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Themed Issue: The Pharmacology of COVID-19

LETTER TO THE EDITOR

Databases for the targeted COVID-19 therapeutics

Many drugs are being developed and clinically tested for treating COVID-19. The knowledge of the targets and the properties of these drugs are highly useful for facilitating the drug repurposing, clinical evaluation, and drug and target discovery efforts. A variety of databases have provided the dedicated information sources and access facilities to support these efforts. The main features of these databases are described.

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1 | INTRODUCTION

New lines of drugs are being clinically tested for treating the corona virus disease 2019 (COVID-19) with their therapeutic mechanisms investigated (Zhou et al., 2020). Many of these drugs have emerged from the drug-repurposing efforts for suppressing the post-infection disease progression and life-threatening symptom, and new targets of high drug-repurposing potential are discovered by investigating virus-host interaction and infection-induced host proteomics change (Guy, DiPaola, Romanelli, & Dutch, 2020). Particularly, the exploration of the host targets is advantageous over the viral ones in target abundance and the reduced chances of drug resistance (Zhou et al., 2020), which has become the focus of drug-repurposing and discovery efforts (Guy et al., 2020).

In drug-repurposing, the knowledge of the drug targets relevant to COVID-19 therapeutics is key for clinical/biologic evaluations of drug efficacies, investigations of therapeutic mechanisms, and searches of drug-repurposing opportunities (Guy et al., 2020; Zhang, Penninger, Li, Zhong, & Slutsky, 2020). Drug discovery efforts for COVID-19 can be facilitated by the data of target and drug structures for enabling the uses of such drug discovery methods as molecular docking, molecular similarity, pharmacophore, and artificial intelligence (Hong et al., 2020; Jin et al., 2020).

2 | RESULTS AND DISCUSSION

For facilitating COVID-19 drug-repurposing and new drug discovery efforts, several established or newly emerged databases have provided the rich resources and special access facilities for the data of repurposed drugs, investigative agents, and targets of COVID-19 therapeutics (Table 1). ClinicalTrials.gov enables the convenient access to an overwhelming number of ongoing clinical trials by simply searching COVID-19 in "Condition/Disease" box. The resulting data include trial tracking, recruitment, descriptions, and management, which make this database a rich repository for those involving throughout clinical-study life cycle. COVID19 Drug-Repurposing Database (COVIDDRD) focuses on providing the dedicated data of drug-repurposing for COVID-19 (such as investigative agents and their potential target), and it thus promotes COVID-19 drug discovery for biotechnology/pharmaceutical companies. Chemical Abstracts Service (CAS) offers an easy download of 50,000 compounds with either experimentally tested or computationally predicted antiviral activities and provides a highly-motivated library for pharmaceutical chemists working on high-throughput drug screening. PubChem ensures a convenient access to antiviral chemicals and gives a comprehensive description (including medication data, targets, clinical trials, toxicity, hazard, bioassay, molecular interactions, biological pathways, patent, and manufacturer) on each. It is recognized as the largest library for extremely large-scale lead-screening by the scientists of computer-aided drug design. DrugBank designs a "COVID-19 Information Dashboard" to enable the direct access to ~40 repurposed drugs and their data of pharmacology, drug–drug interactions, pharmaco-economics, clinical trials, and targets. These data are related to the wide audiences of pharmacy, medicine, and popular science. **IUPHAR/BPS Guide to PHARMACOLOGY** (GtoPdb) contains the expert-curated ligand-activity-target relationships on investigative COVID-19 drugs, which has emerged as popular source for pharmacologists evaluating drug efficacy. Therapeutic Target Database (TTD) constructs a subdatabase providing abundant data of clinical/preclinical COVID-19 drugs and structure/sequence. It is unique in providing the target validation data and therefore identifying the primary therapeutic target(s) for each drug. Particularly,

TABLE 1 Statistics of COVID-19 relevant drugs and targets in Chemical Abstract Service (CAS), ClinicalTrials.gov, COVID19 Drug Repurposing DB (COVIDDRD), DrugBank, IUPHAR/BPS Guide to PHARMACOLOGY (GtoPdb), PubChem, and Therapeutic Target Database (TTD)

