Nucleic Acids Research, 2025, **53**, D1476–D1485
https://doi.org/10.1093/nar/gkae859
Advance access publication date: 3 October 2024
Database issue

PDCdb: the biological activity and pharmaceutical information of peptide–drug conjugate (PDC)

Xiuna Sun[1,2,†], Hanyang Li[2,†], Zhen Chen[2,†], Yang Zhang[1,†], Zhangle Wei[2], Hangwei Xu[2], Yang Liao[2], Wanghao Jiang[2], Yichao Ge[2], Lingyan Zheng[2], Teng Li[2], Yuting Wu[2], Meiyin Luo[2], Luo Fang[3], Xiaowu Dong[2], Mang Xiao[2], Lianyi Han[4,*], Qingzhong Jia[1,*] and Feng Zhu[1,2,*]

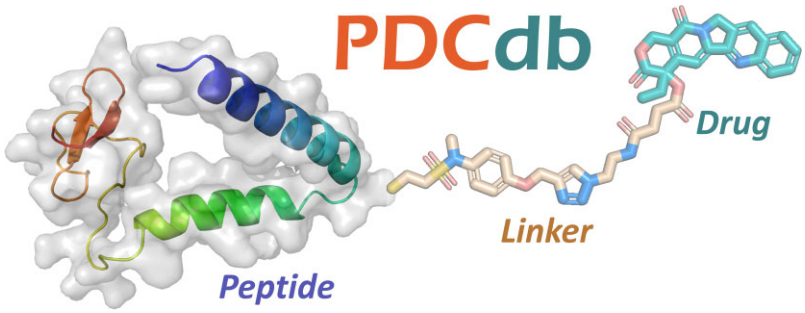
[1]School of Pharmacy, Hebei Medical University, Shijiazhuang 050017, China
[2]College of Pharmaceutical Sciences, Department of Otolaryngology Head and Neck Surgery, Sir Run Run Shaw Hospital, The Second Affiliated Hospital, Zhejiang University School of Medicine, State Key Laboratory of Advanced Drug Delivery and Release Systems, Zhejiang University, Hangzhou 310058, China
[3]Department of Pharmacy, Zhejiang Cancer Hospital, Institute of Basic Medicine and Cancer (IBMC), Chinese Academy of Sciences, Hangzhou 310005, China
[4]Greater Bay Area Institute of Precision Medicine (Guangzhou), School of Life Sciences, Fudan University, Shanghai 315211, China

[*]To whom correspondence should be addressed. Tel: +86 189 8946 6518; Email: zhufeng@zju.edu.cn
Correspondence may also be addressed to Qingzhong Jia. Email: qizhjia@hebmu.edu.cn
Correspondence may also be addressed to Lianyi Han. Email: hanlianyi@ipm-gba.org.cn
[†]The first four authors should be regarded as Joint First Authors.

Abstract

Peptide–drug conjugates (PDCs) have emerged as a promising class of targeted therapeutics with substantial pharmaceutical advantages and market potentials, which is a combination of a peptide (selective to the disease-relevant target), a linker (stable in circulation but cleavable at target site) and a cytotoxic/radioactive drug (efficacious/traceable for disease). Among existing PDCs, those based on radiopharmaceuticals (a.k.a. radioactive drugs) are valued due to their accurate imaging and targeted destruction of disease sites. It's demanded to accumulate the biological activity and pharmaceutical information of PDCs. Herein, a database *PDCdb* was thus constructed to systematically describe these valuable data. Particularly, biological activities for 2036 PDCs were retrieved from literatures, which resulted in 1684, 613 and 2753 activity data generated based on clinical trial, animal model and cell line, respectively. Furthermore, the pharmaceutical information for all 2036 PDCs was collected, which gave the diverse data of (a) ADME property, plasma half-life and administration approach of a PDC and (b) chemical modification, primary target, mode of action, conjugating feature of the constituent peptide/linker/drug. In sum, *PDCdb* systematically provided the biological activities and pharmaceutical information for the most comprehensive list of PDCs among the available databases, which was expected to attract broad interest from related communities and could be freely accessible at: https://idrblab.org/PDCdb/

Graphical abstract



Introduction

Peptide–drug conjugates (PDCs) have emerged as a promising class of targeted therapeutics with tremendous pharmaceutical advantages and profitable market potentials, which have resulted in seven therapeutic/diagnostic agents approved by U.S. FDA (1–3). Among available PDCs, those based on radiopharmaceuticals (a.k.a. radioactive drugs) are valued due to their accurate imaging and targeted destruction of disease site (4–6). An effective PDC, as demonstrated in Figure 1, is considered to be a combination of a peptide (selectively targeting

Received: August 8, 2024. **Revised:** September 10, 2024. **Editorial Decision:** September 17, 2024. **Accepted:** September 20, 2024

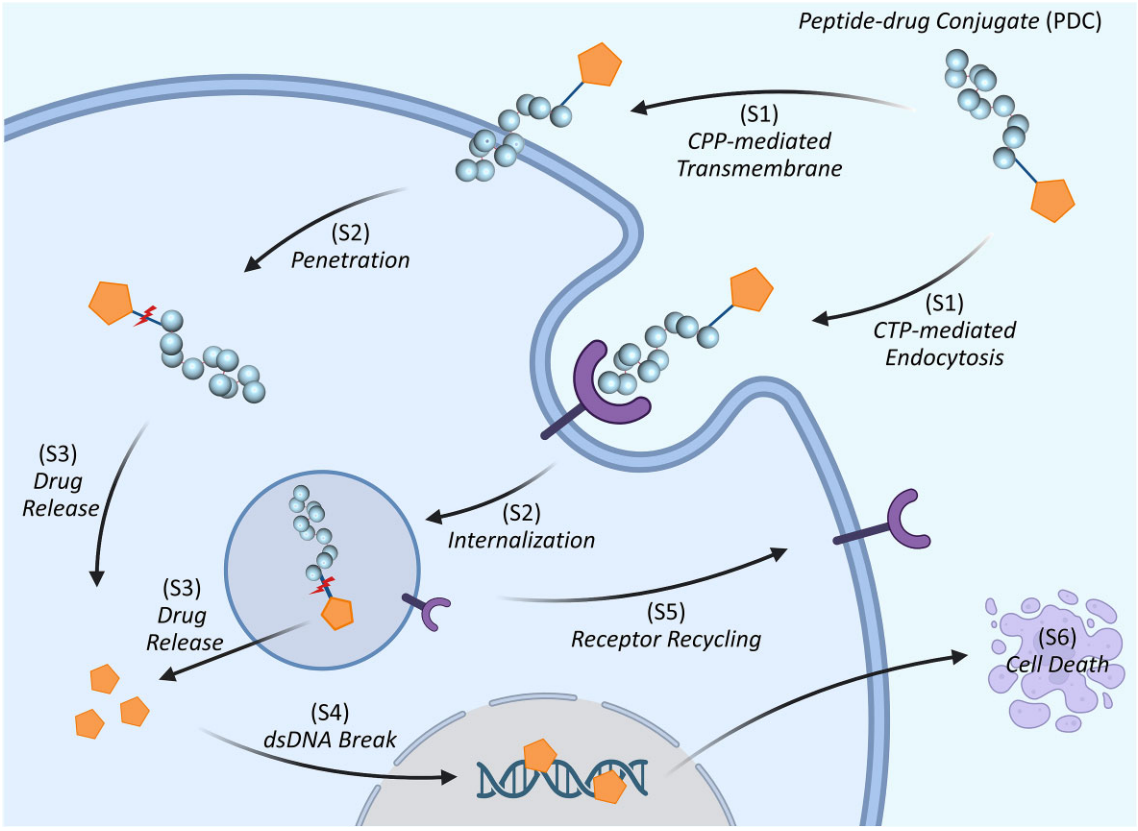


Figure 1. A schematic illustration of the mechanism of action (MOA) of *peptide–drug conjugates* (PDCs). (**S1**) two types of peptide carrier, CPP and CTP, mediating the entry of PDCs into disease cells; (**S2**) direct penetration of PDCs or internalization of their receptor-binding complexes; (**S3**) drug release in cytoplasm; (**S4**) molecular interaction leading to the impairment of target function; (**S5**) receptor recycling; (**S6**) drug-induced disease cell death (created using Biorender.com).

the disease-associated sites), a linker (stable in circulation but cleavable at targeted disease sites) & a cytotoxic/radioactive drug (efficacious/traceable for a studied disease indication) (7,8). Particularly, the biological activities (a) between a PDC peptide and its binding receptor on the membrane of disease cell, (b) between a PDC drug and its therapeutic target/aimed disease cell and (c) between the entire PDC and its aimed disease model are key for determining the drug-like of properties of PDC peptide (9), off-target toxicity of PCD drug (10) and the overall efficacy of studied PDC (11), respectively.

