IUPHAR/BPS Guide to PHARMACOLOGY

Database Report

November 2021

www.guidetopharmacology.org

enquiries@guidetopharmacology.org

Contents

Introduction

This database report provides an overview of recent progress and the current status of the IUPHAR/BPS Guide to PHARMACOLOGY (GtoPdb) since our last NC-IUPHAR meeting held in November 2020. Previous reports are online for Apr 2020, Nov 2020 and April 2021. We have reduced redundancy between the reports by purging sections without significant changes. Thus, if you remember any aspect that is not here, it may well be in a previous report (and by all means enquire).

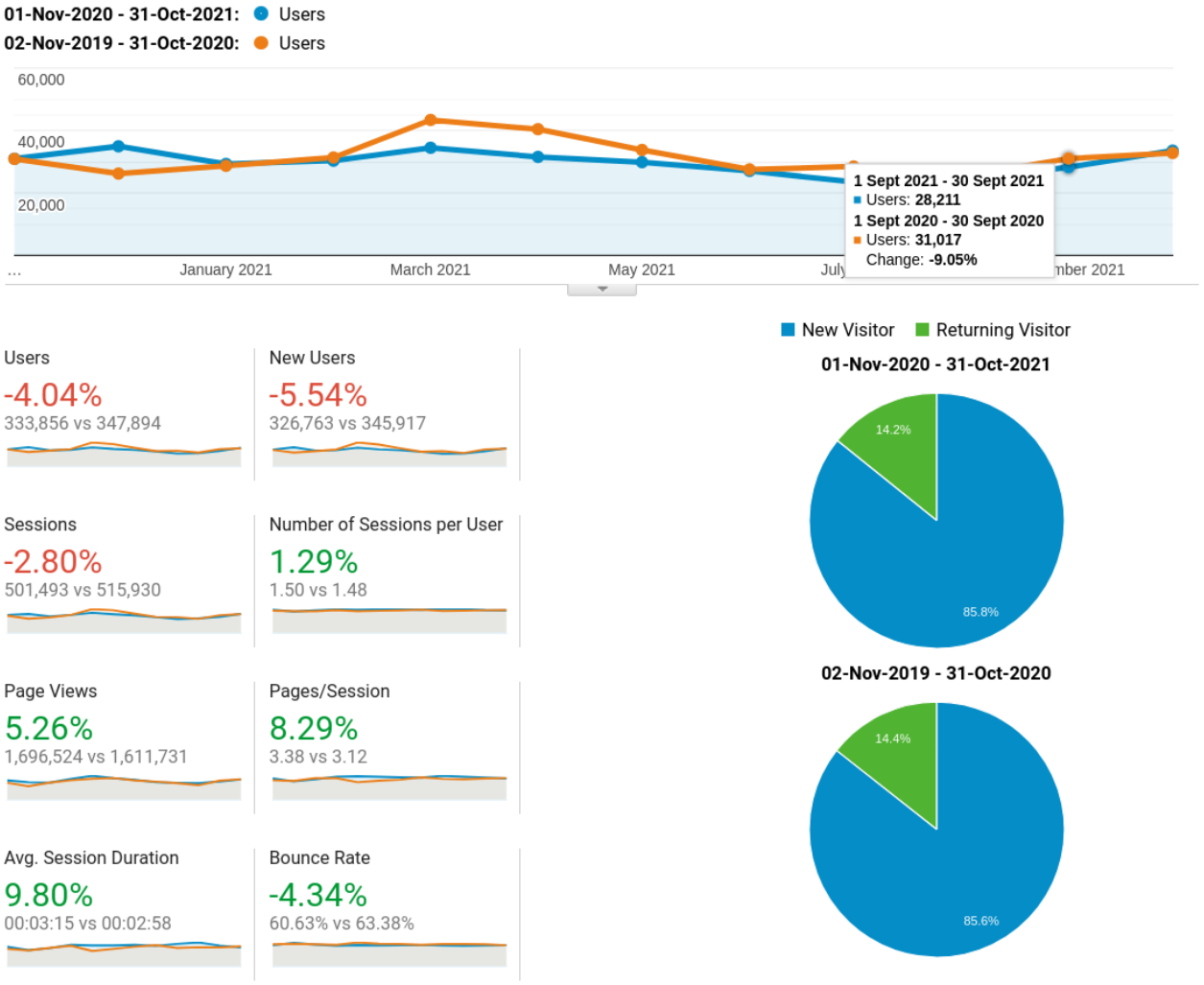
Over the last 5 months the 5th edition of the Concise Guide to Pharmacology (2021/22) as been published and we have have also published our latest NAR update:

Harding SD, Armstrong JF, Faccenda E, Southan C, Alexander SPH, Davenport AP, Pawson AJ, Spedding M, Davies JA; NC-IUPHAR. The IUPHAR/BPS Guide to PHARMACOLOGY in 2022: curating pharmacology for COVID-19, malaria and antibacterials. Nucleic Acids Res. 2021 Oct 30:gkab1010. doi: 10.1093/nar/gkab1010. Epub ahead of print. PMID: 34718737.

Curation has remained focussed on data relevant to the pharmacological mitigation SARS-CoV-2 infection (COVID-19) and on updates for the Medicines for Malaria Venture (MMV) funded Guide to MALARIA PHARMACOLOGY (GtoMPdb).

GtoPdb Website Analytics

GtoPdb Website Access Statistics



Graphs comparing visitors to guidetopharmacology.org for the 12 months from November 2020 to October 2021, with the previous 12 months.

Monthly statistics	**Nov 2020 - Oct 2021 (previous 12 months)**
Sessions	41,791 (42,994)
Users	27,821 (28,991)
Page views	141,377 (134,311)
Pages / Session	3.38 (3.12)
Avg. Session Duration	00:03:15 (00:03:12)

	Country	Sessions	Sessions
		501,493 % of Total: 100.00% (501,493)	501,493 % of Total: 100.00% (501,493)
1.	United States	109,166	21.77%
2.	United Kingdom	56,947	11.36%
3.	China	41,150	8.21%
4.	India	39,839	7.94%
5.	Germany	17,731	3.54%
6.	Japan	15,992	3.19%
7.	Australia	14,123	2.82%
8.	Canada	13,117	2.62%
9.	South Korea	12,939	2.58%
10.	France	9,296	1.85%

Total website sessions connecting to the Guide to PHARMACOLOGY website split by country. Data taken from 01 Nov 2021 to 31 Oct 2021.

Although access to GtoPdb is dominated by the UK and USA (~33% of sessions), access comes from across the globe. In the last 12 months, a total of 216 different countries recorded at least one session and 54 countries recorded 1000 or more sessions.

Query Performance

QUERIES | PAGES | COUNTRIES | DEVICES | SEARCH APPEARANCE | DATES

2

Top queries	Clicks	Impressions	CTR	Position
iuphar	5,979	8,952	66.8%	1.1
guide to pharmacology	2,164	2,553	84.8%	1
molnupiravir chemical structure	827	2,802	29.5%	2
phenylephrine mechanism of action	750	21,266	3.5%	1.1
guidetopharmacology	723	900	80.3%	1
molnupiravir structure	507	7,044	7.2%	1.5
iuphar gpcr	414	465	89%	1
opioid receptors	389	28,502	1.4%	5.5
molnupiravir ingredients	335	14,148	2.4%	8.4
regdanvimab	254	23,138	1.1%	5.6

Rows per page: 10 1-10 of 1000

Screenshot from Google Search Console showing top queries (order by clicks) to the Guide to PHARMACOLOGY website in the last 6 months (14th May 21 - 14th Nov 21)

We can monitor queries to see whether the GtoPdb website/page produces high impressions and ultimately clicks through to the website. Over the last few months the GtoPdb has gained impressions and good ranking for **molnupiravir** searches.

Download Statistics

Yearly period 01 Nov 2020-31 Oct 2021 (comparing with 02 Nov 2019 - 31 Oct 2020)

Google Analytics: Comparison of Downloads

Event Category: Downloads

	Count
2019-2020	4,068
2020-2021	4,033
Change	-0.86%

This corresponds to files downloaded from our main downloads page:
http://www.guidetopharmacology.org/download.jsp

A more specific breakdown is shown here:

	2020-2021	2019-2020	Change
Targets CSV/TSV file	1331	1313	1%
Interactions CSV/TSV file	384	400	-4%
Ligands CSV/TSV file	1245	1010	23%
*Covid ligand/target files **	89	275	-67%
UniProt Mapping file	148	190	-22%
HGNC mapping file	135	143	-6%
*PostgreSQL***	189	192	-1.5%

* This download was available from April 2020, and downloads significantly peaked between April-May 2020.