The Number of	CAS	Clinical Trials.gov	COVID DRD	Drug Bank	GtoPdb	Pub Chem	TTD
All COVID-19 drugs/targets	~50,000	171	61	36	56	73	315
	64	**21**	**36**	**50**	**31**	**228**	**76**
Drugs with target identified	82	32	52	21	34	57	119
	64	**21**	**36**	**50**	**31**	**228**	**76**
Drugs in phase 3 clinical trial	0	21	5	7	2	19	59
	0	**6**	**6**	**16**	**1**	**56**	**22**
Drugs in phase 2 clinical trial	0	78	4	4	6	31	106
	0	**8**	**5**	**16**	**6**	**132**	**30**
Drugs in phase 1 clinical trial	0	38	2	1	1	3	43
	0	**9**	**1**	**1**	**1**	**4**	**7**
Drugs tested in preclinical	0	2	3	1	9	9	7
	0	**1**	**1**	**1**	**6**	**86**	**6**
Drugs of investigative 1	0	14	39	16	34	8	94
	0	**3**	**22**	**5**	**17**	**9**	**33**
Drugs of investigative 2	~50,000	18	8	7	4	3	6
	64	**4**	**5**	**18**	**1**	**1**	**3**

Note: The investigative 1 and 2 represent drugs experimentally tested and untested on COVID-19, respectively. The digital numbers in each cell: the number of drugs (underlined and upper) and the number of corresponding drug targets (bold and lower).

TABLE 2 The statistics of divergence and convergence among databases for targeted COVID-19 drugs: Chemical Abstract Service (CAS), ClinicalTrials.gov, COVID-19 Drug Repurposing DB (COVIDDRD), DrugBank, IUPHAR/BPS Guide to PHARMACOLOGY (GtoPdb), PubChem, and Therapeutic Target Database (TTD)

	CAS	Clinical Trials.gov	COVID DRD	Drug Bank	GtoPdb	Pub Chem	TTD
(a) The numbers of *ALL* COVID-19 drugs and targets in each database							
	~50,000	171	61	36	56	73	315
	64	**21**	**36**	**50**	**31**	**228**	**76**
(b) The numbers of *UNIQUE* COVID-19 drugs and targets provided by each database							
	~50,000	16	0	1	0	0	44
	42	**0**	**0**	**17**	**0**	**192**	**15**
(c) The numbers of *OVERLAPPING* COVID-19 drugs and targets between any two databases							
CAS	—	58	24	15	21	23	208
		6	**5**	**1**	**4**	**6**	**13**
Clinical Trials.gov	58	—	11	13	13	26	141
	6		**5**	**2**	**4**	**13**	**19**
COVID DRD	24	11	—	9	11	7	58
	5	**5**		**6**	**4**	**13**	**26**
Drug Bank	15	13	9	—	16	10	30
	1	**2**	**6**		**7**	**26**	**5**
GtoPdb	21	13	11	16	—	16	50
	4	**4**	**4**	**7**		**5**	**17**
Pub Chem	23	26	7	10	16	—	68
	6	**13**	**13**	**26**	**5**		**17**
TTD	208	141	58	30	50	68	—
	13	**19**	**26**	**5**	**17**	**17**	

Note: Digital numbers in each cell: No. of drugs (underlined and upper) and no. of targets (bold and lower).

for every target, its relevance to COVID-19 is systematically evaluated by the literature review for experimentally determined activity of each repurposed drug against its primary therapeutic target, with particular focus on the target's relevance to the regulations of disease progression/life-threatening symptom of COVID-19. This relevance is comprehensively provided in TTD, which makes it a distinctive database for the scientists specialized in the target-based discovery of "first-in-class" drugs.

A comprehensive statistical analysis further reveals the divergence and convergence among these available databases. As shown in Table 2a, CAS contains the largest number of experimentally tested/computationally predicted antiviral agents, while ClinicalTrials.gov and TTD provide the widest coverage of COVID-19 drugs in clinical and preclinical test. For the targets, PubChem and TTD surpass other databases by covering 228 and 76 targets, respectively. An intensive analysis on all these targets in these two databases identifies their varied emphases on their collected data. PubChem considers all interacting proteins of a studied drug as the drug's targets (which provides comprehensive interactome for each drug and is important for assessing drug efficacy and safety), while TTD focuses on identifying the primary therapeutic target for each drug by excluding other interacting proteins. These primary therapeutic targets are essential for the target-based discovery and de-novo design of "first-in-class" drugs. Moreover, the numbers of unique COVID-19 drugs and targets in each database (Table 2b) and overlapping data among databases (Table 2c) are analysed. Although there are extensive overlaps among seven databases (Table 2c), the unique data are also described in CAS, ClinicalTrials.gov, DrugBank, PubChem, and TTD (Table 2b). The timely updating nature of TTD makes it the most comprehensive source for COVID-19 drugs in clinical/preclinical trials and their therapeutic targets, while ClinicalTrials.gov and DrugBank provide some novel therapeutic strategies, other than the targeted ones, for COVID-19 treatments (such as convalescent plasma therapy and ozone/nitric oxide inhalation therapy). All in all, due to the divergences discussed above and the variations in the affiliated data, these seven databases can be a very valuable compliment to each other and should therefore be collectively considered and analysed in the discovery of targeted COVID-19 therapeutics.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest

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