjugate + biological activity', 'ADC name + activity', etc. Furthermore, for patent-protected ADCs, their bioactivity data were collected from both literature review and the corresponding patents. As a result, a total of 9171 biological activities were collected, including 739 from clinical trial, 2707 from *in-vivo* model and 5725 from cell line data. ADCdb covered the most diverse set of pharma-information and biological activities for the largest number of ADCs among all existing databases. Moreover, the disease classes of these collected data were very diverse, which included not only cancer but also many other diseases (such as arthritis, atherosclerosis, bacteremia, HIV infection, etc.).

Explicit description on the pharma-information of each studied ADC

The development of novel ADC was frequently inspired by the valuable pharma-information of the pre-existed ADCs (16–18). Such information included: the aimed disease indications together with their corresponding clinical status, ADC's structure describing antibody, linker and payload, diverse clinical response data (such as the clinical details of both tested ADC and enrolled patient, the reported ADMET properties of ADC, administration dosage, reported adverse drug reactions and clinical primary endpoints), drug-antibody ratio of each studied ADC (19–24). Moreover, the pharma-information of three components (mAb, linker and payload) of each studied ADC should also be explicitly described in any ADC-related pharmaceutical knowledgebase, since these data were discovered to be valuable for the clinical evaluations of ADC's ther-

Table 1. A list of worldwide *antibody–drug conjugates* that have been approved for clinical use (as of August 2023, in a reverse chronological order of their approval dates)

ADC Name (developing company)	Antigen	Linker	Payload	Target	Approval office (approved date)	Approved disease indications
Mirvetuximab soravtansine (ImmunoGen)	FRα	Sulfo-SPDB (cleavable)	DM4	DNA (*human*)	U.S. FDA (Nov, 2022)	FRα-positive epithelial ovarian cancer
Tisotumab vedotin (Seagen)	TF	Mc-Val-Cit-PABC (cleavable)	MMAE	Microtubule (*human*)	U.S. FDA (Sep, 2021)	Recurrent or metastatic cervical cancer
Disitamab vedotin (RemeGen)	HER2	Mc-Val-Cit-PABC (cleavable)	MMAE	Microtubule (*human*)	China NMPA (Jun, 2021)	Advanced or metastatic gastric cancer
Loncastuximab tesirine (ADC Therapeutics)	CD19	Mal-PEG8-Val-Ala-PABC (cleavable)	SG3199	DNA (*human*)	U.S. FDA (Apr, 2021)	Relapsed or refractory large B-cell lymphoma
Cetuximab sarotalocan (Rakuten Medical)	EGFR	Linear alkyl/alkoxy linker (uncleavable)	IRDye 700DX	*not available*	Japan PMDA (Sep, 2020)	Advanced or recurrent head and neck cancer
Belantamab mafodotin (GlaxoSmithKline)	BCMA	Maleimido-caproyl (uncleavable)	MMAF	Microtubule (*human*)	U.S. FDA (Aug, 2020)	Relapsed or refractory multiple myeloma
Sacituzumab govitecan (Gilead Sciences)	TROP2	CL2A (cleavable)	SN38	TOP1 (*human*)	U.S. FDA (Apr, 2020)	Metastatic triple-negative breast cancer
Enfortumab vedotin (Astellas)	Nectin-4	Mc-Val-Cit-PABC (cleavable)	MMAE	Microtubule (*human*)	U.S. FDA (Dec, 2019)	Advanced or metastatic urothelial cancer
Trastuzumab deruxtecan (Daiichi Sankyo)	HER2	Mc-Gly-Gly-Phe-Gly (cleavable)	DXd	TOP1 (*human*)	U.S. FDA (Dec, 2019)	Unresectable HER2-positive breast cancer
Polatuzumab vedotin (Roche)	CD79b	Mc-Val-Cit-PABC (cleavable)	MMAE	Microtubule (*human*)	U.S. FDA (Jun, 2019)	Diffuse large B-cell lymphoma
Moxetumomab pasudotox (AstraZeneca)	CD22	Mc-Val-Cit-PABC (cleavable)	PE38	EEF2K (*human*)	U.S. FDA (Sep, 2018)	Relapsed or refractory hairy cell leukemia
Inotuzumab ozogamicin (Pfizer)	CD22	AcButDMH (cleavable)	N-acetyl-γ-calicheamicin	DNA (*human*)	U.S. FDA (Aug, 2017)	B-cell precursor acute lymphoblastic leukemia
Trastuzumab emtansine (Roche)	HER2	SMCC (uncleavable)	DM1	Microtubule (*human*)	U.S. FDA (Feb, 2013)	HER2-positive metastatic breast cancer
Brentuximab vedotin (Seagen)	CD30	Mc-Val-Cit-PABC (cleavable)	MMAE	Microtubule (*human*)	U.S. FDA (Aug, 2011)	Hodgkin lymphoma; Large-cell lymphoma
Gemtuzumab ozogamicin (Pfizer)	CD33	AcButDMH	N-acetyl-γ-calicheamicin	DNA (human)	U.S. FDA (Mar, 2000)	CD33-positive acute myeloid leukemia