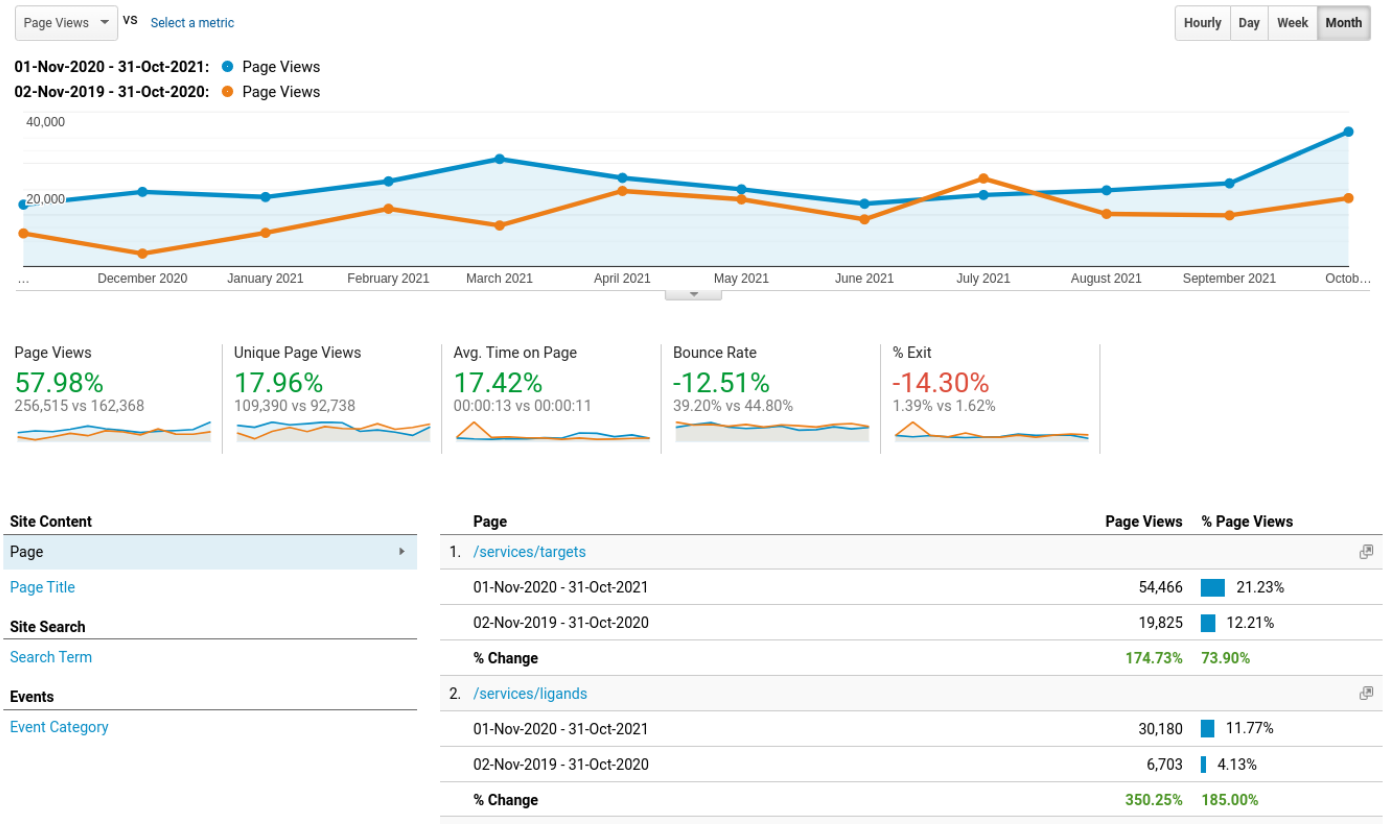
** Total downloads of PostgreSQL database dump files (versions 2020.1 onwards).

Web Services

We have tracked our web-services since March 2017. Calls to the web-service are generally from client computers to our server and are not recorded in the same way as visits to our website. Therefore, we can

not resolve these to specific users, locations or number of visits but we can record hits for each distinct URL.

The image below shows that there were approximately 256,515 total page views over the year, which is an increase on the previous year (162,368).



Traffic to GtoPdb web services over the past year

GtoPdb Content

These database statistics were compiled from our 2nd September release (v2021.3). All database statistics can be found at http://www.guidetopharmacology.org/about.jsp#content.

Targets	Number of (Human) UniProt IDs
7TM receptors	399
Nuclear hormone receptors	48
Catalytic receptors	253
Ligand-gated ion channels	81
Voltage-gated ion channels	144
Other ion channels	53
Enzymes	1246
Transporters	555

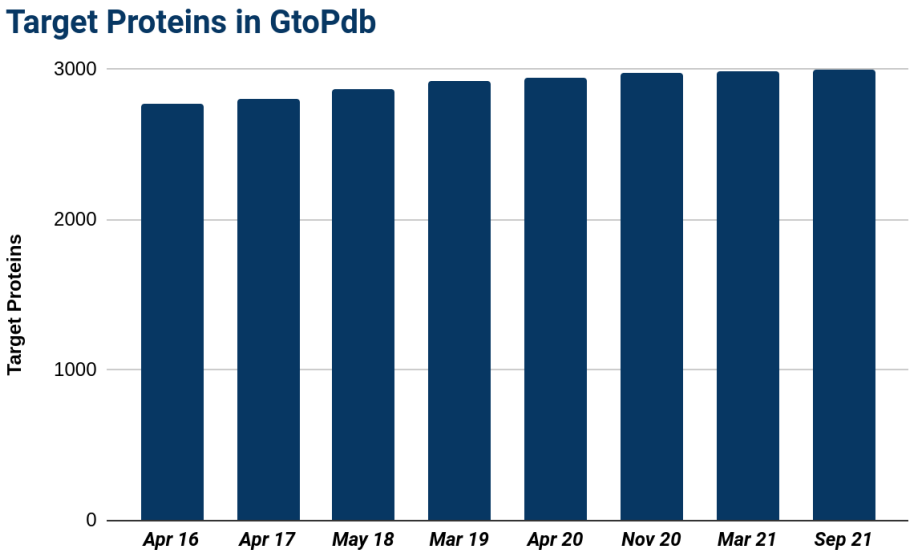
Other protein targets	216
Targets with ligand interactions	1847
Targets with quantitative ligand interactions	1596
Targets with approved drug interactions	674
Primary Targets with approved drug interactions	335
Total number of targets	**2995**

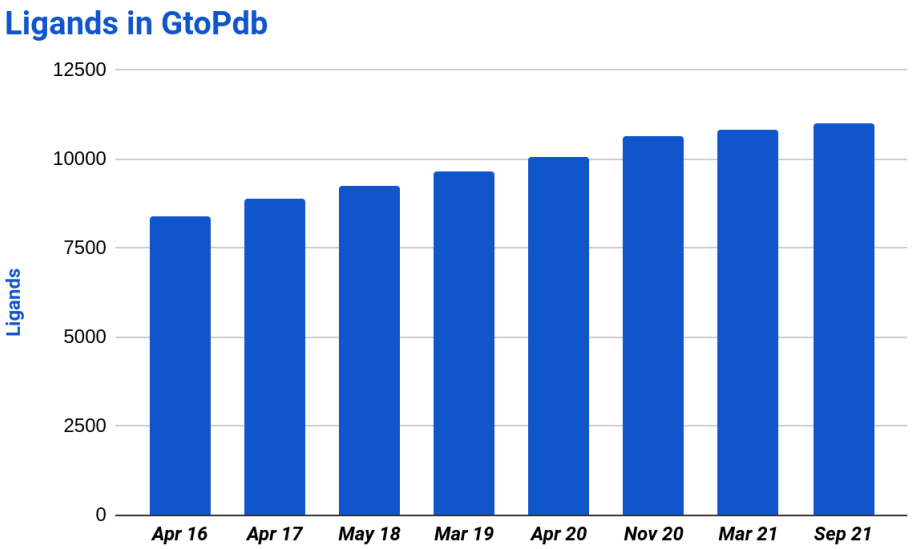
Ligands	**Number of Ligands**
Synthetic organics	7593
Metabolites	516
Endogenous peptides	803
Other peptides including synthetic peptides	1423
Natural products	334
Antibodies	317
Inorganics	39
Approved drugs	1689
Withdrawn drugs	88
Ligands with INNs	2884
Labelled ligands	631
Unique PubChem CIDs (total CID links)	8262 (8463)
Ligands with target interactions	9263
Ligands with quantitative interactions (approved drugs)	8161 (1018)
Ligands with clinical use summaries (approved drugs)	3005 (1685)
Total number of ligands (PubChem SIDs)	**11025**
Number of binding constants	49831
Number of binding constants curated from the literature	18624

GtoPdb Entity Growth

Growth rates over the span of the previous Wellcome Trust grant are documented in earlier reports and our 2016, 2018, 2020 and 2022 NAR papers. Updates come via subcommittee contributions to the Concise Guide, and the continued tagging of pre-existing targets and ligands with comments and references to GtoImmuPdb and GtoMPdb. Note that, while we highlight newly-liganded targets in release notes, the growth of new targets is slow but ligand expansion continues.

	Apr 16	Apr 17	May 18	Mar 19	Apr 20	Nov 20	Mar 21	Sep 21
Target protein IDs	**2775**	**2808**	**2872**	**2920**	**2943**	**2976**	**2985**	**2995**
Ligands total	**8400**	**8872**	**9251**	**9662**	**10053**	**10659**	**10821**	**11025**
Approved drugs	1273	1322	1364	1421	1471	1614	1643	1689
Antibodies	172	212	240	255	270	295	303	317
Peptides	2007	2063	2092	2122	2150	2180	2206	2226
Synthetic small molecules	5363	5729	6048	6401	6816	7303	7428	7593
PubChem SIDs	8328	8831	9251	9662	10053	10659	10821	11025
PubChem CIDs	6163	6813	7109	7407	7483	7994	8102	8262
Binding constants	45534	46287	47058	48071	48902	49363	49558	49831
References	29247	31239	33245	35723	37261	39133	40022	18624





GtoPdb Updates

Targets

There have been no major updates to any target families since the revisions made for the Concise Guide (21-22 ed).

