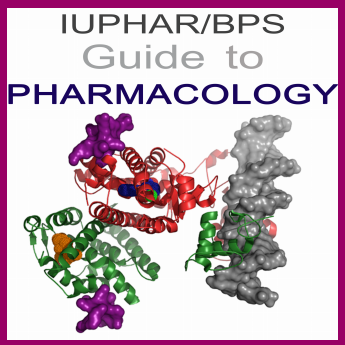
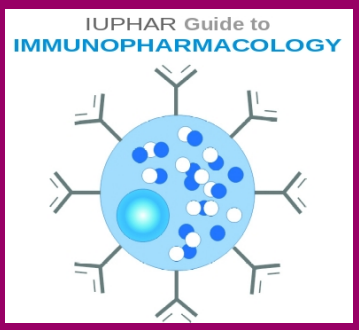
IUPHAR
International Union of Basic and Clinical Pharmacology

BRITISH PHARMACOLOGICAL SOCIETY





IUPHAR/MMV
Guide to MALARIA PHARMACOLOGY

DATABASE Report

May 2018

enquiries@guidetopharmacology.org

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SLIDESETS

This report was compiled in preparation for our joint NC-IUPHAR and BPS Meeting, held in Edinburgh 18-20 May 2018.

The database team presented 2 updates on the database, one for the Core Database and a one for the Guide to IMMUNOPHARMACOLOGY. Dr. Chris Southan also presented on 'Linking GtoPdb, PubChem and Pubmed'.

The presentation slides are available on SlideShare:

1 Database Status Report: Core GtoPdb
2 Database Status Report: GtoImmuPdb
3 Linking GtoPdb, PubChem & Pubmed

Introduction

This May 2018 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 Paris in October 2017. Previous reports are online for April 2017 and Oct 2017.

We are rapidly approaching the termination of our 3-year Wellcome Trust funded project to develop the "The Guide to IMMUNOPHARMACOLOGY (GtoImmuPdb): Integration of targets, diseases and therapies into an expert-driven database". This grant began on the 1st of November 2015. More details can be found in our blog, which includes technical blog posts highlighting aspects of the development of the resource.

An inclusion in the report this year are details of our new Guide to Malaria Pharmacology project. We have very recently been funded by the Medicines for Malaria Venture (MMV) to add information about antimalarials to GtoPdb, along with a purpose-built parasitologist-friendly portal for the website interface.

This report (along with the accompanying slide set) will detail our progress on the GtoPdb and GtoImmuPdb projects. It is based on the October 2017 version as a reference. A few general sections have been left in for context, but most have been updated. As usual informal minutes will be taken at the Edinburgh May 2018 meeting but please also talk to us regarding points, issues and suggestions from this report and the accompanying slide set.

GENERAL OVERVIEW OF DATABASE TEAM ACTIVITIES

PUBLIC ENGAGEMENT – PROMOTING OUR RESOURCES

CONFERENCES/MEETINGS (SINCE OCTOBER 2017 AND UPCOMING)

- Bioschemas Adoption Meeting, Hinxton, October 2017, Joanna Sharman
- International Conference on Scientific Information, Heidelberg, Oct 2017, Chris Southan (slides)
- Invited seminar Heidelberg University Oct 2017, Chris Southan
- ELIXIR-UK All Hands meeting, Edinburgh, Nov 2017, Joanna Sharman, Chris Southan, Simon Harding.
- British Society for Immunology Congress, Brighton, Dec 2017, Simon Harding
- Pharmacology Dec 2017 London, Joanna Sharman, Chris Southan, Simon Harding, Adam Pawson
- ELIXIR-UK SME industry meeting, Cambridge, January 2018, Chris Southan
- Selective Agonists For Serotonin Receptors project meeting, Copenhagen, Feb 2018, Chris Southan
- Phyre (protein prediction) SAB, and invited seminar March, Imperial College London, Chris Southan
- SciLife Science Lab, Chemical and Genetic Screening, April 2018, Stockholm, Chris Southan
- Pharmacology Futures, Edinburgh, May 2018, Adam Pawson, Chris Southan, Jamie Davies
- ELIXIR All Hands 2018, Berlin, June 2018, Simon Harding
- 18th World Congress of Basic and Clinical Pharmacology (WCP 2018) July 2018, Kyoto, Adam Pawson and Chris Southan. The team will be in a Symposium on Computational Pharmacology, Databases and Drug Discovery, and have two talks and several posters

Our slideshare account includes slide sets and posters presented by team members. Some are also posted on Christopher Southan's own slideshare.