Moreover, the pharmaceutical information of a PDC (such as toxicology profile, ADME property, plasma half-life, circulation stability and administration method) and its constituent components (such as chemical modifications & renal clearance of PDC peptide, primary target & mechanisms of action of PDC drug and chemical type & conjugating features of PDC linker) are reported as essential for the design, optimization and clinical assessment of PDC (12–17). In other words, it is highly demanded to accumulate the biological activity and pharmaceutical information of PDC. Furthermore, with the booming applications of *Artificial Intelligence* (AI) in biomedical research (18–20), it is imperative to accumulate such kind of *big data* of PDCs to facilitate the learning of the drug-like patterns that effectively promote the discovery of new PDCs (21–23).

So far, several databases have been developed to describe the PDC-related information. Some of them provide a few PDCs (especially, the FDA-approved ones) as part of a broader collection of chemical or biological information, such as PubChem (24), Drugs@FDA (25), DrugCentral (26), DrugBank (27) and NCATS Inxight Drugs (28); some others offer the cell-penetrating/targeting peptides that are capable of functioning as one of the key components of a PDC, such as HORDB (29), CPPsite (30) and APD3 (31); the remaining focus on collecting and providing the structural and physicochemical features of PDC, such as ConjuPepDB (32). These databases have received extensive research interest from worldwide users, but none of them provide the data of biological activity and pharmaceutical information of PDC. In other words, it is urgently needed to have a database systematically describing those valuable data for a comprehensive set of PDCs.

In this work, a knowledge base titled '*PDCdb*' was therefore developed to systematically provide those valuable data described above for a substantial number of PDCs. In particular, a variety of biological activities for 2036 PDCs were retrieved from literatures, which resulted in 1684, 613 and 2753 activity data generated based on clinical trial, animal model and cell line, respectively. Furthermore, the pharmaceutical information of all 2036 PDCs were comprehensively collected, which gave the diverse data of (a) ADME property, plasma half-life and administration approach of a PDC and (b) chemical modification, primary target, mode of action, conjugating feature and chemical type of the constituent peptide/linker/drug. Moreover, a variety of search engines based on keywords, sequence-similarity, structure-

Table 1. A list of peptide–drug conjugates that have been approved so far for clinical use (as of August 2024). The approved administration/office is U.S. Food and Drug Administration (U.S. FDA)

	PDC name (sponsor or company)	Brand name	Receptor	Cytotoxic or radioactive drug	Year of approval	diseases
Diagnostic PDC	^{64}Cu oxodotreotide (Radiomedix)	Detectnet	SSTR2	Copper-64	2020 Sep	SSTR$^+$ NE tumors
	^{68}Ga PSMA-11 (Telix Pharma)	Illuccix	PSMA	Gallium-68	2020 Dec	PSMA$^+$ prostate cancer
	^{68}Ga edotreotide (UIHC-PET Imaging)	N.A.	SSTR2	Gallium-68	2019 Aug	SSTR$^+$ NE tumors
	^{68}Ga oxodotreotide (AAA, Novartis)	Netspot	SSTR2	Gallium-68	2016 Jun	SSTR$^+$ NE tumors
Therapeutic PDC	^{177}Lu vipivotide tetraxetan (AAA, Novartis)	Pluvicto	PSMA	Lutetium-117	2022 Mar	PSMA$^+$ mCR prostate cancer
	^{177}Lu oxodotreotide (AAA, Novartis)	Lutathera	SSTR2	Lutetium-117	2018 Jan	SSTR$^+$ GEP-NE tumors
	Melphalan flufenamide[a] (Oncopeptides)	Pepaxto	N.A.[b]	Melphalan	2021 Feb	Multiple myeloma

Abbreviations for receptor. PSMA: prostate-specific membrane antigen; SSTR2: somatostatin receptor 2.
Abbreviations for diseases. GEP-NE: gastroenteropancreatic neuroendocrine; mCR: metastatic castration-resistant; NE: neuroendocrine.
[a]Withdrawn by the FDA on 23 February 2024.
[b]A cell-penetrating peptide without targeted receptor.

similarity and disease/chemical-classification were designed and provided in the online database, and all data were cross-linked to existing databases. All in all, *PDCdb* is unique in systematically offering the biological activities and pharmaceutical information for the most comprehensive list of PDCs among available databases. Because of the importance of those collected data, our *PDCdb* was expected to attract broad interest from related research communities and could be freely accessible at: https://idrblab.org/PDCdb/

Factual content and data retrieval

Systematic collection of the information of *peptide–drug conjugates* (PDCs)

Explicit pharmaceutical information and biological activity data of PDCs were collected by the following procedures. First, a comprehensive literature review was performed using keyword search in PubMed, which identified a total of 2036 PDCs (a list of FDA-approved PDCs was explicitly provided in Table 1). Second, the pharmaceutical information of the PDCs and their constituent components were further extracted from literature. Third, the biological activities of the PDCs were identified using keyword combinations such as 'peptide–drug conjugation + activity'. As a result, a total of 5050 biological activities were collected, which resulted in 1684 from clinical trials, 613 from animal models and 2753 from cell line studies. Furthermore, the disease classes of these collected data were very diverse, which included not only cancer but also many other diseases, such as COVID-19, diabetes, rheumatoid arthritis, malaria and so on.

Explicit description on the pharmaceutical information of each studied PDC

The development of PDCs requires a meticulously planned approach that utilizes comprehensive pharmaceutical data to guide their design and optimization (33–35). Those data include structural detail and clinical information, such as targeted disease, PDC structure, clinical response, ADME properties, administration method, peptide modification segments and linking strategy (36–40). Meanwhile, the comprehensive pharmaceutical data of PDC's constituent components were key for effective PDC design (41–44). Specifically, the selection of targeted peptide affects the target binding affinity, efficiency of drug endocytosis, therapeutic indices and therapeutic windows of PDCs, while peptide modifications enhance the circulation stability of PDC (45–50). Meanwhile, pharmaceutical information of the drug, which acts as the primary effector of a PDC, is important (51,52). Various indications exhibit varying sensitivities to specific drug types, and the drug type conjugated to a peptide determines the ultimate application of PDC (therapeutic/diagnostic), highlighting the necessity of selecting appropriate drugs for PDC designs (53,54). Moreover, the physical and chemical properties of drugs as small molecules are also taken into consideration (55,56). The linker, which connects peptide and drug, plays a pivotal role in PDC system. It determines the drug release mechanism, thereby impacting the metabolic properties, off-target toxicity as well as the therapeutic window of PDC (57–60). As a result, comprehensive pharmaceutical information covering the complete PDC conjugate and its components is critical for the design and iterative development of the PDC (61–63), and these aspects are systematically detailed in our newly developed online knowledge base.