New targets:

Coronavirus proteins three of which are active therapeutic targets

Mpro (3CL-pro): target of Pfizer's oral candidate PF-07321332

RNA-dependent RNA polymerase (RdRP): target of remdesivir (approved); molnupiravir (approved); bemnifosbuvir (AT-527; Phase 2/3)

Spike protein: target of a number of approved monoclonal antibodies casirivimab, imdevimab (Regeneron's Ronapreve cocktail), regdanvimab (Celltrion)

Human proteins

coagulation factor III, tissue factor: tisotumab vedotin (approved, oncology)

heat shock protein family A (Hsp70) member 5: potential therapeutic target for viral infections (incl. SARS-CoV-2), chemoresistant cancers and inflammation

HtrA serine peptidase 1: galegenimab (Ph 2 geographic atrophy)

clusterin: sotevtamab (Ph2 immunomodulator, antineoplastic)

transferrin receptor (CD71): exploited to improve site-specific drug delivery, including drug delivery across the blood-brain barrier e.g. pabinafusp alfa, lepunafusp alfa that deliver enzymes that are deficient in lysosomal storage disorders (both approved in Japan)

Ligands

In preparing the NAR update (Harding et al. 2021), the following table was prepared to summarise the new ligands added to GtoPdb in the 2021.3 database release with comparison to the 2019.4 release (Sep 2019).

The *New Ligands* column shows count of new ligands for each category; *Updated Ligands* shows count of existing ligands, already curated in GtoPdb, now included in the categories. Columns 4 and 5 show the total ligands count for each category from our 2021.3 (Sep 2021) and 2019.4 (Sep 2019) database releases.

	New Ligands	Updated Ligands	Total Ligands (2021.3)	Total Ligands (2019.4)
Approved Drugs	190	56	1688	1442
WHO Essential Medicines	55	34	282	193
Antibacterials	280	23	303	0
Ligands with Quantitative Interaction data	679	27	8161	7455
Antimalarials	37	5	114	72
COVID-Relevant Ligands	28	54	82	0
All Ligands	1222	0	11025	9803

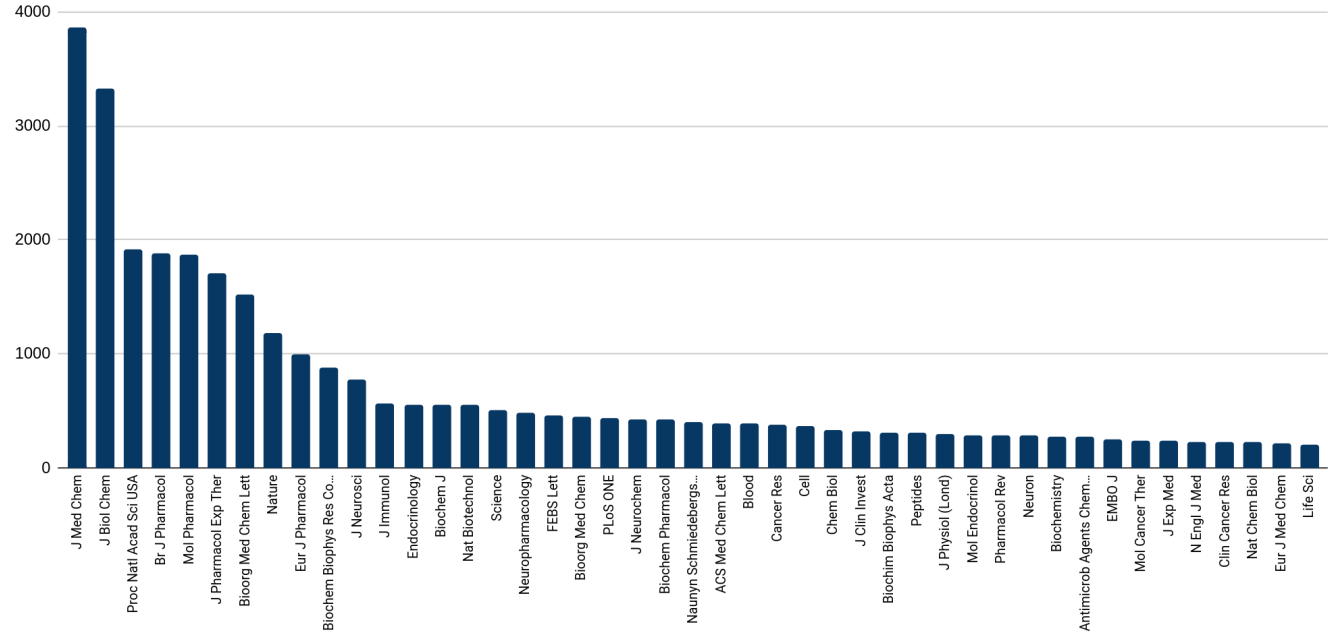
The categories reflect the key areas of curation for antibacterials (in collaboration with AntibioticDB), antimalarials (as part of the continuing MMV funded work) and coronavirus related ligands as a response to the COVID-19 pandemic.

Analysis of journals contributing to curated data

The following table and graph show the count of unique articles from journals curated in the GtoPdb. The table is restricted to those journals with over 500 unique curated articles. The graph expands this to all journals with over 200 unique curated articles.

Title	Count
J Med Chem	3861
J Biol Chem	3331
Proc Natl Acad Sci USA	1914
Br J Pharmacol	1882
Mol Pharmacol	1867
J Pharmacol Exp Ther	1710
Bioorg Med Chem Lett	1516
Nature	1183

Eur J Pharmacol	992
Biochem Biophys Res Commun	878
J Neurosci	776
J Immunol	566
Endocrinology	554
Biochem J	552
Nat Biotechnol	551
Science	513



GtoPdb Coronavirus (COVID-19) Information Page

As a response to the SARS-CoV-2 pandemic, we have been maintaining a coronavirus information page. This page, available since March 2020, is updated weekly (compared to quarterly for the main website) to allow rapid dissemination of reviewed and curated coronavirus therapeutic developments.

Many of these emerging strategies rely on repurposing existing drugs, and others are completely new, but all rely on existing scientific evidence of mechanistic approaches that are effective against either similar viral infections or the serious symptoms that are caused by COVID-19. Compounds that have verified activity, and both established and emerging host and coronavirus targets, are regularly reviewed and updated with detailed curator comments and links to pharmacological data within the GtoPdb.

The page has sections on the key targets and ligands of interest - linked into the more detailed GtoPdb pages. As of Nov 2021 we have 100 unique entries in our table of COVID-19 relevant ligands, of these, 82 have ligand summary pages in GtoPdb, 48 of which are approved drugs.

There are 9 targets listed on the page all with detailed pages in GtoPdb. Seven of these are curated protein targets: ACE2, CD147, furin, Neurophilin 1, SAR-CoV-2 main protease, SARS-CoV-2 nsp3/PL-pro and TMPRSS2, and one, GM-CSF, is a ligand target. The ninth, OAS1, is a protein target listed but not curated in the database.

In addition to the targets and ligands on the coronavirus page, many more entities in the GtoPdb have curator comments regarding evidence of a relationship to SARS-CoV-2 and/or COVID-19 (a search using SARS-CoV-2 retrieves 298 hits).

There are also sections providing useful links to other resources and key publications.

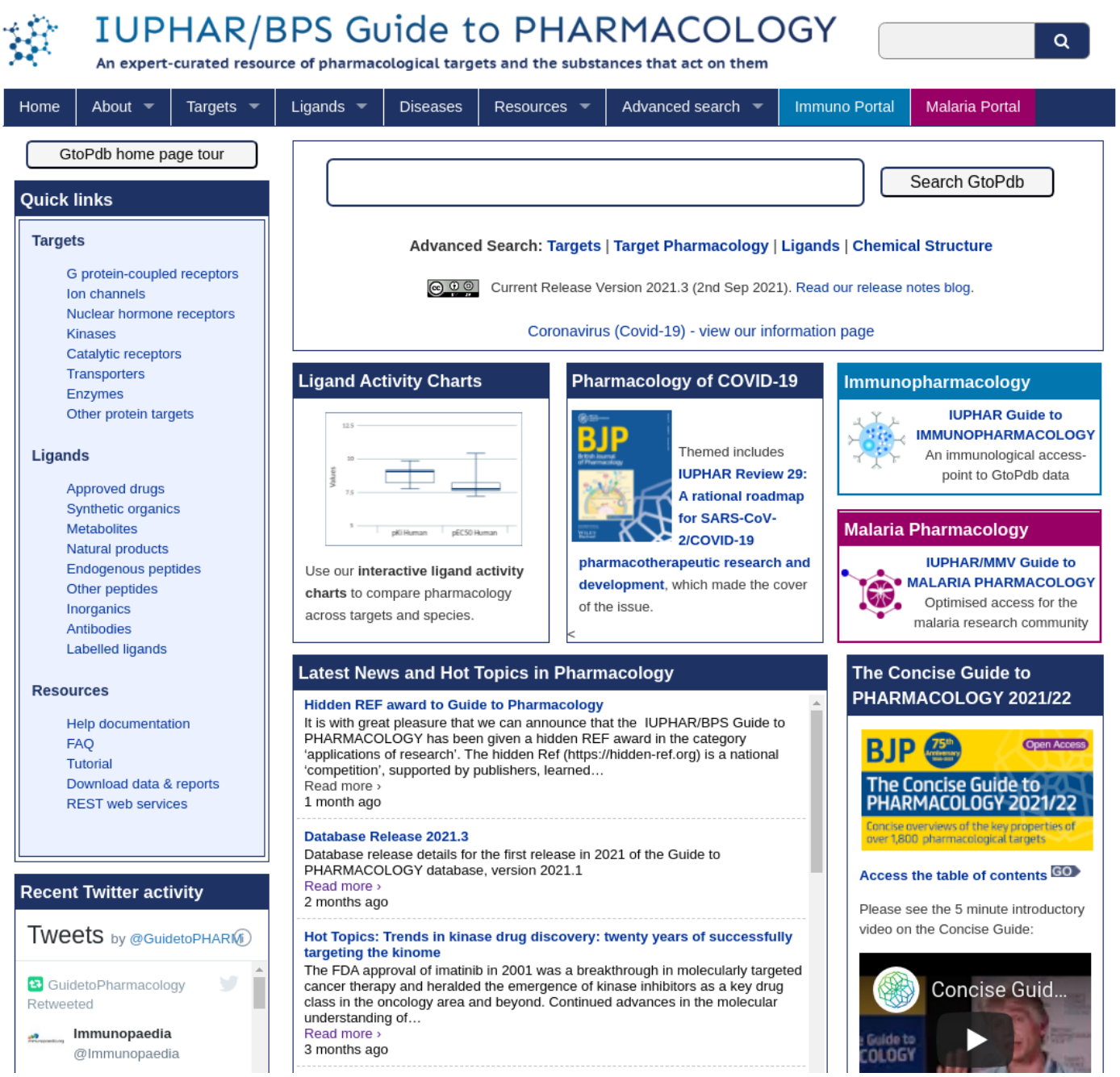
The GtoPdb Coronavirus page has been included in the following data hubs:

- European Data COVID-19 Data Portal, related resource (database) https://www.covid19dataportal.org/related-resources
- ELIXIR-UK https://elixiruknode.org/elixir-uk-our-support-to-covid-19-research/
- ELIXIR https://elixir-europe.org/services/covid-19#access
- BPS COVID-19 trusted resources https://www.bps.ac.uk/covid-19/resources-and-trusted-information/journals-and-publications

New Home Page

The Guide to PHARMACOLOGY home-page is being revised with an aim to give priority to ways users can access the data. The site search and links to advanced search tools will be more prominent, as will panels linking to ligand activity graphs, GtoImmuPdb, GtoMPdb, and current key resources (such as the coronavirus information page and publication).

Page elements are more condensed to the top of the page and the site banner has been updated. We expect to make the new home page available at the next database release.



Ligand Download Files

We have been investigating how best to provide details on endogenous or natural ligands by means of csv download. Currently, GtoPdb provides a simplified list of all endogenous/natural ligands curated in the database https://www.guidetopharmacology.org/DATA/endogenous_ligands.csv. This is a list of the unique ligand-target pairings where the ligand is indicated as being endogenous.

In collaboration with Prof. David Gloriam's research group at the University of Copenhagen, we've been looking at extending this to provide quantitative interaction data for endogenous pairing along with exporting comments fields. This is to make it easier to obtain all data related to endogenous/natural ligands.

We hope to have this update endogenous download file available at our next database release.

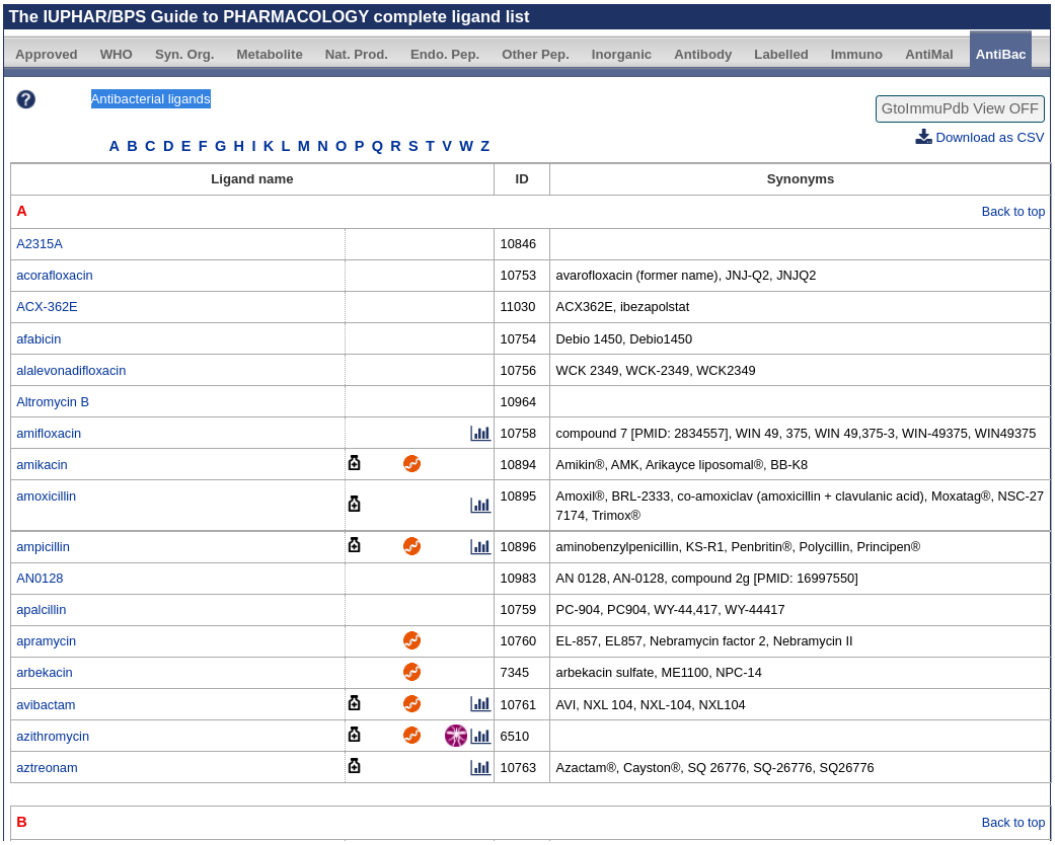
Antibiotic DB Collaboration

We have continued our collaboration with Prof. Laura Piddock (University of Birmingham) and her research group at Antibiotic DB (ADB; www.antibioticdb.com). Through this interaction, GtoPdb provides chemistry and pharmacology for the antibacterial compounds curated within ADB. Currently we have **305 ligands** tagged in GtoPdb as 'antibiotic' and **247** of these have links to compounds at AntibioticDB.

More details are included in our previous report. This collaboration has also been described in more detail in our latest NAR update:

Harding SD, Armstrong JF, Faccenda E, Southan C, Alexander SPH, Davenport AP, Pawson AJ, Spedding M, Davies JA; NC-IUPHAR. The IUPHAR/BPS Guide to PHARMACOLOGY in 2022: curating pharmacology for COVID-19, malaria and antibacterials. Nucleic Acids Res. 2021 Oct 30:gkab1010. doi: 10.1093/nar/gkab1010. Epub ahead of print. PMID: 34718737.

We have since extended the GtoPdb website to display ligands tagged as Antibacterial on the ligand list pages.



Screenshot of the ligand list page showing antibacterial ligands curated in GtoPdb

Connectivity

PubChem Statistics for GtoPdb, GtoImmuPdb and GtoMPdb

The stats for the 2021.3 release (with 2021.1 in brackets) are as follows (N.B. the links below can be slow but if they do time out try purging your browser cache).

1. Substances (SID) that we submit to PubChem (refreshing previous submissions) are up to 11031 (10826).
2. Those that have defined chemical structures are merged into 8976 (8704) Compound Identifiers, CIDs (i.e. small molecules and peptides below ~ 70 residues)
3. From our 8704 CIDs 7503 have vendor matches
4. The select "IUPHAR/BPS Guide to PHARMACOLOGY"[SourceName] AND gtopdb_approved [Comment] now retrieves 1688 SIDs (1643) which link to 1505 approved drug CIDs
5. Of our SIDs, 1345 (1339) are tagged in GtoImmuPdb and 324 (317) of these are approved drugs
6. Of our CIDs 928 are tagged in GtoImmuPdb
7. Of our SIDs, 114 are tagged in GtoMPdb and 24 of these are approved drugs
8. Of our CIDs 112 are tagged in GtoMPdb
9. We have 2093 (2000) structures that ChEMBL does not have, 6367 not in DrugBank.
10. 323 (312) structures where GtoPdb is unique as the source. In most cases this is because we were first to extract the paper or patent and push the ligand structures into PubChem where they get linked to the PubMed entries (see Link out section below). There may be some cases where our stereo configuration is unique (InChIKey) but related to other entries (InChKey inner layer). Inspection of " Related Compounds" and "Same Connectivity" will indicate this.
11. We continue to curate clinical monoclonal antibodies with the PubChem Substance select "IUPHAR/BPS Guide to PHARMACOLOGY"[SourceName] gtopdb_antibody" returning 317 SIDs. Adding "gtopdb_approved" gives 113.
12. We have now included an antibacterial tag in our PubChem upload, the select "IUPHAR/BPS Guide to PHARMACOLOGY"[SourceName] AND gtopdb_antibacterial[All Fields] " returns 302 SIDs, 102 of which are tagged as approved drugs.

The ability to combine selects and filters of our own PubChem entries, find related linked sets (e.g. pivoting from Substances to Compounds) and compare these to other sources in PubChem becomes very informative and powerful. Users are also reminded that, via the InChIKeys or SMILES strings, any of our ligand downloads (including combinations or parts of) can be cast against PubChem using their Identifier Exchange Service to allow detailed exploration of the extensive PubChem links. Users needing guidance for PubChem interrogations are welcome to contact us.

NCBI LinkOuts

GtoPdb maintains sets of links in the NCBI LinkOut service, to the Protein, Nucleotide, Gene and PubMed databases. Our links are updated frequently.. Below is the count of all NCBI database records that contain 'LinkOuts' to GtoPdb. The PubMed count covers all references in the databases including reviews and additional reading for target families. Note that the LinkOut pointers link users back to the database. For various technical reasons associated with NCBI mapping stringencies the three sets of entity links have an element of over-counting with redundancy. However the PubMed links are clean because they are assigned via our own curation.