AcButDMH: AcBut acyl hydrazonedisulfide; BCMA: B-cell maturation antigen; CD19: B-lymphocyte antigen CD19; CD22: B-cell receptor CD22; CD30: lymphocyte activation antigen CD30; CD33: myeloid cell surface antigen CD33; CD79b: immunoglobulin-associated beta; DM1: derivative of maytansine 1; DM4: derivative of maytansine 4; DXd: DX-8951 derivative; EEF2K: eukaryotic elongation factor 2 kinase; EGFR: epidermal growth factor receptor; TF: tissue factor; FRα: folate receptor alpha; HER2: human epidermal growth factor receptor 2; Mc-Gly-Gly-Phe-Gly: maleimidocaproyl-glycine-phenylalanine-glycine- glycine; Mc-Val-Cit-PABC: maleimidocaproyl-valine-citrulline-p-aminobenzoyloxycarbonyl; MMAE: monomethyl auristatin-E; MMAF: monomethyl auristatin-F; Nectin-4: Nectin cell adhesion molecule 4; PE38: 38kD fragment of *Pseudomonas* exotoxin A; SMCC: succinimidyl-4-(N-maleimidomethyl)cyclohexane-1-carboxylate; SN38: active metabolite of irinotecan; Sulfo-SPDB: sulfonyl-N-succinimidyl 4-(2-pyridyldithio) butyrate; TOP1: DNA topoisomerase 1; TROP2: tumor-associated calcium signal transducer 2.
  The approved administrations/offices included: U.S. Food and Drug Administration (U.S. FDA), National Medical Products Administration of China (China NMPA) and Pharmaceuticals and Medical Devices Agency of Japan (Japan PMDA).

apeutic window (25,26), the differentiation of ADCs' sensitivities among various indications (27–29), the identification of ADC's drug-like characteristics (30) and the determination of conjugation strategy and payload release mechanism of studied ADCs (31–35). All in all, such comprehensive pharma-information was crucial for the design and iterative development of ADCs (3), which were thus systematically described in our newly developed online database AD-Cdb (https://idrblab.org/adcdb/).

In ADCdb, detailed pharma-information of each ADC were explicitly provided. As illustrated in Figure 1 (the webpage of a well-known ADC trastuzumab deruxtecan), the pharma-information provided on this page included: ADC name, ADC synonyms, aimed disease & the corresponding clinical status, ADC structure (downloadable in 2D & 3D formats), ADC components (antibody, linker & payload), the antigen of antibody, the target of payload, antibody-linker conjugate type, linker-payload combination type and various external links to many other established molecular biological databases including PubChem (13), DrugMAP (10), TTD (15), Chembl (8), DrugBank (9) and so on (36–39). To have a detailed de-

scription on the pharma-information provided in the ADCdb, explicit illustration on such important information was given. As illustrated in the upper section of Figure 2, detailed data of ADC were described: the aimed disease indications together with their corresponding clinical status, ADC's structure describing antibody, linker and payload, diverse clinical response data (such as the clinical details of both tested ADC and enrolled patient, the reported ADMET properties of ADC, administration dosage, reported adverse drug reactions and clinical primary endpoints), drug-antibody ratio of each studied ADC, etc. Such information could be an indispensable complement to currently available pharmaceutical databases.