In PDCdb, detailed pharmaceutical information of each PDC is explicitly provided. As illustrated in Figure 2, which displayed the webpage of a well-known PDC ^{177}Lu-PSMA-617, the available pharmaceutical information on this page included: PDC name & the corresponding clinical status, disease, PDC structure, three constituent components, peptide receptor, modified type & segment of peptide modification, drug target and external links to several established molecular biological databases such as PubChem (24), TTD (64), Chembl (65) and DrugBank (27). Moreover, explicit illustration is provided to offer a detailed description of the pharmaceutical information available in *PDCdb*. As shown in the upper part of Figure 3, the database offered comprehensive data on PDCs, including targeted disease, PDC structure, di-

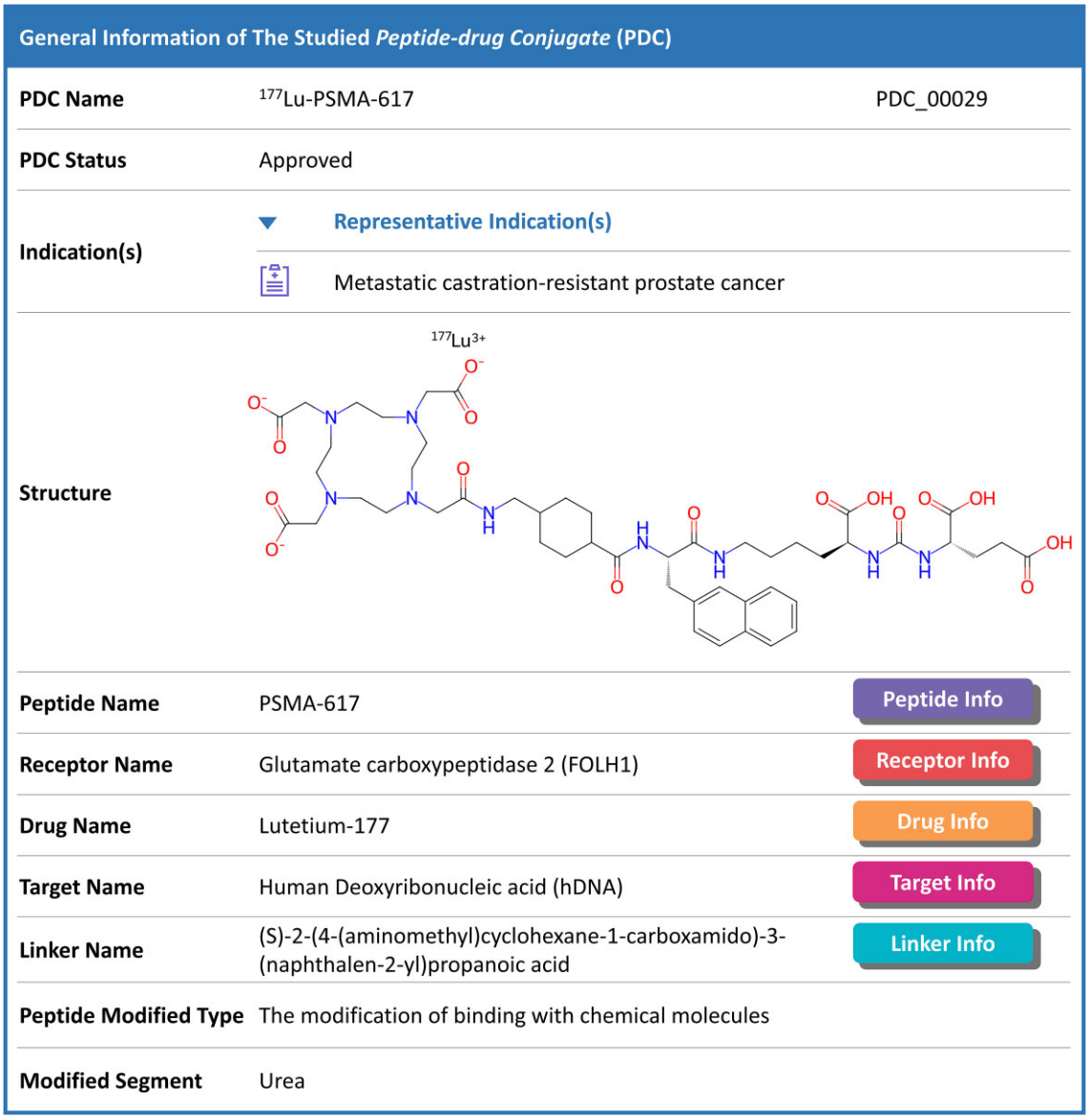


Figure 2. The typical PDC page depicting ^{177}Lu-PSMA-617. A multitude of pharma-information was described by integrating PDC name, clinical status, targeted disease, downloadable structure, three constituent component, peptide receptor, drug target, peptide modified type, corresponding modified segment and a variety of external links to established molecular biological databases.

verse clinical response data (such as the clinical detail of tested PDC & enrolled patient and administration dosage & times), the reported ADME property, drug-like properties (including molecular weight, topological polar surface area, rotatable bonds count, hydrogen bond donor/acceptor count) of the studied PDC, *etc*. Such data could be an indispensable complement to currently available pharmaceutical knowledge base.

Pharmaceutical information of three constituent components of the studied PDC is also explicitly provided in *PDCdb*. As shown in Figure 3, the pharmaceutical information for the corresponding peptide contained: diverse strategies applied to enhance peptide stability and permeability. These strategies were cyclization modification (1C/2C-peptide stapling (66)), amino acid modification (D-amino acid instead of L-amino acid (67) and side-chain variation), binding modification with chemical macromolecules (e.g. addition of polyethylene glycol, fatty chains, or macromolecules over 50 kDa to the N/C-terminals/side chains of peptides) and modification by dosage form (e.g. using acid-stable coatings), and peptide sequences; pharmaceutical information of corresponding linker included: linking strategy (cleavable (68) & uncleavable (69)), and the chemical structures for various linker chemistries (enzyme-sensitive, *pH*-sensitive, GSH-sensitive, uncleavable, *etc*.); pharmaceutical information of corresponding drug contained: the diverse drug types conjugated to studied peptide (such as chemotherapy drugs, radionucleotides and imaging agents), the target of a studied drug, *etc*. To the best of our knowledge, *PDCdb* is the first one systematically giving the pharmaceutical information for not only PDCs but also their individual components.

Diverse biological activities of each studied PDC and its components

Biological activity data are essential for the development and optimization of PDCs (70–72). These data help to assess the