Protein 5986

Nucleotide 5937

Gene 8468

PubMed 30,619 (https://pubmed.ncbi.nlm.nih.gov/?term=loprovguidpharm[SB])

Europe PMC

GtoPdb maintains records in the Europe PMC External Links Service. Unlike the larger set of NCBI Outlinks, these publication links are restricted to papers from which GtoPdb interaction data have been curated. These link targets and/or ligands mentioned in the article back to GtoPdb detailed pages.

The above screengrabs show an example of the links from (Southern et al. 2013). Under the 'Data' tab on the left-hand side the data cited in the article can be found. This shows 31 links beach to GtoPdb ligands and targets.

As of April 2021 there were 7,359 articles in Europe PMC with links to GtoPdb targets and/or ligands. The EPMC interface query is (LABS_PUBS:"1969")

Full URL: https://europepmc.org/search?query=%28LABS_PUBS%3A%221969%22%29

We have recently updated the link at EPMC and once processed expect the number of articles to increase to 7,488.

Bibliometrics and Scholarly Portals

- As outlined in previous reports we track various metrics for the GtoPdb team and NC-IUPHAR affiliated papers in PubMed, PubMed Central , European PubMed Central (EPMC) Kudos entries and Altmetrics.

- Team members have individual Google Scholar pages as well as ResearchGate entries and Edinburgh Research Explorer profiles.

- However, the profile of choice (as EMPC linked with citation graphs) has now become ORCID IDs for which we have JLS 0000-0002-5275-6446 , EF 0000-0001-9855-7103 , AJP 0000-0003-2280-845X, CS 0000-0001-9580-0446, SDH 0000-0002-9262-8318 and JFA 0000-0002-0524-0260.

Below are the (live) April 2021 live bibliometric updates compared to the November 2020 metrics. These are given with EPMC links which have the advantage over PubMed of directly generating a citation ranking for any set (but with lower citation rates than PubMed, Google Scholar or WOS).

- Database team members have 193 cumulative co-authored publications

- The team is on their 8th NAR Database Issue from 2009 to 2022

- IUPHAR reviews in BJP: 31.

- IUPHAR Pharmacological Reviews: 108

- The cumulative BJP “Concise Guide” set now takes us to 40 papers

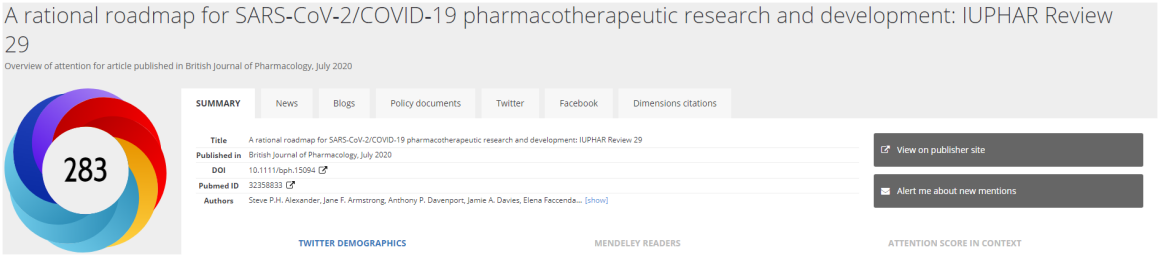
- We continue to get high citation rates in our NAR and Concise Guide articles because BJP and BJCP select these as reference citations for the GtoPdb outlinks. Top of the list is our NAR 2018 entry (PMC5753190) with 1,151 citations (according to EPMC) or 1,212 (according to PubMed). This thus overtakes our 2016 paper (PMC4702778) with 907 (EMPC) or 913 (PubMed) citations, and the 2014 paper (PMC3965070) that reached 698 / 725 .

- The “Concise Guide” citations are currently led by 2017/18 Enzymes (PMC5650666) at 557 followed by 2015/16: Enzymes (PMC4718211) at 511 and 2013/14: G protein-coupled receptors (PMC3892287) at 468.

- While these two papers are not BJP reference citations, we are pleased to note that our 2020 NAR article has already picked up 59 PubMed citations. Our BJP SARS-Cov-2 review acquired 32 PubMed citations.

- The overall citation performance has resulted in team members AJF, SDH, JLS, EF, AJP, CS and JAD, along with IUPHAR co-authors, SPHA, MS, and APD being listed in the Clarivate 2021 rankings of Highly Cited Researchers.

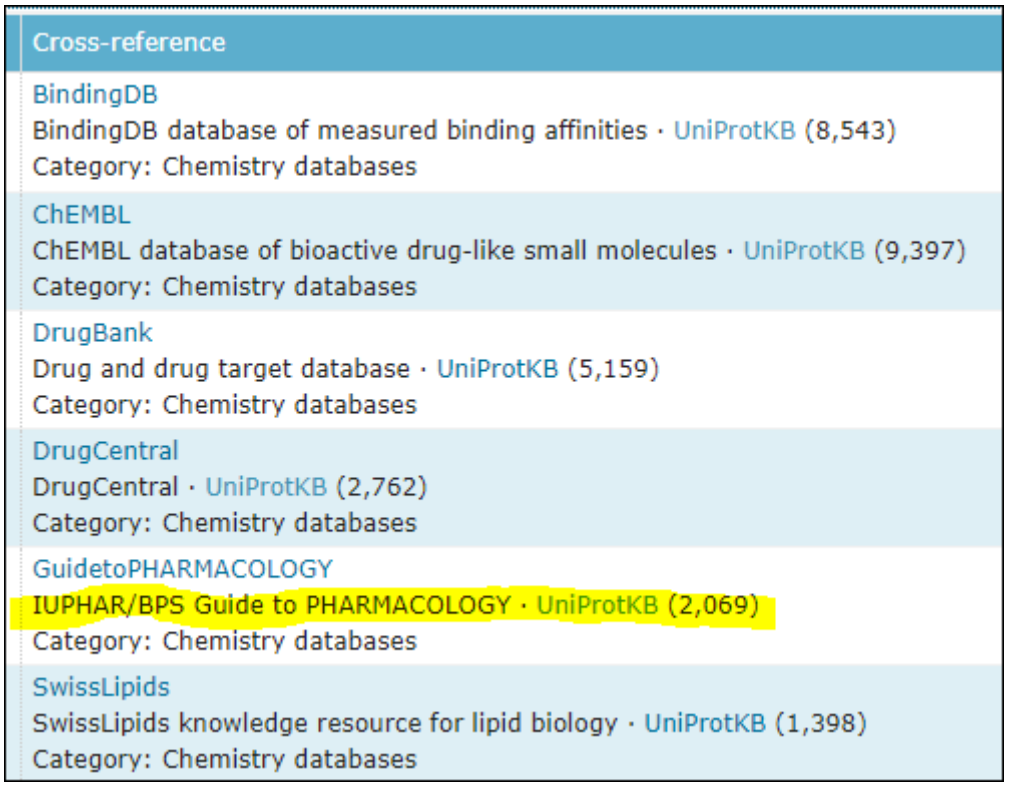
- The Altmetric rankings for all our OA papers are indexed in ScienceOpen. Top of the list by some margin at 283 is our BJP SARS-Cov-2 review



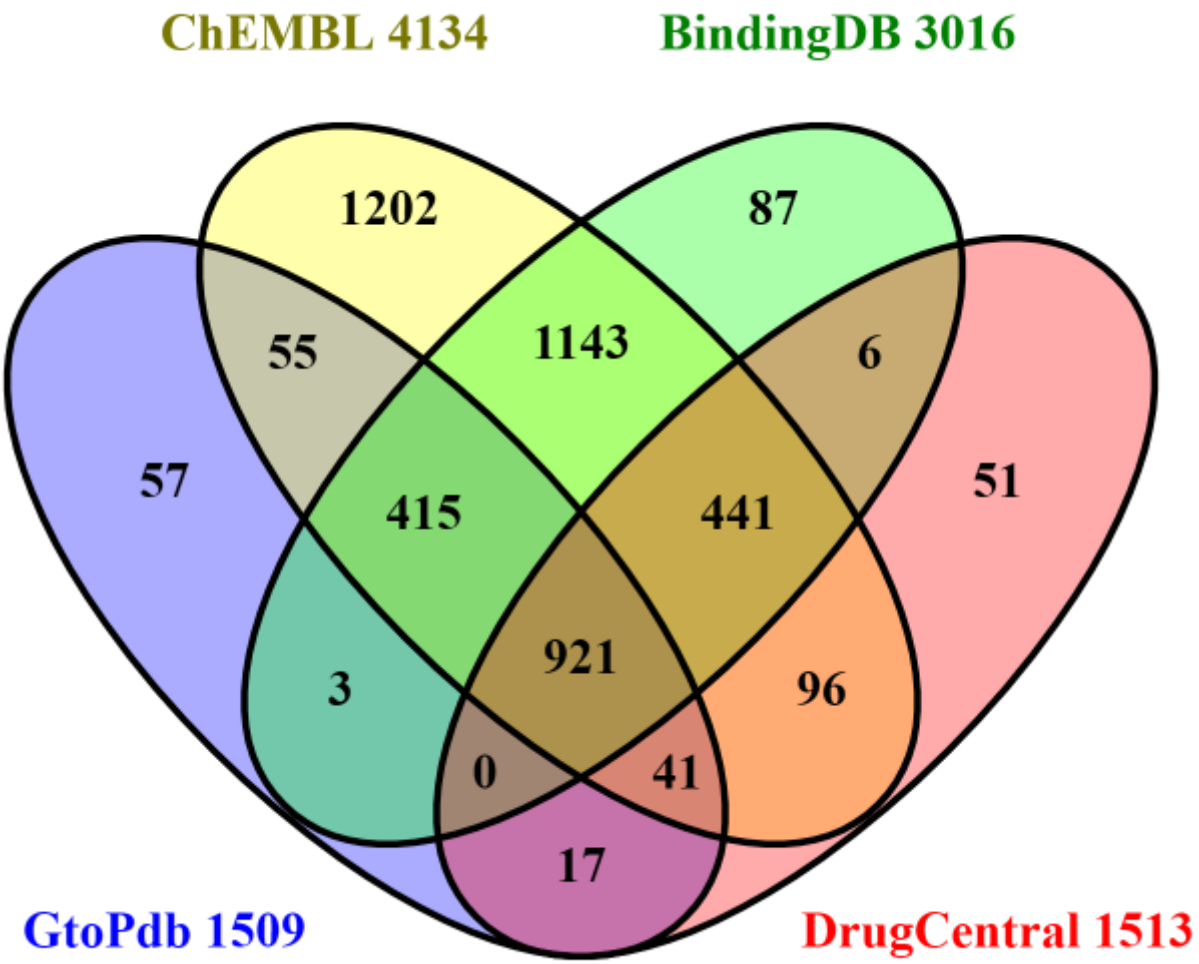
In second place we have [The Concise Guide to PHARMACOLOGY 2015/16: Enzymes](). The more modest score of 55 still puts this in the top 5% of all research outputs scored by Altmetric (n.b. Altmentric sores are also displayed under the “Citations & impact” tab in EPMC for both open or paywalled articles).