The pharma-information of those three key components of each studied ADC was also explicitly shown in ADCdb. As illustrated in Figure 2, the pharma-information of corresponding **antibody** included: antibody sequence, targeted antigen, tissue-specific abundances of antigen and various pharmaceutical data of this antibody (such as disease, clinical status, brand name and developing company); the pharma-information of corresponding **linker** contained: diverse linking strategies (cleavable (40–45) & uncleavable (46–48)), and
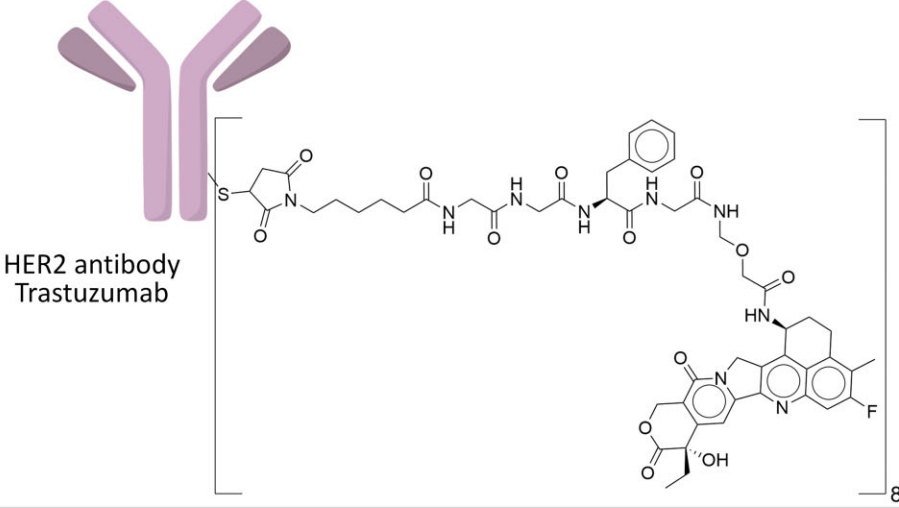
General Information of The Studied *Antibody-drug Conjugate* (ADC)

ADC Name	Trastuzumab deruxtecan	DRG00032

▼ Representative Indication(s)

Indication(s)		
	Breast cancer	Approved
	Gastric cancer	Approved
	Esophageal cancer	Phase 3
	Ovarian cancer	Phase 2

Structure

HER2 antibody
Trastuzumab

Antibody Name	Trastuzumab	Antibody Info
Antigen Name	Receptor tyrosine-protein kinase erbB-2 (ERBB2)	Antigen Info
Payload Name	DX-8951 derivative (DXd)	Payload Info
Target Name	DNA topoisomerase I (TOP1)	Target Info
Linker Name	Mc-Gly-Gly-Phe-Gly	Linker Info
Conjugate Type	Random conjugation through reduced inter-chain cysteines	
Combination Type	Deruxtecan	