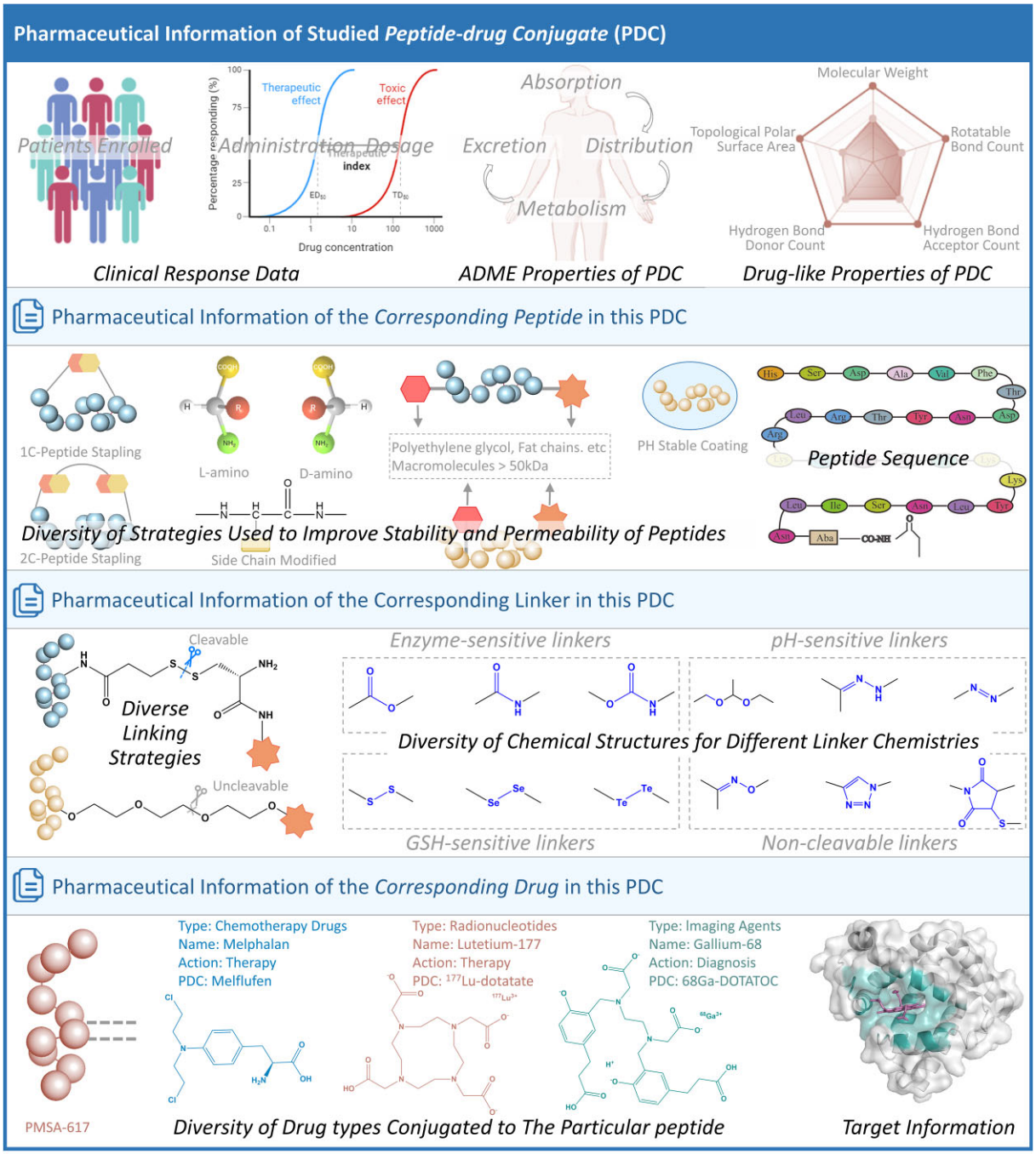


Figure 3. The comprehensive pharmaceutical information of PDC covered by this database. First, detailed PDC data were described, which included: targeted diseases, structure, clinical response, ADME property, drug-like property, *etc*. Second, detailed pharmaceutical information of PDC's three constituent components was explicitly illustrated by providing the data for (**A**) peptide (such as the peptide sequence and strategies used to improve peptide's stability/permeability, (**B**) linker (such as the linking strategies and structure of different linker chemistries) and (**C**) drug (such as the binding target and drug types conjugated to corresponding peptide).

critical functional characteristics of PDC (73), such as the binding affinity between peptide and its receptor on the disease cell membrane, efficacies between cytotoxic/radioactive drug and its therapeutic target/disease cell, and MOA between entire PDC and its targeted model (74–78). Additionally, these data can contribute to the validation of the functional characteristics of targeted receptors and shed light on the identification of novel receptor targets (79–81). These assessments are critical for determining the off-target toxicity of cytotoxic/radioactive drug, as well as evaluating the drug-like properties and overall therapeutic efficacy of PDC (82–84). Moreover, characterizing the biological activity data of the entire PDC, including its peptide or drug, is key for identifying the optimal combination that maximizes efficacy while minimizing off-target effects (85–87). Such activities included: objective response rates (ORRs) and complete remissions (CRs) among a series of clinical trial stages, inhibition level and growth delay of PDC in PDX models/cell lines, and half maximal inhibitory concentration (IC50) across different disease cell lines. All in all, such diverse biological activities were

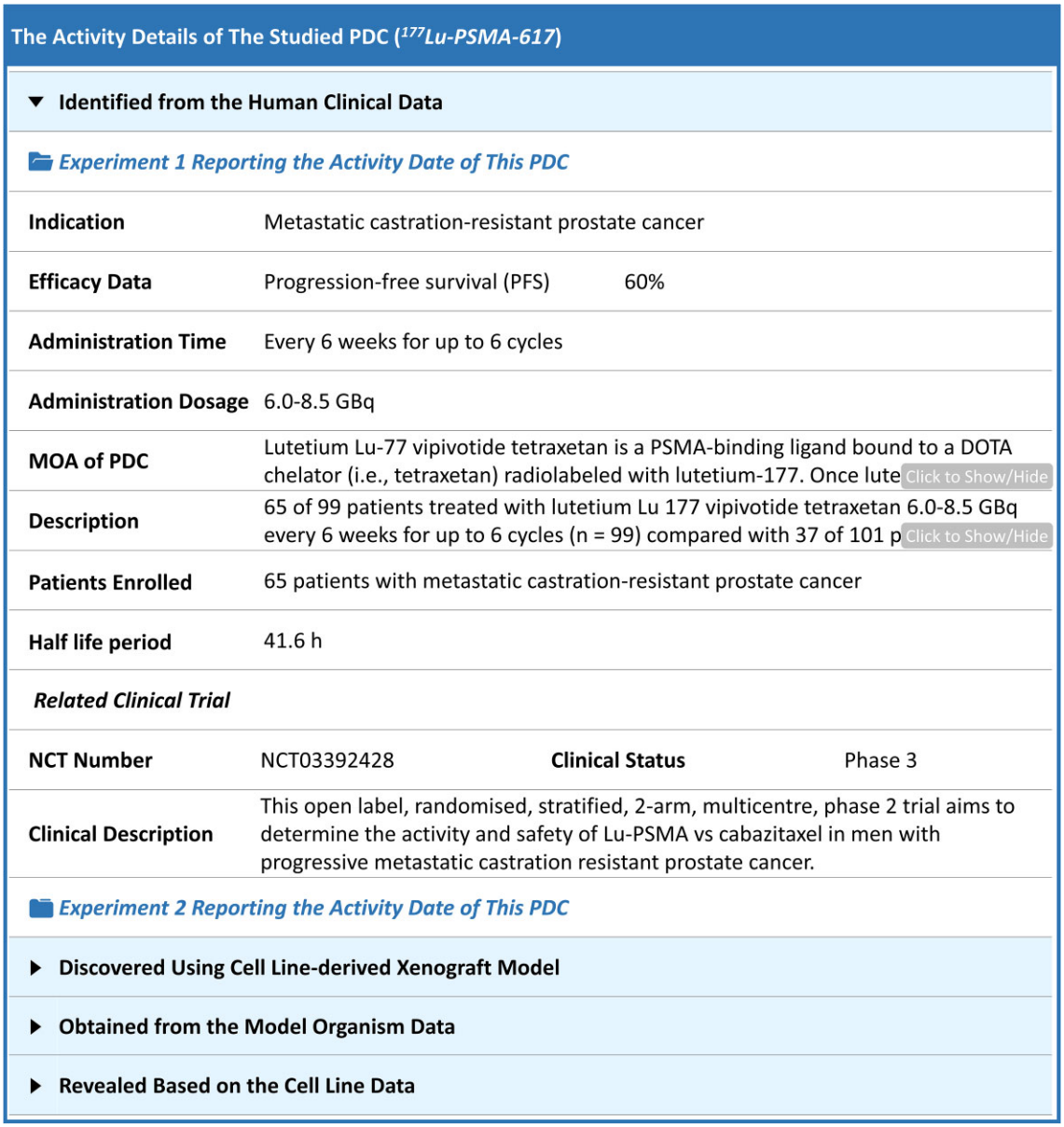


Figure 4. The typical PDC activity page for ^{177}Lu-PSMA-617. Various activity data of PDC were provided, which contained the ones identified from human clinical study, the ones discovered by cell line-derived xenograft model, the ones obtained from model organism and the ones revealed based on cell line. For each type of activity data, specific activity values together with the activity type and experimental/clinical information were explicitly provided.

essential for the design, optimization and clinical evaluation of PDCs, which were systematically provided by our knowledge base.

A variety of biological activities of each peptide–drug conjugate

As shown in Figure 4, the biological activities of a typical PDC ^{177}Lu-PSMA-617 were explicitly described. These activity data included results from human clinical studies, cell line-derived xenograft models, model organism and cell line. For each activity type, specific activity values were described, along with the corresponding activity type (such as ORR and CR of PDC in various clinical stages, inhibition level and growth delay of PDC in disease model/cell line and IC50 of PDC in disease cells), as well as units and experimental labels (such as NCT number, cell line & disease model). Taking the activity data of '^{177}Lu-PSMA-617' as an example (shown in Figure 4), its biological activity includes: efficacy information of PDC, aimed disease, patient enrollment details, half-life periods, administration dosage & time, the reported MOA of PDC, *etc*. In *PDCdb*, details for 5050 biological activities were collected. Moreover, a variety of experimental details were provided, including the in-*vivo* models (lung cancer CDX A549, breast cancers CDX MDA-MB-468, malaria *Plasmodium falciparum* 3D7,*etc*.) and various disease cell lines (e.g. MCF-7, SMMC-7721, Hep-G2, U-87, A-549, *etc*.). The ADME property of PDC were also systematically identified and explicitly described in the constructed database.