EBI UniProtKB/Swiss-Prot cross-references

Below are the metrics for UniProt 2021_04 chemistry sources (updated from 2021_02 in April). Context for these has been given in previous reports. They provide valuable protein < > chemistry mappings including our own targets where we have curated quantitative ligand interactions of generally < 1uM. Note that SwissLipids is the odd-man-out where the curated chemical interactions are for metabolites rather than activity modulators but nonetheless useful.



Even though these sources have slightly different ways of going about their curatorial business it is informative to compare and contrast the four below (omitting DrugBank which has a tendency to over-map and has not recently updated these cross-refs) to give both a druggable proteome snapshot and our unique contribution to the aggregate coverage. The Venn diagram for the November human Swiss-Prot entries are shown below.



There are interesting aspects of relative coverage that cannot be expanded on here (n.b. individual entries can be followed through to their sources via UniProt). However salient observations include that, cumulatively, ~20% of the human proteome is druggable. A second observation is that each source has complementary unique content, including the 57 GtoPdb-only targets. The divergences are of interest but need deeper analysis to discern what curatorial selectivity (e.g. journal choice) explains these differences.

HGNC

We continued to use HGNC gene identifiers and names for targets in GtoPdb. In total this covers 3,000 human targets. We also use HGNC nomenclature for updating protein names in some cases.

GPCRdb

372 targets in GtoPdb have links to GPCRdb. https://gpcrdb.org/

DrugCentral and Pharos

We continue to engage with these two resources that are part of the Illuminating the Druggable Genome (IDG) program. We now include links from ligand pages to DrugCentral where we are one of their

acknowledged sources and cited in their latest NAR PMID 33151287. The process for mapping our ligands to their compounds is downloading the structures in SMILES/InChI format from DrugCentral (https://unmtid-shinyapps.net/download/DrugCentral/2021_09_01/structures.smiles.tsv) and map, via InChI Key to GtoPdb ligands. In our next database release (late in 2021) the links to DrugCentral will be updated and there will be **1577 GtoPdb ligands to mapped 1521 DrugCentral compounds**. In total this is an additional 54 mappings. The links to DrugCentral are shown on our ligand summary pages and DrugCentral IDs are included in the new ligand ID mapping file (https://www.guidetopharmacology.org/DATA/ligand_id_mapping.csv).

On the protein side the role of Pharos in the IDG is enriching knowledge around human targets and monitoring their therapeutic development levels. We are also a declared source and cited in their recent NAR PMID 33156327. Because Pharos offers a particularly rich set of functional genomic and genetic links for targets we have now added this as one of our protein links.

Reactome

We continue to collaborate with Reactome to identify mappings between GtoPdb ligand IDs (identifiers) and Reactome Drug and Reaction pages. See our previous report for more details. 554 links from 323 ligands.

Alphafold

Links have also been recently added from target pages to Alphafold (https://alphafold.ebi.ac.uk/), which means the majority of protein targets in GtoPdb link to a predicted 3D structure.

RESOLUTE Knowledgebase

Specialist links have been added to the RESOLUTE Knowledgebase (https://re-solute.eu/knowledgebase). RESOLUTE aims, through systematic and coordinated efforts, to improve understanding of the solute carrier (SLCs) proteins. These are a relatively understudied class of proteins and represent a largely untapped source of new potential drug targets. So building links between GtoPdb and RESOLUTE will bring benefits to users of both resources.

HELM Notation

We have extended the database to be able to curate and display HELM notation for peptides. Currently this has been added to over 60 peptides, with more planned in future releases.

IUPHAR Pharmacology Education project (PEP)

The IUPHAR Pharmacology Education Project continues to be developed “as a learning resource to support education and training in pharmacological sciences” and celebrated its 5th birthday on 1st April 2021.

Financial support is in place for one 0.5 FTE for the next year.

Succession Planning

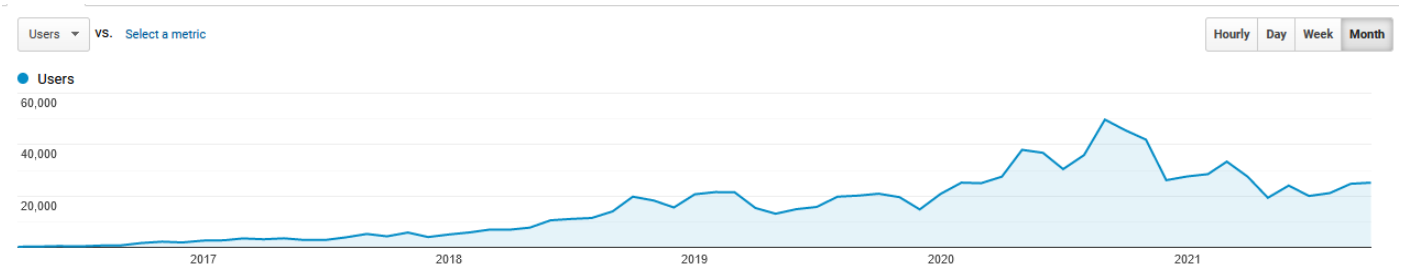
Clare Guilding (PEP Deputy Director; Newcastle University, Vice-Chair of IUPHAR’s Education Section & contributor to BPS Education and Training Committee), John Szarek and Simon Maxwell (PEP co-Directors) are liaising with IUPHAR to arrange taking stewardship of PEP into the remit of IUPHAR-ed. This is likely to result in a revised job description for the new IUPHAR-ed chairperson, with the expectation that the role will include:

- Coordinating IUPHAR’s activities in education in basic and clinical pharmacology, including educational database initiatives.
- Ensure financial and content viability of Pharmacology Education Project (PEP) and its worldwide utility and impact.
- Liaise with Pharmacology Education Project office.

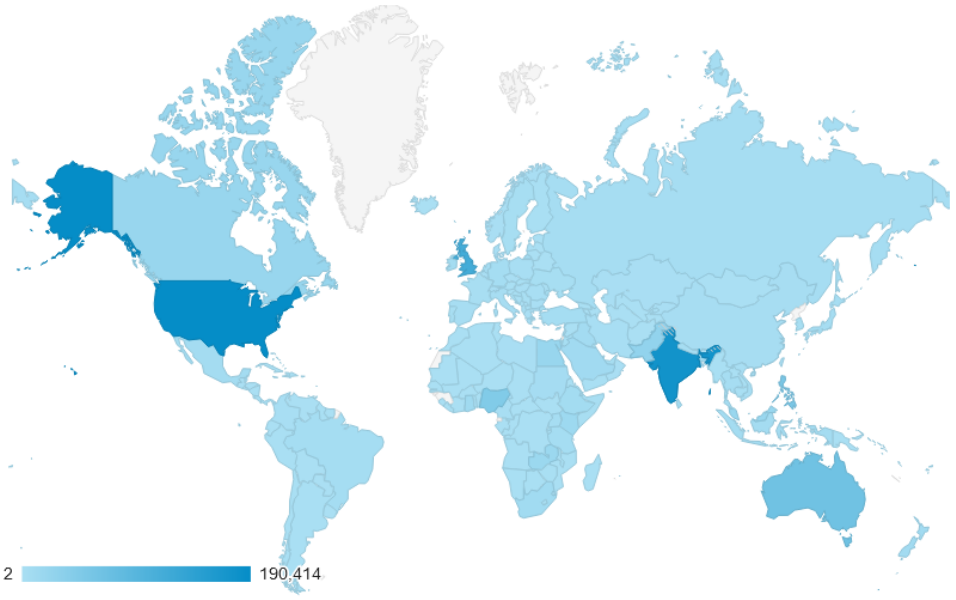
Google Analytics data charts for PEP site usage since 1st April 2016

Google Analytics shows that user sessions continue to average >25K/month.

Monthly user sessions



Global Access



Social Media

PEP has >1500 followers of our twitter handle, @PharmacologyEd (up 300 since the last report in April 2021).

The Guide to Immunopharmacology Database (GtoImmuPdb)

GtoImmuPdb is an extension of GtoPdb and its development involved modifications and extensions to the underlying GtoPdb schema to incorporate new immune system specific data types (such as processes, cell types and disease). It also involved further development of the existing GtoPdb website to surface this new data and incorporate it into the existing search and browse mechanisms. The GtoImmuPdb portal is available at (www.guidetoimmunopharmacology.org).