Figure 1. A typical webpage showing the general information of ADC (trastuzumab deruxtecan). Diverse pharma-information were provided, which included: ADC name, ADC synonym, aimed disease and the corresponding clinical status, ADC structures (downloadable in 2D & 3D format), key ADC components (antibody, linker & payload), the antigen of antibody, the target of payload, antibody-linker conjugate type, linker-payload combination type and a variety of external links to established molecular biological databases (PubChem, DrugMAP, TTD, DrugBank, etc.).
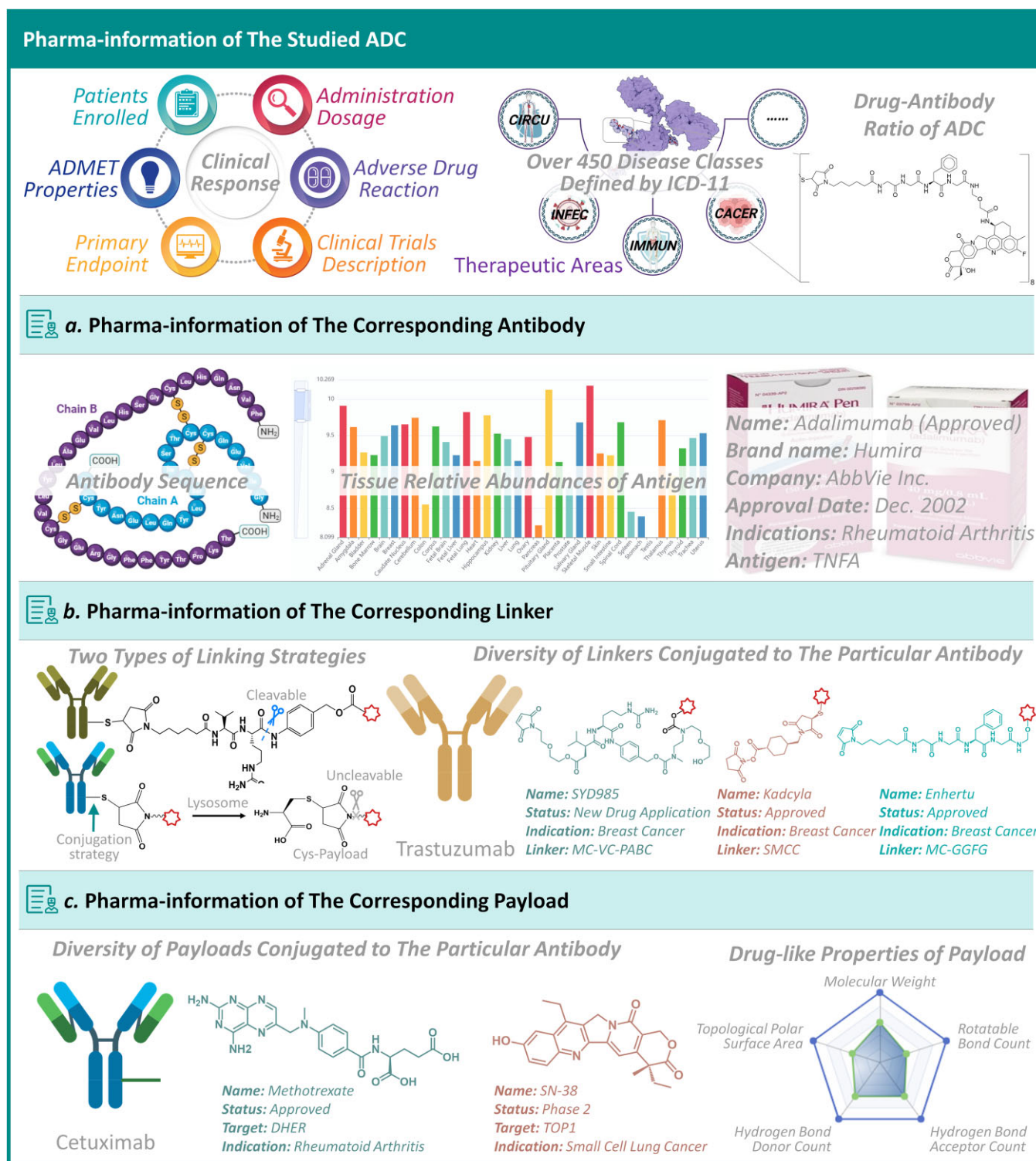
Figure 2. A comprehensive set of pharma-information for studied ADC. First, the detailed ADC data were described, which included: aimed disease indications together with their corresponding clinical status, ADC's structure describing antibody, linker and payload, diverse clinical response data (such as the clinical detail of both ADC and enrolled patient, the reported ADMET properties of ADC, administration dosages, reported adverse drug reactions and clinical primary endpoints), drug-antibody ratio of ADC, *etc.* Second, the pharma-information of the key components of each ADC was explicitly illustrated. (**a**) the pharma-information of corresponding antibody included: antibody sequence, targeted antigen, tissue-specific antigen abundances, various pharmaceutical data of this antibody (disease, clinical status, brand name, developing company); (**b**) the pharma-information of corresponding linker contained: linking strategies (cleavable/uncleavable), those linkers conjugated to antibody; (**c**) the pharma-information of payload covered: the target of any studied payload, diverse payloads conjugated to studied antibody and the drug-like properties of studied payloads (such as: molecular weight, topological polar surface area, rotatable bond count, hydrogen bond donor count and hydrogen bond acceptor count).

those diverse linkers conjugated to each antibody, which kept witnessing advancement in linker chemistry, thereby enhancing the safety & efficacy of a studied ADC; the pharma-information of **payload** covered: the target of any studied payload, diverse payloads conjugated to studied antibody and the drug-like properties of studied payloads (such as: molecular weight, topological polar surface area, rotatable bond count, hydrogen bond donor count and hydrogen bond acceptor count). To the best of our knowledge, ADCdb was the first database that describing the comprehensive pharma-information for not only ADCs but also their components, which should be carefully considered in the development of new ADC.

Diverse biological activities of each studied ADC and its components

The extensive and reliable biological activity data were key for developing and optimizing ADCs (49). These valuable data were essential for evaluating ADC's functional property and assessing its efficacy, selectivity, metabolic properties and safety (50,51). The efficacy of any studied ADC could be determined by different perspectives: whether the antibody could accurately bind to the antigen in lesion site (52–58) and whether the payload could exert effective therapeutic effects in disease tissue (59,60). Moreover, during the discovery process of ADCs, the biological activities of various related ADCs were reported to be informative in determining the optimal combination of maximum efficacy and minimum off-target effects (61). Such activities included: the objective response rates (ORRs) and complete remissions (CRs) of ADC in different stages of clinical trial, the inhibition level and growth delay of ADC in diverse disease PDX models/cell lines, and the half maximal inhibitory concentration (IC50) of ADC across different disease cell lines. Because these activities were found capable of enabling the selection of suitable candidates for preclinical and clinical studies, advancing therapeutic strategies in oncology and others (49–66), such critical data were systematically collected to and provided by the newly constructed ADCdb.