The biological activities of the receptor and drug in each PDC

In addition to the PDC itself, the activity data of its constituent components (peptide/drug) were reported to be critical in determining the overall effectiveness of PDC (88–91).

a. **The Activity Details of The Studies Peptide (*PSMA-617*)**

Peptide Activity Information 1		[1]
Half Maximal Inhibitory Concentration (IC50)	11.10 ± 0.80	nM
Binding Affinity Assay	Assays were carried out by incubating PSMA-positive cells with 0.2 nM MIP-1095 in the presence of 1 μM PSMA-617.	
Experimental Condition	PC3-PIP cell	

b. **The Activity Details of The Studied Drug (*Doxorubicin*)**

Standard Type	Value	Administration times	Dosage	Cell Line
Cell Survival Rate (CSR)	20.00 %	24 h	20 μg/mL	MCF-7 cell
Cell Survival Rate (CSR)	37.00 %	24 h	15 μg/mL	MCF-7 cell
Tumor Growth Inhibition value (TGI)	23.13 %	14 days	5 mg/kg	SK-BR-3 cell
Half Maximal Inhibitory Concentration (IC50)	0.06 uM	48 h	N.A.	U87 cell
Median Effect Concentration(EC50)	6.78 uM	24 h	N.A.	HeLa cell
Cell Viability Rate (CVR)	9.00 %	48 h	1.87 μM	MDA-MB-231 cell

Figure 5. Activity data of PDC's constituent components. (**A**) activity details of a peptide *PSMA-617*. The representative activities included peptide's binding affinity to its receptor, experimental method adopted to measure its binding affinity. (**B**) Activity details of a drug *Doxorubicin*. In each activity datum, the corresponding experimental validation methods (such as administration times, dosage and cell line) were systematically collected and explicitly described.

Consequently, the activity information of both peptide and drug in a studied PDC were also covered by *PDCdb*. As demonstrated in Figure 5A, the activity details for an exemplar peptide PSMA-617, including quantitative measures of its binding affinity, were shown. Moreover, the systematic experimental method used to measure this binding affinity was also described. Similarly, the activity detail of the exemplar drug *doxorubicin* was also provided in PDCdb (as shown in Figure 5B). Under each activity information, the corresponding experimental validation methods (including administration time, dosage and cell line) were fully collected and described. Based on such valuable information, the reader could easily retrieve relevant activity data that might be capable of facilitating the development of studied PDCs, such as increasing the PDC efficacy and reducing the corresponding cytotoxicity (92–94).

Standardization, access and download of PDCs and their activity data

To make the access and analysis of *PDCdb* data convenient for all readers, the collected raw data were carefully cleaned up and then systematically standardized. These standardizations included: (a) all the PDCs, receptors, linkers, drugs, targets and cell lines were cross-linked to established databases; (b) all disease indications were standardized by the latest *International Classification of Disease* (ICD-11) that was officially released by *World Health Organization* (95). Furthermore, a user-friendly interface was created by our database to enable convenient browse and search of data. All PDC-related data could be viewed, accessed and downloaded from *PDCdb*, which could be freely accessed without login requirement at: https://idrblab.org/PDCdb/

Conclusion and perspective

Herein, a database *PDCdb* providing comprehensive biological activities and pharmaceutical data for thousands of PDCs was developed. These data were expected to significantly aid in the effective design of new PDCs for the treatment of various disorders. Since PDCs had emerged as a promising class of targeted therapeutics with substantial pharmaceutical advantages and market potentials, there would be an exponentially increasing amount of new PDC information derived from pa-

tients with different diseases in the future. So, the information in *PDCdb* will be updated promptly, with regular enhancements to the webpages. Furthermore, the accumulation of such 'big data' in PDCdb will facilitate AI-based learning of PDC drug-like patterns, thereby guiding modern drug discovery.

Data availability

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

Funding

Funded by National Natural Science Foundations of China [82373790, 22220102001, 81872798, U1909208]; Natural Science Foundation of Zhejiang Province [LR21H300001]; Fundamental Research Funds for Central Universities [2018QNA7023]; National Key R&D Program of China [2022YFC3400501]; Double Top-Class University [181201*194232101]; Key R&D Program of Zhejiang [2020C03010]; Westlake Laboratory (Westlake Lab of Life Sciences and Biomedicine); Leading Talent of the 'Ten Thousand Plan' National High-Level Talents Special Support Plan of China; Alibaba-Zhejiang University Joint Research Center of Future Digital Healthcare; Alibaba Cloud; The Information Technology Center of Zhejiang University. Funding for open access charge: Natural Science Foundation of Zhejiang Province [LR21H300001].

Conflict of interest statement

None declared.