In October 2018, we officially launched the IUPHAR Guide to IMMUNOPHARMACOLOGY, having made the first public release back in June 2018. Technical details on its development and blog posts related to the resource can be found here.

GtoImmuPdb target and ligand curation

642 targets tagged as immuno-relevant. 642 targets, 446 have quantitative interaction data

1345 ligand tagged as immuno-relevant. 989 of the immuno ligands have quantitative interaction data, 214 of which are approved drugs

Detailed lists on:

www.guidetoimmunopharmacology.org/immuno/immunoHelpPage.jsp

Immuno Process Data

The table below summarises the unique targets (UniProtKB) annotated to each category and the total target-GO annotations (data here is from the 2021.3 release).

Process Category	GtoPdb Human UniProtKB	Target-GO annotations
Barrier integrity	60	86
Inflammation	761	1715
Antigen presentation	174	279
T cell (activation)	255	568
B cell (activation)	207	354
Immune regulation	647	1771
Tissue repair	55	60
Immune system development	303	585
Cytokine production & signalling	577	1725
Chemotaxis & migration	290	633
Cellular signalling	555	1435

Immuno Cell Type Data

The table below shows the top-level cell type categories used in GtoImmuPdb along with the Cell Ontology (CO) terms mapped to each category. The Cell Ontology provides the formalised vocabulary against which we annotate targets to cell type associations.

Cell Type Category	Cell Ontology Terms	Targets annotated
B cells	CL:0000945 lymphocyte of B lineage	58

T cells	CL:0000789 alpha-beta T cell CL:0000815 regulatory T cell CL:0000911 effector T cell	85
Dendritic cells	CL:0000451 dendritic cell	44
Other T cells	CL:0000798 gamma-delta T cell CL:0000814 mature NK T cell CL:0000898 naive T cell CL:0000940 mucosal invariant T cell	4
Macrophages & monocytes	CL:0000235 macrophage CL:0000576 monocyte	60
Granulocytes	CL:0000094 granulocyte	48
Natural killer cells	CL:0000623 natural killer cell	31
Mast cells	CL:0000097 mast cell	40
Innate lymphoid cells	CL:0001065 innate lymphoid cell	6
Stromal cells	CL:0000499 stromal cell	1

The Guide to Malaria Pharmacology Database (GtoMPdb)

Introduction

The Guide to MALARIA PHARMACOLOGY (GtoMPdb) has been developed as an extension to the main GtoPdb database, with the aim of providing optimized access for the malaria research community to the data in GtoPdb. Although the initial phase of the project has been completed, MMV have provided further funding (0.2 FTE until December 2021) to allow malaria pharmacology content to be maintained and expanded.

The IUPHAR/MMV Guide to MALARIA PHARMACOLOGY was officially released in September 2019 and the resource is available at www.guidetomalariapharmacology.org. Blog posts related to the resource and technical reports on its development can be found here.

GtoMPdb Target and Ligand Curation

Curation Summary

The number of ligands in the public database with antimalarial activity has continued to increase. The most recent database release (2021.3) contains:

- 114 ligands tagged as in GtoMPdb (selectable in PubChem, see section)

https://www.guidetomalariapharmacology.org/GRAC/FamilyDisplayForward?familyId=999

- 39 targets tagged as in GtoMPdb:

https://www.guidetomalariapharmacology.org/GRAC/FamilyDisplayForward?familyId=970

Target and Ligand Review

We are currently working with members of the Malaria Drug Accelerator (MalDA), an international consortium whose goal is to identify novel druggable targets in *Plasmodium*, to update the 'Antimalarial targets' and 'Antimalarial ligands' families. MalDA has provided target descriptions for 25 of our *Plasmodium* targets, allowing us to review the information we display for these targets and to curate any additional data. This process has helped inform target subfamily classification (see our April 2021 report for more details), identify interaction data for new antimalarial ligands and update a number of existing ligands.

These target descriptions are also the basis of an IUPHAR Review on recent advances in malaria pharmacology and the GtoMPdb resource (manuscript in preparation).

GtoMPdb Web Interface and Database Development

The GtoMPdb uses the same underlying database as GtoPdb and in previous reports we have described changes to the database structure and the web interface that were necessary for the capture and presentation of antimalarial data (please see our November 2020 and April 2021 reports for a summary). The major part of the required development work was completed prior to the public release of the GtoMPdb but we have continued to implement updates and improvements following user recommendations.

GtoMPdb Page View Analytics

In August 2021 we ran a detailed analysis of page views for malaria content in GtoMPdb. The figures in the table below are taken from our Google Analytics for the period April 20 - July 21. We analysed the number page views malaria tagged targets, ligands and families received in addition to the malaria focussed lifecycle and species pages. We also counted page views to the malaria portal index, about and help pages.

Total shows over 22,400 unique views (~1,200 per month).

	Page Views	Page Views per month	Unique Page Views	Unique Page Views per month
Index	2916	162	2346	130
About	114	6	95	5
Help	87	5	61	3
Targets	2310	128	1808	100
Ligands	14927	829	12235	680
Families	2282	127	1775	99
Malaria Species	1101	61	246	14
Parasite Lifecycle	4536	252	3839	213
Total	**28273**	**1571**	**22405**	**1245**

General overview of database team activities

GtoPdb Team Interactions

For more details of previous and continuing interactions please see previous reports. Only significant changes since April 21 are reported below.

ELIXIR

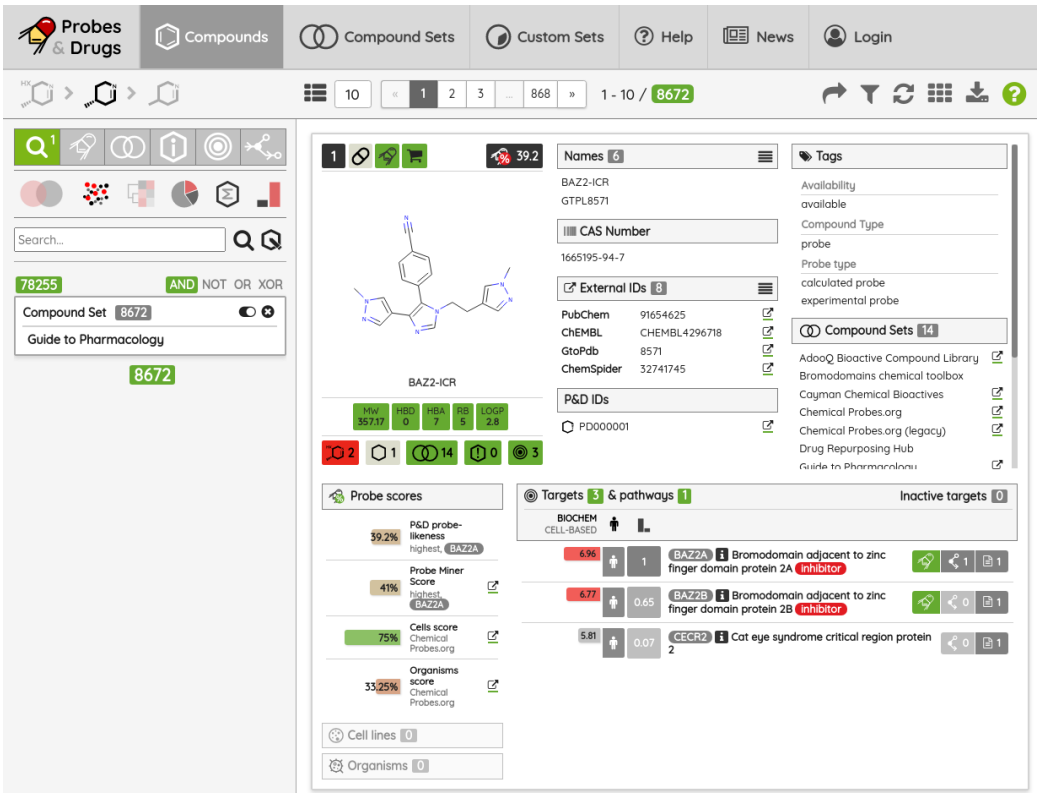
Engagements continue with this important Europe-wide bioinformatics infrastructure initiative. Our involvement with ELIXIR-UK brings closer ties with other key UK bioinformatics resources and facilitates collaboration on the use of standard ontologies and identifiers. This is valuable as we continue seeking to ensure GtoPdb is a FAIR-compliant (Findable, Accessible, Interoperable, Reusable) resource.

As reported before, we have an entry in the ELIXIR bio-tools directory as one of the official UK ELIXIR Node Services and part of the Excelerate initiative.

Dr. Simon Harding attended the virtual ELIXIR-UK All-Hands Meeting held in September 2021.

Probes and Drugs

We continue useful interactions with The Probes & Drugs portal (P&D) and on 6th October 21 they have just released an update (03.2021) with new probes, Concise Guide to Pharmacology 2021/22, GtoPdb (version 2021.3) and updated HQCP set. They are the quickest metasource to pick up the chemistry from each of our releases and provide an independant, very detailed and filterable breakdown of cheminformatic properties and links. This is the third time Probes & Drugs have picked up data from the Concise Guide and in comparison with the previous version (2019/20), there are 191 newly added compounds. The analytics for GtoPdb can be drilled down into from this link (representative screenshot below).