A variety of biological activities of each antibody–drug conjugate

As illustrated in Figure 3, the Activity Outline of a typical ADC (named: trastuzumab deruxtecan) was provided, which offered comprehensive description on multiple types of biological activities. As discussed above, those ADC activity data that were covered in ADCdb included: the objective response rates (ORRs) and complete remissions (CRs) of ADC in different stages of clinical trial, the inhibition level and growth delay of ADC in diverse disease PDX models/cell lines, and the half maximal inhibitory concentration (IC50) of ADC in various disease cells. Taking the activity data of 'trastuzumab deruxtecan' as an example (shown in Figure 3), the specific activity values were provided, together with the corresponding activity type, unit and experimental labels (such as NCT number, PDX name, cell line & disease model) and the detailed information underlying these activities could be further accessed by simply clicking on the provided hyperlinks.

Detailed biological activities were also explicitly described in ADCdb, which could significantly expand the knowledge in ADC's 'Activity Outline' section. Taking the 'trastuzumab deruxtecan' as an example (shown in Figure 4), its detailed

biological activity data were also provided in our newly constructed database. As illustrated, such valuable data included: the efficacy information of ADC, the clinical status, primary endpoint, patient enrollment information of the clinical study of ADC, the reported adverse drug reaction of ADC, etc. In ADCdb, the details of a total of 9171 biological activity data were collected. Moreover, a variety of experimental details were included: clinical response information (patient enrollment data, administration dosage, primary endpoint, antigen expression level, *etc.*), analyzed *in-vivo* model (breast cancer PDX ST313 model, gastric cancer PDX A11068 model, acute contact hypersensitivity model, etc.), disease cell lines (GCIY, JIMT-1, SK-BR-3, NCI-N87 and SNU1, etc.) and so on. ADC's ADMET property together with its reported adverse drug reaction were also identified and provided in ADCdb.

The biological activities of the antibody & payload in each ADC

Apart from the activities of a studied ADC, the activity information of its key components (mAb and payload) was also reported to be critical in determining ADC's overall effectiveness (67,68). Therefore, the activity details of both antibody & payload in any studied ADC were also covered by ADCdb. As illustrated in Figure 5a, the activity details of an exemplar antibody (trastuzumab) were described (which quantitatively provided the binding affinity of this antibody on its antigen), and its therapeutic mechanism together with the experimental method used to measure its binding affinity to antigen were also systematically provided. Meanwhile, activity details of the exemplar payload (monomethyl auristatin E) were also covered by ADCdb (as demonstrated in Figure 5b), under each activity datum, the corresponding experimental validation method (including various cell line, diseased model and experimental detail) were fully collected and described. According on such valuable information, the users of our ADCdb could readily retrieve a list of activity data that might be capable of facilitating the improvement of their studied ADCs, including increasing ADC efficacy, reducing adverse drug reaction and reversing ADC resistance (69–73).

Constructing antigen-centric panorama for promoting ADC discovery

The random combinations among the antibodies, linkers and payloads provided in ADCdb could result in numerous potential ADCs, which were found to have different therapeutic effectiveness (most were ineffective) on diseases (74). Taking three marketed ADCs as examples, trastuzumab deruxtecan, trastuzumab emtansine and disitamab vedotin had been approved for the treatments of HER2-positive breast cancer, uroepithelial carcinoma, gastric cancer and non-small cell lung cancer, since the antigens of the antibodies (trastuzumab & disitamab) of these three ADCs were identical (HER2). However, due to their distinct combinations among different mAbs, linkers & payloads, their resulting biological activities and targeted disease indications varied significantly (75–79). Particularly, the approved indications (including HER2-positive uroepithelial carcinoma) of 'disitamab vedotin' were substantially different from that of the other two ADCs; 'trastuzumab deruxtecan' exhibited the greatly enhanced clinical efficacy compared to 'trastuzumab emtansine' owing to their distinct strategies in selecting linkers and payloads (78–84). In other words, it was possible that a given payload might

The Activity Outline of The Studied ADC (*Trastuzumab Deruxtecan*)

▼ The Activities Identified Based on Clinical Trial

Standard Type	NCT Number	Clinical Status	Clinical Trial Description
Objective response rate (ORR) ↗	NCT03734029	Phase 3	A phase 3, active controlled trial of DS-8201a, versus treatment for HER2-low, breast cancer subjects.
Objective response rate (ORR) ↗	NCT03505710	Phase 2	A phase 2, multicenter study for HER2-over-expressing/mutated, unresectable metastatic NSCLC of DS-8201a.