References

1. Mullard,A. (2023) 2022 FDA approvals. *Nat. Rev. Drug Discov.*, **22**, 83–88.
2. Muttenthaler,M., King,G.F., Adams,D.J. and Alewood,P.F. (2021) Trends in peptide drug discovery. *Nat. Rev. Drug Discov.*, **20**, 309–325.
3. Wang,L., Wang,N., Zhang,W., Cheng,X., Yan,Z., Shao,G., Wang,X., Wang,R. and Fu,C. (2022) Therapeutic peptides: current applications and future directions. *Signal Transduct. Target Ther.*, **7**, 48.
4. Banerjee,S., Pillai,M.R. and Knapp,F.F. (2015) Lutetium-177 therapeutic radiopharmaceuticals: linking chemistry, radiochemistry, and practical applications. *Chem. Rev.*, **115**, 2934–2974.
5. Pomykala,K.L., Hadaschik,B.A., Sartor,O., Gillessen,S., Sweeney,C.J., Maughan,T., Hofman,M.S. and Herrmann,K. (2023) Next generation radiotheranostics promoting precision medicine. *Ann. Oncol.*, **34**, 507–519.
6. Sun,X., Zhang,Y., Li,H., Zhou,Y., Shi,S., Chen,Z., He,X., Zhang,H., Li,F., Yin,J., *et al.* (2023) DRESIS: the first comprehensive landscape of drug resistance information. *Nucleic Acids Res.*, **51**, D1263–D1275.
7. Fu,C., Yu,L., Miao,Y., Liu,X., Yu,Z. and Wei,M. (2023) Peptide-drug conjugates (PDCs): a novel trend of research and development on targeted therapy, hype or hope?*Acta Pharm. Sin. B*, **13**, 498–516.
8. Zhu,Y.S., Tang,K. and Lv,J. (2021) Peptide-drug conjugate-based novel molecular drug delivery system in cancer. *Trends Pharmacol. Sci.*, **42**, 857–869.
9. Pechenov,S., Bhattacharjee,H., Yin,D., Mittal,S. and Subramony,J.A. (2017) Improving drug-like properties of insulin and GLP-1 via molecule design and formulation and improving diabetes management with device & drug delivery. *Adv. Drug. Deliv. Rev.*, **112**, 106–122.
10. Cho,Y.S., Kim,H.R., Park,S.J., Chung,S.W., Ko,Y.G., Yeo,J.H., Lee,J., Kim,S.K., Choi,J.U., Kim,S.Y., *et al.* (2022) Sustained potentiation of bystander killing via PTEN-loss driven macropinocytosis targeted peptide–drug conjugate therapy in metastatic triple-negative breast cancer. *Biomaterials*, **289**, 121783.
11. Wang,Y., Cheetham,A.G., Angacian,G., Su,H., Xie,L. and Cui,H. (2017) Peptide-drug conjugates as effective prodrug strategies for targeted delivery. *Adv. Drug. Deliv. Rev.*, **110-111**, 112–126.
12. Bodei,L., Herrmann,K., Schoder,H., Scott,A.M. and Lewis,J.S. (2022) Radiotheranostics in oncology: current challenges and emerging opportunities. *Nat. Rev. Clin. Oncol.*, **19**, 534–550.
13. Gong,L., Zhao,H., Liu,Y., Wu,H., Liu,C., Chang,S., Chen,L., Jin,M., Wang,Q., Gao,Z., *et al.* (2023) Research advances in peptide–drug conjugates. *Acta Pharm. Sin. B*, **13**, 3659–3677.
14. Lu,M.K., Yin,J.Y., Zhu,Q., Lin,G.L., Mou,M.J., Liu,F.Y., Pan,Z.Q., You,N.X., Lian,X.C., Li,F.C., *et al.* (2023) Artificial intelligence in pharmaceutical sciences. *Engineering*, **27**, 37–69.
15. Yin,J., Li,F., Zhou,Y., Mou,M., Lu,Y., Chen,K., Xue,J., Luo,Y., Fu,J., He,X., *et al.* (2021) INTEDE: interactome of drug-metabolizing enzymes. *Nucleic Acids Res.*, **49**, D1233–D1243.
16. Li,Y.H., Li,X.X., Hong,J.J., Wang,Y.X., Fu,J.B., Yang,H., Yu,C.Y., Li,F.C., Hu,J., Xue,W.W., *et al.* (2020) Clinical trials, progression-speed differentiating features and swiftness rule of the innovative targets of first-in-class drugs. *Brief. Bioinform.*, **21**, 649–662.
17. Fu,T., Li,F., Zhang,Y., Yin,J., Qiu,W., Li,X., Liu,X., Xin,W., Wang,C., Yu,L., *et al.* (2022) VARIDT 2.0: structural variability of drug transporter. *Nucleic Acids Res.*, **50**, D1417–D1431.
18. Zheng,L., Shi,S., Lu,M., Fang,P., Pan,Z., Zhang,H., Zhou,Z., Zhang,H., Mou,M., Huang,S., *et al.* (2024) AnnoPRO: a strategy for protein function annotation based on multi-scale protein representation and a hybrid deep learning of dual-path encoding. *Genome Biol.*, **25**, 41.
19. Wang,Y., Pan,Z., Mou,M., Xia,W., Zhang,H., Zhang,H., Liu,J., Zheng,L., Luo,Y., Zheng,H., *et al.* (2023) A task-specific encoding algorithm for RNAs and RNA-associated interactions based on convolutional autoencoder. *Nucleic Acids Res.*, **51**, e110.
20. Zhang,Y., Sun,H., Lian,X., Tang,J. and Zhu,F. (2023) ANPELA: significantly enhanced quantification tool for cytometry-based single-cell proteomics. *Adv. Sci. (Weinh)*, **10**, e2207061.
21. Ma,B., Fan,Y., Zhang,D., Wei,Y., Jian,Y., Liu,D., Wang,Z., Gao,Y., Ma,J., Chen,Y., *et al.* (2022) De novo design of an androgen receptor dna binding domain-targeted peptide protac for prostate cancer therapy. *Adv. Sci. (Weinh.)*, **9**, e2201859.
22. Yang,Q., Li,B., Tang,J., Cui,X., Wang,Y., Li,X., Hu,J., Chen,Y., Xue,W., Lou,Y., *et al.* (2020) Consistent gene signature of schizophrenia identified by a novel feature selection strategy from comprehensive sets of transcriptomic data. *Brief. Bioinform.*, **21**, 1058–1068.
23. Xue,W., Fu,T., Deng,S., Yang,F., Yang,J. and Zhu,F. (2022) Molecular mechanism for the allosteric inhibition of the human serotonin transporter by antidepressant escitalopram. *ACS Chem. Neurosci.*, **13**, 340–351.
24. Kim,S., Chen,J., Cheng,T., Gindulyte,A., He,J., He,S., Li,Q., Shoemaker,B.A., Thiessen,P.A., Yu,B., *et al.* (2023) PubChem 2023 update. *Nucleic Acids Res.*, **51**, D1373–D1380.
25. Schwartz,L.M., Woloshin,S., Zheng,E., Tse,T. and Zarin,D.A. (2016) ClinicalTrials.gov and Drugs@FDA: a comparison of results reporting for new drug approval trials. *Ann. Intern. Med.*, **165**, 421–430.