P&D have also uniquely downloaded many boutique compound sets (some of which we have recommended) that can be directly compared with GtoPdb and the individual intersections inspected. As examples, we can simply read off the following numbers of compounds-in-common we have with other sources in P&D

1377 from 2323 ChEMBL approved drugs

4234 from 20916 in BindingDB

135 from 537 in BiasDB

2676 from 11043 in DrugBank

1545 from 4047 in DrugCentral

231 from 415 in Chemical Probes.org

2701 from 2701 extracted from Concise Guide to Pharmacology 2021/22

78 from 4486 in CovalentInDB

24 from 2258 in PROTAC-DB

141 From 299 in the NURSA ligand set

194 from 242 Clinical kinase drugs (PMID: 29191878)

BindingDB

We continue interactions on complementary coverage for the extensive extraction of SAR sets from COVID-19 literature and patents they have accomplished. We alert them to key papers on the M-protease from which we typically curate one or two leads from a paper on an SARS CoV-2 target whereas BindingDB will extract all compound data from the same papers.

PubChem

We continue our important interactions with Evan Bolton, Paul Theissen and other members of the team. The intersection statistics are shown in the section above and aspects of our PubChem ligand content were outlined in our 2022 NAR paper PMID 34718737 Their team has also cited us in some detail in their 2021 publication "Discovering and Summarizing Relationships Between Chemicals, Genes, Proteins, and Diseases in PubChem" PMID 34322655

Public Engagement and Promotion

hiddenREF Award

We are pleased that the IUPHAR/BPS Guide to PHARMACOLOGY was given a hidden REF award in the category 'applications of research'.

The hidden Ref (https://hidden-ref.org) is a national 'competition', supported by publishers, learned societies etc. (https://hidden-ref.org/supporters/) , designed to celebrate and recognise the range of important research achievements that may not fit neatly into a REF submission.

"The ways in which the research impact is judged overlooks many of the people who are vital to the success of research. It's only by recognising everyone who is vital to the conduct of research that we will create an environment in which to advance it."

We are of course very grateful to receive this award, and our thanks go to the hidden REF committees.

Being recognised in this way is a testament to the hard work of the entire Guide to PHARMACOLOGY team, both past and present, who's vision and dedication has provided the research community with such an invaluable resource.

Conferences/meetings (since April 2021)

- BPS Pharmacology 2021:
  - iPoster 09 Sep - Simon Harding - New features, families and friends in the IUPHAR/BPS Guide to PHARMACOLOGY in 2021
  - iPoster 09 Sep - Chris Southan - Chemical Probes for Pharmacology
- BioITWorld 2021, Track 6, Pharmaceutical Informatics, Sept 21st, Chris Southan, SARS-CoV-2 Antivirals: A Study in Open Science, FAIR Data, and Other Challenges in R&D, Track 9, Genome Informatics, Sept 21st, Chris Southan, Chemical Probes as Functional Genomics Tools: Sources, Content, and Availability
- ELIXIR-UK All Hands 2021 (attended by Dr. Simon Harding and Dr. Chris Southan)

Publications

Listed here are our most recent publications which includes the fifth edition of The Concise Guide to PHARMACOLOGY 2021/22 (28), published online in September 2021. The concise guide chapters are listed here:

Alexander SP, Kelly E, Mathie A, et al. . THE CONCISE GUIDE TO PHARMACOLOGY 2021/22: Introduction and Other Protein Targets. Br J Pharmacol. 2021;178 Suppl 1:S1-S26. doi:10.1111/bph.15537. PMID: 34529830

Alexander SP, Christopoulos A, Davenport AP, et al. THE CONCISE GUIDE TO PHARMACOLOGY 2021/22: G protein-coupled receptors. Br J Pharmacol. 2021;178 Suppl 1:S27-S156. doi:10.1111/bph.15538. PMID: 34529832

Alexander SP, Mathie A, Peters JA, et al. THE CONCISE GUIDE TO PHARMACOLOGY 2021/22: Ion channels. Br J Pharmacol. 2021;178 Suppl 1:S157-S245. doi:10.1111/bph.15539. PMID: 34529831

Alexander SP, Cidlowski JA, Kelly E, et al. THE CONCISE GUIDE TO PHARMACOLOGY 2021/22: Nuclear hormone receptors. Br J Pharmacol. 2021;178 Suppl 1:S246-S263. doi:10.1111/bph.15540. PMID: 34529827

Alexander SP, Fabbro D, Kelly E, et al. THE CONCISE GUIDE TO PHARMACOLOGY 2021/22: Catalytic receptors. Br J Pharmacol. 2021;178 Suppl 1:S264-S312. doi:10.1111/bph.15541. PMID: 34529829

Alexander SP, Fabbro D, Kelly E, et al. THE CONCISE GUIDE TO PHARMACOLOGY 2021/22: Enzymes. Br J Pharmacol. 2021;178 Suppl 1:S313-S411. doi:10.1111/bph.15542. PMID: 34529828

Alexander SP, Kelly E, Mathie A, et al. THE CONCISE GUIDE TO PHARMACOLOGY 2021/22: Transporters. Br J Pharmacol. 2021;178 Suppl 1:S412-S513. doi:10.1111/bph.15543. PMID: 34529826

Will the chemical probes please stand up? Škuta C, Southan C, Bartůněk P. RSC Med Chem. 2021 Jul 16;12(8):1428-1441. doi: 10.1039/d1md00138h. eCollection 2021 Aug 18. PMID: 34447939

We have also recently published a database update paper for the Nucleic Acids Research Database Issue. Published online on 30th october 2021.

Harding SD, Armstrong JF, Faccenda E, Southan C, Alexander SPH, Davenport AP, Pawson AJ, Spedding M, Davies JA; NC-IUPHAR. The IUPHAR/BPS Guide to PHARMACOLOGY in 2022: curating pharmacology for COVID-19, malaria and antibacterials. Nucleic Acids Res. 2021 Oct 30:gkab1010. doi: 10.1093/nar/gkab1010. Epub ahead of print. PMID: 34718737.

Outreach and Social Media

We use mainstream social media outlets for five primary purposes 1) outreach to potential new users and/or followers 2) informing on new features or releases 3) enhancing awareness of our publications and presentations 4) fostering contacts with our direct collaborators and other followers (including many other databases) 5) establishing reciprocity with key followers and collaborators.

Twitter

@GuidetoPHARM has, as of 10th November 2021, output 2,303 tweets; followers have increased to 4,489, from 4,248 in April 2021. The value of this platform continues to increase as an alerting system for our blog posts, key papers, including from BJP, other pharmacology journals, immunology, biochemistry and medicinal chemistry, new PDB structures, etc.

Our tweet announcing the latest database release reached 2,824 impressions with an engagement rate of 2.4%. The announcement of the online publication of the new Concise Guide to Pharmacology has reached 3,921 impressions and an engagement rate of 4.4%.

Most of our Hot Topics are now first picked up from Twitter. We also engage in a discrete re-tweeting for reciprocal outreach. These include @BritPharmSoc (who are active in promoting the Concise Guide) @BrJPharmacol, @PharmRevJournal, @PRandP_Journal @IUPHAR, @PharmacologyEd @immunopaedia @cdsouthan and @mqzspa (NC-IUPHAR chair).

(NB readers of this document are mSteve Alexander (@mqzspa)ost welcome to follow @GuidetoPHARM and re-tweet posts of interest).

LinkedIn

The Curation Team continues to encourage Subcommittee Chairs and collaborators to increase their reciprocal connectivity as individual LinkedIN users. This expands our collective inter-network reach for posting updates, new papers etc. (N.B. interested readers of this report are encouraged to make connection requests from GtoPdb and IUPHAR scientists they know). Our own LinkedIN group page now has 325 followers, up from 297 in April 2021.

Guide to Pharmacology Blog

Our Edinburgh blog (http://blog.guidetopharmacology.org/) has received ~260 views on average per month since April 2021. This is a reduction from an average in the previous 6 months of ~420 views.

The blog is our primary news feed and includes database release updates, new features, technical items or articles. Our regular posts with expert commentaries on hot topics relevant to pharmacology are particularly popular, always ranking in the top 5 posts for any given month.

Team member Chris Southan maintains his own (http://cdsouthan.blogspot.com/) where relevant posts include cross-pointers to GtoPdb.

Hot Topics

An established feature, our Hot Topics in Pharmacology track and highlight new significant papers in pharmacology and drug discovery. These are communicated to us from Subcommittee members or picked up from Social Media. For a selection we commission concise commentaries from our expert contacts.

Since April 2021 we've added 88 new hot topic articles, including a commentary by Misty Attwood and Helgi Schiöth, University of Uppsala, Sweden on "Trends in kinase drug discovery: twenty years of successfully targeting the kinome". The commentary discusses two new analyses that present the historical development of kinase inhibitors as well as the current outlook on kinase drug discovery. See:

Cohen, P., Cross, D. & Jänne, P.A. Kinase drug discovery 20 years after imatinib: progress and future directions. Nat Rev Drug Discov 20, 551–569 (2021). [PMID: 34002056]

Attwood, M. M., Fabbro, D., Sokolov, A. V., Knapp, S., Schiöth, H. B. Trends in kinase drug discovery: targets, indications and inhibitor design. Nat Rev Drug Discov. In press (2021). [PMID: 34354255]

The commentary was published in July 2021 and has received over 80 views.

Slides

We continue to provide a set of generic slides which can be used by anyone presenting or teaching on GtoPdb and a generic poster which can be printed out in various sizes and taken to meetings or handed out as flyers.

Engaging with Us

As is implicit from the Social Media section above, it is crucial to extend our external presence and impact. Thus, the more readers of this document who "connect" with us, (via whichever of the channels above they use for their own professional profile) the more our outreach extends. This also has mutual advantages. In

particular re-tweets and LinkedIN likes are useful for extending the alerting network for new releases, publications, meeting slide sets and blog posts. Note also that each time you either save one of our publications to your own Mendeley account or mention it in a tweet, blog or PubMed commons comment (but make sure you specify a DOI or PubMed link for the auto-indexing) the Altmetrics score.