▼ The Activities Discovered Based on Patient-derived Xenograft Model

Standard Type	Value	Units	PDX Model
Tumor growth inhibition value (TGI) ↗	≈ 96.30	%	Breast cancer PDX ST313 model
Tumor growth inhibition value (TGI) ↗	≈ 98.20	%	Breast cancer PDX ST565 model

▼ The Activities Assessed Based on Cell Line-derived Xenograft Model

Standard Type	Value	Units	Cell Line	Disease Model
Tumor growth inhibition value (TGI) ↗	≈ 28.80	%	GCIY cells	Gastric adenocarcinoma
Tumor growth inhibition value (TGI) ↗	≈ 58.50	%	JIMT-1 cells	Breast ductal carcinoma

▼ The Activities Revealed Based on Cell Line-based Disease Model

Standard Type	Value	Units	Cell Line	Disease Model
Half maximal inhibitory concentration ↗	6.70	ng/mL	SK-BR-3 cells	Breast adenocarcinoma
Half maximal inhibitory concentration ↗	25.40	ng/mL	NCI-N87 cells	Gastric tubular adenocarcinoma

Figure 3. A typical page describing the activity outline of ADC (trastuzumab deruxtecan). Such activity data included: objective response rates (ORRs) and complete remissions (CRs) of ADCs in different stages of clinical trial, inhibition levels and growth delays of ADCs in diverse disease PDX models/cell lines and half maximal inhibitory concentrations of ADCs in different disease cells. The specific activity values of 'trastuzumab deruxtecan' were provided, together with the corresponding activity type, unit and experimental labels (such as NCT number, PDX name, cell line and disease model), and the detailed information underlying these activities could be further accessed by simply clicking on those provided hyperlinks.

The Activity Details of The Studied ADC (*Trastuzumab Deruxtecan*)

▼ The Activities Identified Based on Clinical Trial

📁 *Experiment 1 Reporting the Activity Date of This ADC*

Efficacy Data	Objective Response Rate (ORR) 79.70%
Patients Enrolled	HER2-positive unresectable or metastatic breast cancer who were previously treated with trastuzumab and a taxane in the advanced or metastatic setting.
Administration Dosage	Intravenously every 3 weeks at a dose of 5.4 mg per kilogram of body weight.

Related Clinical Trial

NCT Number	NCT03529110 ↗	**Clinical Status**	Phase 3
Clinical Description	A Phase 3, multicenter, randomized, open-label, active controlled trial of DS-8201a, an anti-HER2 -antibody drug conjugate (ADC), versus treatment of physician's choice for HER2-low, unresectable and/or metastatic breast cancer subjects.		
Primary Endpoint	In HR+ cohort, for ENHERTU (N=331), median progression-free survival (mFPS) = 10.10 months (95% CI 9.50-11.50), for chemotherapy (N=163), mFPS=5.40 months (95% CI 4.40-7.10), hazard radio=0.51(95% CI 0.40-0.64) and p-value <0.0001.		
Adverse Drug Reaction	In the phase 3 study (NCT03529110), AEs of grade ≥3 were reported in 135 patients (135/257, 52.53%). The most common grade ≥3 AEs were anaemia (9.00%), platelet count decreased (8%), white blood cell count decreased (9.10%), nausea (9.10%), neutrophil count decreased (16.00%), alanine aminotransferase increased (2.00%), decreased appetite (2.00%), and bodyweight decreased (2%).		

📁 *Experiment 2 Reporting the Activity Date of This ADC*

▼ The Activities Discovered Based on Patient-derived Xenograft Model

📁 *Experiment 1 Reporting the Activity Date of This ADC*

Efficacy Data	Tumor Growth Inhibition value ≈ 96.30% Low HER2 expression (**HER2+**; IHC 1+)
Method Description	The antitumor activity of DS-8201a was evaluated in various patient-derived xenograft models with different HER2 expression levels. Each cell suspension or tumor fragment was inoculated subcutaneously into specific pathogen-free female nude mice. The tumor-bearing mice were randomized into treatment and control groups based on the tumor volumes, and dosing was initiated on day 0. In this group, 10mg/kg DS-8201a was i.v. to the tumor-bearing mice.
In Vivo Model	Breast cancer PDX model (PDX: ST313)

Figure 4. A typical webpage offering the activity details of ADC (trastuzumab deruxtecan). Such activity data included: efficacy information of ADC, the clinical status, primary endpoint, patient enrollment information of the clinical study of ADC, the reported adverse drug reactions of ADC, etc. Various experimental details were also provided based on the original publications.

a. The Activity Details of The Studies Antibody (*Trastuzumab*)

Antibody Activity Information 1			[1]
Half Maximal Effective Concentration (EC50)	1.35	nM	
Antibody Function	Confirm the effect of the drug conjugation with the anti-HER2 (Trastuzumab) Ab on binding activity to HER2.		
Antibody Antigen Binding Assay	Evaluate the antigen binding capacity of our antibody drug conjugate (ADC) by indirect ELISA binding.		