26. Avram,S., Wilson,T.B., Curpan,R., Halip,L., Borota,A., Bora,A., Bologa,C.G., Holmes,J., Knockel,J., Yang,J.J., *et al.* (2023) DrugCentral 2023 extends human clinical data and integrates veterinary drugs. *Nucleic Acids Res.*, **51**, D1276–D1287.
27. Knox,C., Wilson,M., Klinger,C.M., Franklin,M., Oler,E., Wilson,A., Pon,A., Cox,J., Chin,N.E.L., Strawbridge,S.A., *et al.* (2024) DrugBank 6.0: the DrugBank knowledgebase for 2024. *Nucleic Acids Res.*, **52**, D1265–D1275.
28. Siramshetty,V.B., Grishagin,I., Nguyen Eth,T., Peryea,T., Skovpen,Y., Stroganov,O., Katzel,D., Sheils,T., Jadhav,A., Mathe,E.A., *et al.* (2022) NCATS Inxight drugs: a comprehensive and curated portal for translational research. *Nucleic Acids Res.*, **50**, D1307–D1316.
29. Zhu,N., Dong,F., Shi,G., Lao,X. and Zheng,H. (2022) HORDB: a comprehensive database of peptide hormones. *Sci. Data*, **9**, 187.
30. Agrawal,P., Bhalla,S., Usmani,S.S., Singh,S., Chaudhary,K., Raghava,G.P. and Gautam,A. (2016) CPPsite 2.0: a repository of experimentally validated cell-penetrating peptides. *Nucleic Acids Res.*, **44**, D1098–D1103.
31. Wang,G., Li,X. and Wang,Z. (2016) APD3: the antimicrobial peptide database as a tool for research and education. *Nucleic Acids Res.*, **44**, D1087–D1093.
32. Balogh,B., Ivanczi,M., Nizami,B., Beke-Somfai,T. and Mandity,I.M. (2021) ConjuPepDB: a database of peptide–drug conjugates. *Nucleic Acids Res.*, **49**, D1102–D1112.
33. Muratspahic,E., Deibler,K., Han,J., Tomasevic,N., Jadhav,K.B., Olive-Marti,A.L., Hochrainer,N., Hellinger,R., Koehbach,J., Fay,J.F., *et al.* (2023) Design and structural validation of peptide–drug conjugate ligands of the kappa-opioid receptor. *Nat. Commun.*, **14**, 8064.
34. Grabeck,J., Lutzenburg,T., Frommelt,P. and Neundorf,I. (2022) Comparing variants of the cell-penetrating peptide sC18 to design peptide–drug conjugates. *Molecules*, **27**, 6656.
35. Vernen,F., Harvey,P.J., Dias,S.A., Veiga,A.S., Huang,Y.H., Craik,D.J., Lawrence,N. and Troeira Henriques,S. (2019) Characterization of tachyplesin peptides and their cyclized analogues to improve antimicrobial and anticancer properties. *Int. J. Mol. Sci.*, **20**, 4184.
36. Ozer,I., Slezak,A., Sirohi,P., Li,X., Zakharov,N., Yao,Y., Everitt,J.I., Spasojevic,I., Craig,S.L., Collier,J.H., *et al.* (2023) An injectable PEG-like conjugate forms a subcutaneous depot and enables sustained delivery of a peptide drug. *Biomaterials*, **294**, 121985.
37. Drucker,D.J. (2020) Advances in oral peptide therapeutics. *Nat. Rev. Drug Discov.*, **19**, 277–289.
38. Philippe,G.J.B., Craik,D.J. and Henriques,S.T. (2021) Converting peptides into drugs targeting intracellular protein-protein interactions. *Drug Discov Today*, **26**, 1521–1531.
39. Yin,J., Sun,W., Li,F., Hong,J., Li,X., Zhou,Y., Lu,Y., Liu,M., Zhang,X., Chen,N., *et al.* (2020) VARIDT 1.0: variability of drug transporter database. *Nucleic Acids Res.*, **48**, D1042–D1050.
40. Zhang,Y., Liu,X., Li,F., Yin,J., Yang,H., Li,X., Liu,X., Chai,X., Niu,T., Zeng,S., *et al.* (2024) INTEDE 2.0: the metabolic roadmap of drugs. *Nucleic Acids Res.*, **52**, D1355–D1364.
41. Davis,R.A., Ganguly,T., Harris,R., Hausner,S.H., Kovacs,L. and Sutcliffe,J.L. (2023) Synthesis and evaluation of a monomethyl auristatin E horizontal line integrin alpha(v)beta(6) binding peptide–drug conjugate for tumor targeted drug delivery. *J. Med. Chem.*, **66**, 9842–9852.
42. Wang,M.D., Hou,D.Y., Lv,G.T., Li,R.X., Hu,X.J., Wang,Z.J., Zhang,N.Y., Yi,L., Xu,W.H. and Wang,H. (2021) Targeted in situ self-assembly augments peptide drug conjugate cell-entry efficiency. *Biomaterials*, **278**, 121139.
43. Guo,X., Jiang,Y. and Zou,Q. (2022) Structured sparse regularized TSK fuzzy system for predicting therapeutic peptides. *Brief Bioinform*, **23**, bbac135.
44. Shen,L., Sun,X., Chen,Z., Guo,Y., Shen,Z., Song,Y., Xin,W., Ding,H., Ma,X., Xu,W., *et al.* (2024) ADCdb: the database of antibody-drug conjugates. *Nucleic Acids Res.*, **52**, D1097–D1109.
45. Rizvi,S.F.A., Abbas,N., Zhang,H. and Fang,Q. (2023) Identification of a pH-responsive peptide-paclitaxel conjugate as a novel drug with improved therapeutic potential. *J. Med. Chem.*, **66**, 8324–8337.
46. Vrettos,E.I., Mezo,G. and Tzakos,A.G. (2018) On the design principles of peptide–drug conjugates for targeted drug delivery to the malignant tumor site. *Beilstein J. Org. Chem.*, **14**, 930–954.
47. Gowland,C., Berry,P., Errington,J., Jeffrey,P., Bennett,G., Godfrey,L., Pittman,M., Niewiarowski,A., Symeonides,S.N. and Veal,G.J. (2021) Development of a LC-MS/MS method for the quantification of toxic payload DM1 cleaved from BT1718 in a phase I study. *Bioanalysis*, **13**, 101–113.
48. Soudy,R., Chen,C. and Kaur,K. (2013) Novel peptide-doxorubucin conjugates for targeting breast cancer cells including the multidrug resistant cells. *J. Med. Chem.*, **56**, 7564–7573.
49. Ziaei,E., Paiva,I.M., Yao,S.J., Sarrami,N., Mehinrad,P., Lai,J., Lavasanifar,A. and Kaur,K. (2023) Peptide-drug conjugate targeting keratin 1 inhibits triple-negative breast cancer in mice. *Mol Pharm*, **20**, 3570–3577.
50. Mou,M., Pan,Z., Zhou,Z., Zheng,L., Zhang,H., Shi,S., Li,F., Sun,X. and Zhu,F. (2023) A transformer-based ensemble framework for the prediction of protein-protein interaction sites. *Research*, **6**, 0240.
51. Deshaies,R.J. (2020) Multispecific drugs herald a new era of biopharmaceutical innovation. *Nature*, **580**, 329–338.
52. Li,F., Yin,J., Lu,M., Mou,M., Li,Z., Zeng,Z., Tan,Y., Wang,S., Chu,X., Dai,H., *et al.* (2023) DrugMAP: molecular atlas and pharma-information of all drugs. *Nucleic Acids Res.*, **51**, D1288–D1299.
53. Fizazi,K., Herrmann,K., Krause,B.J., Rahbar,K., Chi,K.N., Morris,M.J., Sartor,O., Tagawa,S.T., Kendi,A.T., Vogelzang,N., *et al.* (2023) Health-related quality of life and pain outcomes with [(177)Lu]Lu-PSMA-617 plus standard of care versus standard of care in patients with metastatic castration-resistant prostate cancer (VISION): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol.*, **24**, 597–610.
54. van Leeuwen,P.J. and Emmett,L. (2022) ^{18}F-PSMA-11 as an attractive ^{68}Ga-PSMA-11 alternative for prostate cancer imaging. *Eur. Urol.*, **82**, 510–511.
55. Long,A., Oswood,C.J., Kelly,C.B., Bryan,M.C. and MacMillan,D.W.C. (2024) Couple-close construction of polycyclic rings from diradicals. *Nature*, **628**, 326–332.
56. Huang,R.F., Wei,Y.J., Inbaraj,B.S. and Chen,B.H. (2015) Inhibition of colon cancer cell growth by nanoemulsion carrying gold nanoparticles and lycopene. *Int J Nanomedicine*, **10**, 2823–2846.
57. Alas,M., Saghaeidehkordi,A. and Kaur,K. (2021) Peptide-drug conjugates with different linkers for cancer therapy. *J. Med. Chem.*, **64**, 216–232.
58. Fu,J., Zhang,Y., Wang,Y., Zhang,H., Liu,J., Tang,J., Yang,Q., Sun,H., Qiu,W., Ma,Y., *et al.* (2022) Optimization of metabolomic data processing using NOREVA. *Nat. Protoc.*, **17**, 129–151.
59. Yang,Q., Wang,Y., Zhang,Y., Li,F., Xia,W., Zhou,Y., Qiu,Y., Li,H. and Zhu,F. (2020) NOREVA: enhanced normalization and evaluation of time-course and multi-class metabolomic data. *Nucleic Acids Res.*, **48**, W436–W448.
60. Yang,Q., Li,B., Chen,S., Tang,J., Li,Y., Li,Y., Zhang,S., Shi,C., Zhang,Y., Mou,M., *et al.* (2021) MMEASE: online meta-analysis of metabolomic data by enhanced metabolite annotation, marker selection and enrichment analysis. *J. Proteomics*, **232**, 104023.
61. Hope,T.A., Pavel,M. and Bergsland,E.K. (2022) Neuroendocrine tumors and peptide receptor radionuclide therapy: when is the right time?*J. Clin. Oncol.*, **40**, 2818–2829.
62. Langer,M., Kratz,F., Rothen-Rutishauser,B., Wunderli-Allenspach,H. and Beck-Sickinger,A.G. (2001) Novel peptide conjugates for tumor-specific chemotherapy. *J. Med. Chem.*, **44**, 1341–1348.
63. Li,B., Tang,J., Yang,Q., Li,S., Cui,X., Li,Y., Chen,Y., Xue,W., Li,X. and Zhu,F. (2017) NOREVA: normalization and evaluation of

MS-based metabolomics data. *Nucleic Acids Res*., **45**, W162–W170.
64. Zhou,Y., Zhang,Y., Zhao,D., Yu,X., Shen,X., Zhou,Y., Wang,S., Qiu,Y., Chen,Y. and Zhu,F. (2024) TTD: therapeutic target database describing target druggability information. *Nucleic Acids Res*., **52**, D1465–D1477.
65. Mendez,D., Gaulton,A., Bento,A.P., Chambers,J., De Veij,M., Felix,E., Magarinos,M.P., Mosquera,J.F., Mutowo,P., Nowotka,M., *et al.* (2019) ChEMBL: towards direct deposition of bioassay data. *Nucleic Acids Res*., **47**, D930–D940.
66. Muratspahic,E., White,A.M., Ciotu,C.I., Hochrainer,N., Tomasevic,N., Koehbach,J., Lewis,R.J., Spetea,M., Fischer,M.J.M., Craik,D.J., *et al.* (2023) Development of a selective peptide kappa-opioid receptor antagonist by late-stage functionalization with cysteine staples. *J. Med. Chem*., **66**, 11843–11854.
67. Henriques,S.T., Peacock,H., Benfield,A.H., Wang,C.K. and Craik,D.J. (2019) Is the mirror image a true reflection? Intrinsic membrane chirality modulates peptide binding. *J. Am. Chem. Soc*., **141**, 20460–20469.
68. Shim,M.K., Moon,Y., Yang,S., Kim,J., Cho,H., Lim,S., Yoon,H.Y., Seong,J.K. and Kim,K. (2020) Cancer-specific drug-drug nanoparticles of pro-apoptotic and cathepsin B-cleavable peptide-conjugated doxorubicin for drug-resistant cancer therapy. *Biomaterials*, **261**, 120347.
69. Zhou,J., Meng,N., Lu,L., Lu,J., Wu,S., Ding,Y., Wu,S., Bao,Y., Xu,Q., Chen,R., *et al.* (2024) A novel peptide–drug conjugate for glioma-targeted drug delivery. *J. Control Release*, **369**, 722–733.
70. Guo,Q., Liu,Y., Mu,G., Yang,L., Wang,W. and Liu,J. (2020) A peptide–drug hydrogel to enhance the anti-cancer activity of chlorambucil. *Biomater. Sci*., **8**, 5638–5646.
71. Fan,M., Yang,D., Liang,X., Ao,J., Li,Z., Wang,H. and Shi,B. (2015) Design and biological activity of epidermal growth factor receptor-targeted peptide doxorubicin conjugate. *Biomed. Pharmacother*., **70**, 268–273.
72. Zhang,P., Cui,Y., Anderson,C.F., Zhang,C., Li,Y., Wang,R. and Cui,H. (2018) Peptide-based nanoprobes for molecular imaging and disease diagnostics. *Chem. Soc. Rev*., **47**, 3490–3529.
73. Ziaei,E., Saghaeidehkordi,A., Dill,C., Maslennikov,I., Chen,S. and Kaur,K. (2019) Targeting triple negative breast cancer cells with novel cytotoxic peptide-doxorubicin conjugates. *Bioconjug. Chem*., **30**, 3098–3106.
74. Azmat,M., Ghalandari,B., Jessica,J., Xu,Y., Li,X., Su,W., Qiang,Z., Deng,S., Azmat,T., Jiang,L., *et al.* (2023) PepDRED: de novo peptide design with strong binding affinity for target protein. *Anal. Chem*., **95**, 12264–12272.
75. Ahrens,V.M., Kostelnik,K.B., Rennert,R., Bohme,D., Kalkhof,S., Kosel,D., Weber,L., von Bergen,M. and Beck-Sickinger,A.G. (2015) A cleavable cytolysin-neuropeptide Y bioconjugate enables specific drug delivery and demonstrates intracellular mode of action. *J. Control Release*, **209**, 170–178.
76. Etayash,H., Norman,L., Thundat,T., Stiles,M. and Kaur,K. (2014) Surface-conjugated antimicrobial peptide leucocin a displays high binding to pathogenic gram-positive bacteria. *ACS Appl. Mater. Interfaces*, **6**, 1131–1138.
77. Ayo,A. and Laakkonen,P. (2021) Peptide-based strategies for targeted tumor treatment and imaging. *Pharmaceutics*, **13**, 481.
78. Xue,W., Yang,F., Wang,P., Zheng,G., Chen,Y., Yao,X. and Zhu,F. (2018) What contributes to serotonin-norepinephrine reuptake inhibitors' dual-targeting mechanism? The key role of transmembrane domain 6 in human serotonin and norepinephrine transporters revealed by molecular dynamics simulation. *ACS Chem. Neurosci*., **9**, 1128–1140.
79. Li,F., Zhou,Y., Zhang,Y., Yin,J., Qiu,Y., Gao,J. and Zhu,F. (2022) POSREG: proteomic signature discovered by simultaneously optimizing its reproducibility and generalizability. *Brief Bioinform*, **23**, bbac040.
80. Tang,J., Fu,J., Wang,Y., Li,B., Li,Y., Yang,Q., Cui,X., Hong,J., Li,X., Chen,Y., *et al.* (2020) ANPELA: analysis and performance assessment of the label-free quantification workflow for metaproteomic studies. *Brief. Bioinform*., **21**, 621–636.
81. Li,F., Yin,J., Lu,M., Yang,Q., Zeng,Z., Zhang,B., Li,Z., Qiu,Y., Dai,H., Chen,Y., *et al.* (2022) ConSIG: consistent discovery of molecular signature from OMIC data. *Brief. Bioinform*., **23**, bbac253.
82. Wu,W., Luo,Y., Sun,C., Liu,Y., Kuo,P., Varga,J., Xiang,R., Reisfeld,R., Janda,K.D., Edgington,T.S., *et al.* (2006) Targeting cell-impermeable prodrug activation to tumor microenvironment eradicates multiple drug-resistant neoplasms. *Cancer Res*., **66**, 970–980.
83. Lupaescu,A.V., Iavorschi,M. and Covasa,M. (2022) The use of bioactive compounds in hyperglycemia- and amyloid fibrils-induced toxicity in type 2 diabetes and Alzheimer's disease. *Pharmaceutics*, **14**, 235.
84. Saghaeidehkordi,A., Chen,S., Yang,S. and Kaur,K. (2021) Evaluation of a keratin 1 targeting peptide-doxorubicin conjugate in a mouse model of triple-negative breast cancer. *Pharmaceutics*, **13**, 661.
85. Demeule,M., Charfi,C., Currie,J.C., Zgheib,A., Danalache,B.A., Beliveau,R., Marsolais,C. and Annabi,B. (2022) The TH1902 docetaxel peptide–drug conjugate inhibits xenografts growth of human SORT1-positive ovarian and triple-negative breast cancer stem-like cells. *Pharmaceutics*, **14**, 1910.
86. AghaAmiri,S., Ghosh,S.C., Hernandez Vargas,S., Halperin,D.M. and Azhdarinia,A. (2024) Somatostatin receptor subtype-2 targeting system for specific delivery of temozolomide. *J. Med. Chem*., **67**, 2425–2437.
87. Luan,X., Wu,Y., Shen,Y.W., Zhang,H., Zhou,Y.D., Chen,H.Z., Nagle,D.G. and Zhang,W.D. (2021) Cytotoxic and antitumor peptides as novel chemotherapeutics. *Nat. Prod. Rep*., **38**, 7–17.
88. Wang,F., Su,H., Xu,D., Dai,W., Zhang,W., Wang,Z., Anderson,C.F., Zheng,M., Oh,R., Wan,F., *et al.* (2020) Tumour sensitization via the extended intratumoural release of a STING agonist and camptothecin from a self-assembled hydrogel. *Nat Biomed Eng*, **4**, 1090–1101.
89. Petho,L., Olah-Szabo,R. and Mezo,G. (2023) Influence of the drug position on bioactivity in angiopep-2-daunomycin conjugates. *Int. J. Mol. Sci*., **24**, 3106.
90. Yousef,M., Szabo,I., Muranyi,J., Illien,F., Soltesz,D., Bato,C., Toth,G., Batta,G., Nagy,P., Sagan,S., *et al.* (2022) Cell-penetrating dabcyl-containing tetraarginines with backbone aromatics as uptake enhancers. *Pharmaceutics*, **15**, 141.
91. Thell,K., Hellinger,R., Sahin,E., Michenthaler,P., Gold-Binder,M., Haider,T., Kuttke,M., Liutkeviciute,Z., Goransson,U., Grundemann,C., *et al.* (2016) Oral activity of a nature-derived cyclic peptide for the treatment of multiple sclerosis. *Proc. Natl. Acad. Sci. U.S.A*., **113**, 3960–3965.
92. Currie,J.C., Demeule,M., Charfi,C., Zgheib,A., Larocque,A., Danalache,B.A., Ouanouki,A., Beliveau,R., Marsolais,C. and Annabi,B. (2022) The peptide–drug conjugate TH1902: a new sortilin receptor-mediated cancer therapeutic against ovarian and endometrial cancers. *Cancers*, **14**, 1877.
93. Kim,H.R., Cho,Y.S., Chung,S.W., Choi,J.U., Ko,Y.G., Park,S.J., Kim,S.Y. and Byun,Y. (2022) Caspase-3 mediated switch therapy of self-triggered and long-acting prodrugs for metastatic TNBC. *J. Control Release*, **346**, 136–147.
94. Dokus,L.E., Lajko,E., Randelovic,I., Mezo,D., Schlosser,G., Kohidai,L., Tovari,J. and Mezo,G. (2020) Phage display-based homing peptide-daunomycin conjugates for selective drug targeting to PANC-1 pancreatic cancer. *Pharmaceutics*, **12**, 576.
95. Lancet,T. (2019) Icd-11. *Lancet*, **393**, 2275.

Received: August 8, 2024. **Revised:** September 10, 2024. **Editorial Decision:** September 17, 2024. **Accepted:** September 20, 2024