b. The Activity Details of The Studied Payload (*Monomethyl Auristatin E*)

Standard Type	Value	Units	Disease Model	Cell Line	Cell Line ID
Half Maximal Inhibitory Concentration (IC50)	0.13	nM	Breast adenocarcinoma	MDA-MB-231 cells	CVCL_0062 ↗
Half Maximal Inhibitory Concentration (IC50)	0.25	nM	Diffuse large B-cell lymphoma	SU-DHL-4 cells	CVCL_0539 ↗
Half Maximal Inhibitory Concentration (IC50)	0.25	uM	Mantle cell lymphoma	Granta-519 cells	CVCL_1818 ↗
Half Maximal Inhibitory Concentration (IC50)	0.54	nM	Burkitt lymphoma	BJAB cells	CVCL_5711 ↗
Half Maximal Inhibitory Concentration (IC50)	0.33	nM	Breast adenocarcinoma	MDA-MB-468 cells	CVCL_0419 ↗
Half Maximal Inhibitory Concentration (IC50)	1.19	nM	Diffuse large B-cell lymphoma	SU-DHL-4 cells	CVCL_0539 ↗

Figure 5. The activity information of ADC's key components (antibody & payload). The activity detail of an exemplar antibody (trastuzumab) was described (the binding affinity of this antibody on its antigen), and its therapeutic mechanism together with the experimental method applied to measure its antigen affinity were also systematically provided. Meanwhile, activity details of the exemplar payload (monomethyl auristatin E) were also provided. Under each activity datum, the corresponding experimental validation method (including various cell lines, diseased models and experimental details) were described. The detailed information underlying these activities could be further accessed by simply clicking on those provided hyperlinks.

be poorly active in a specific indication and that a change of payload while conserving the same antibody might result in promising clinical outcome (85–87); it was crucial to have the diverse combination data of ADCs (with discovered clinical importance and targeted the same antigen), since such combinations were found to be critical for discovering new ADC (88–91). Therefore, an antigen-centric panorama was provided in our newly developed ADCdb to establish the correlations between diverse ADCs & different component combinations, which might facilitate the future discovery of ADC analogous based on QSAR analysis (92–96).

Taking the epidermal growth factor receptor ErbB2 (HER2) as an example, it had been frequently found overexpressed in the patients of various cancer types, and therefore attracted considerable attentions from the community of ADC develop-

ment (2,49). Therefore, in ADCdb, HER2-centric panorama was provided (illustrated in Figure 6) for establishing the correlations between diverse ADCs and different components combinations. As shown, antigen ERBB2 was first linked to a list of its binding antibodies (indicated by the 'Y' shape in blue color), and these linked antibodies were then connected to their resulting ADCs (denoted by the ADC icon colored by both blue and orange; which were further linked to the corresponding payload highlighted in orange and placed in the outermost layer). By placing the mouse on any of the antibodies, ADCs and payloads, their brief introduction would be retrieved (including the name of the selected antibody/ADC/payload, the isotype & antigen of studied antibody, the indication & linker of selected ADC, the targets & structure of studied payload, etc.). By clicking any of the
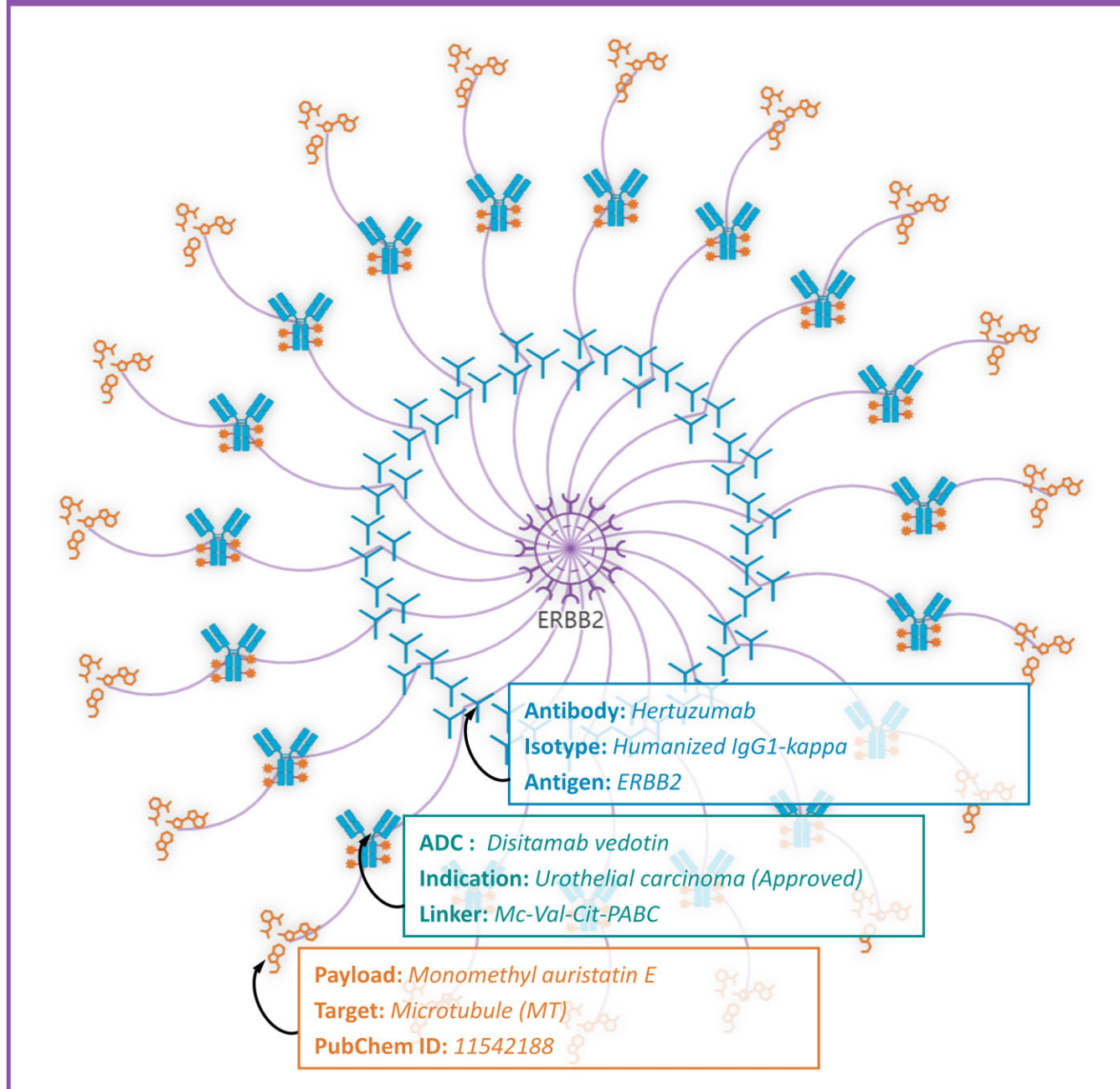
Figure 6. A typical antigen-centric panorama (using ERBB2 as an example) for establishing the correlations between diverse ADCs and different components combinations. The antigen ERBB2 was first linked to a list of its binding antibodies (indicated by 'Y' shape in blue color), and these linked antibodies were then connected to their resulting ADCs (denoted by the ADC icon colored by both blue and orange; which were further linked to the corresponding payload highlighted in orange and placed in the outermost layer). By placing the mouse on any of the antibodies, ADCs and payloads, their introduction would be retrieved (the name of selected antibody/ADC/payload, the isotype & antigen of studied antibody, the indication & linker of selected ADC, the targets & structure of studied payload, *etc.*).

antibody/ADC/payload, the user would be redirected to the corresponding page of the selected antibody/ADC/payload. All in all, ADCdb was unique in providing an antigen-centric panorama that enabled visualization of all antibodies and payloads in the development of ADCs targeting specific antigens, which was useful for users in understanding the component combination profile of any clinically-important ADCs.

Standardization, access & download of ADCs and their activity data

To make the access and analysis of ADCdb data convenient for all readers, the collected raw data were carefully cleaned up and then systematically standardized. These standardizations included: (a) all those ADCs, antigens, targets, linkers, payloads and cell lines in ADCdb were cross-linked to

established databases; (b) all the disease indications were standardized by the last International Classification of Disease (ICD-11) that was officially released by the World Health Organization (97). Moreover, a user-friendly interface was provided by ADCdb to enable a convenient browse and search of data. ADC-relevant data could be viewed, accessed and downloaded from ADCdb, which could be freely accessed without any login requirement at: https://idrblab.org/adcdb/.

Conclusion and perspectives

In this study, the first database, named ADCdb, specialized in describing the biological activities and pharma-information for thousands of antibody–drug conjugates (ADCs) was developed. Due to the importance of these newly collected data and severe lack of these data in existing databases, this newly constructed database is highly expected to attract broad research interests from diverse cutting-edge directions of current biopharmaceutical drug discovery.

Data availability

All antibody–drug conjugate data can be viewed, accessed and downloaded from ADCdb, which is freely accessible without any login requirement by all users at: https://idrblab.org/adcdb/.

Conflict of interest statement

None declared.

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