PUBLICATIONS

PUBLISHED (SINCE OCT 2017)

- **The Concise Guide to PHARMACOLOGY 2017/18,** Alexander SP, Kelly E, Marrion NV, Peters JA, Faccenda E, Harding SD, Pawson AJ, Sharman JL, Southan C, Davies JA, CGTP Collaborators (a series of 9 papers , *British Journal of Pharmacology*, Dec 2017)
- **The IUPHAR/BPS Guide to PHARMACOLOGY in 2018: Updates and expansion to encompass the new Guide to IMMUNOPHARMACOLOGY.** Harding, S.D., J. L. Sharman, Southan, C., E. Faccenda, A. J. Pawson, S. Ireland, A.J.G. Gray, L. Bruce, S. P. Alexander, S. Anderton, C. Bryant, A. P. Davenport, C. Doerig, D. Fabbro, F. Levi-Schaffer, M. Spedding, J. A. Davies and NC-IUPHAR. *Nucleic Acids Res*. 2018 Jan 4;46(D1):D1091-D1106. PMID 29149325 (Gold Open Access)
- **Accessing expert-curated pharmacological data in the IUPHAR/BPS Guide to PHARMACOLOGY.** Joanna L Sharman, Elena Faccenda, Simon D Harding, Adam J Pawson, Christopher Southan, Jamie A Davies and NC-IUPHAR (2018). *Current Protocols in Bioinformatics*. 61: 1.34.1-1.34.46 (PubMed pending). There was unfortunately no APC provision in this case but Wiley have made the PDF freely downloadable during May (and we have copies if you miss this window)
- **Caveat usor: assessing differences between major chemistry databases.** (2018) Chris Southan. *ChemMedChem*, 13(6):470-481. PMID 29451740 (Gold Open Access)

SUBMITTED

The two papers below have been submitted to ACS Omega who also encouraged us to post on ChemRxiv. This is becoming popular and gives us open surfacing (e.g. on social media) for papers immediately post-submission during what can be an interval of some months awaiting refereeing. Note also that any readers of this report are welcome to feedback on either of these papers before we engage with the expected post-refereeing edits.

- **An open-access tool for designing drug control into engineered proteins.** Sam Ireland, Christopher Southan, Alazne Dominguez, Simon Harding, Joanna Sharman, Jamie Davies. *ACS Omega.* (submitted April 2018). The Rx version has garnered 1187, views, 40 downloads and an Altmetic score of 15 in five weeks.
- **Challenges of connecting chemistry to pharmacology: perspectives from curating the IUPHAR/BPS Guide to PHARMACOLOGY.** Christopher Southan, Joanna L Sharman, Elena Faccenda, Adam J Pawson, Simon D Harding, Jamie A Davies. *ACS Omega*. (Invited Perspective, submitted May 2018).The Rx version has garnered 161 views and 40 downloads in the first week.

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) keeping collaborators and other followers (including many other databases) aware of our activities. 5) establishing reciprocity with key followers and collaborators.

FACEBOOK

The number of 'likes' increased to 3378 (May 2018), from 3215 in September 2017.

TWITTER

@GuidetoPHARM has just pipped 1,769 tweets, followers have increased to 1808 from 1797 in September 2017 and our re-tweet rate has also gone up. 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. 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 have been very active in promoting the Concise Guide) @BrJPharmacol, @PharmRevJournal, @PRandP_Journal @IUPHAR, @PharmacologyEd @cdsouthan and @mqzspa (NC-IUPHAR chair). From our recent publications listed above we saw useful tweet boosts via @ChemRxiv as well as Wiley @currentprotocol and @ChemMedChem

LINKEDIN

The Curation Team have been encouraging Subcommittee Chairs and collaborators to increase their reciprocal connectivity as individual LinkedIN users. This expands our collective inter-network outreach for posting updates, new papers *etc*. (N.B. interested readers of this report are encouraged make connection requests from GtoPdb and IUPHAR scientists they know). Our own LinkedIN group page now has 178 followers.

BLOGGING

Our Edinburgh blog (http://blog.guidetopharmacology.org/) is receiving over 625 views on average per month, which has increased because we are now posting more content. This is our primary news feed and includes database release updates, new features, technical items or articles. We also post all Hot Topics that have comments and announcements of IUPHAR reviews, which we announce on social media. This replaces our old RSS feed which we no longer maintain. Team member Chris Southan maintains his own (http://cdsouthan.blogspot.com/) where relevant posts include cross-pointers to GtoPdb.

HOT TOPICS

As an established and popular feature our Hot Topics are seeded in the form of new significant pharmacology, drug discovery and key human genomics papers. These are communicated to us from Subcommittee members or picked up from Twitter. We have introduced a CiteUlike tag, htopic, used for collation from which we move them to their own website page. For a selection, as before, we commission concise commentaries from our expert contacts. We've had recent guest commentaries from Steve Alexander, Charles Kennedy, Stephan Kellenberger, and Shane C. Wright and Gunnar Schulte (all commentaries are posted under the Hot topic category on our blog).

SLIDESHARE

Our account (http://www.slideshare.net/GuidetoPHARM) allows the database team to share slide sets and posters with the community thereby extending the reach way beyond conference session direct attendees. Our slidesets received 2,787 views over the past year. We have also recently updated the 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.

ENQUIRIES RECEIVED FROM USERS

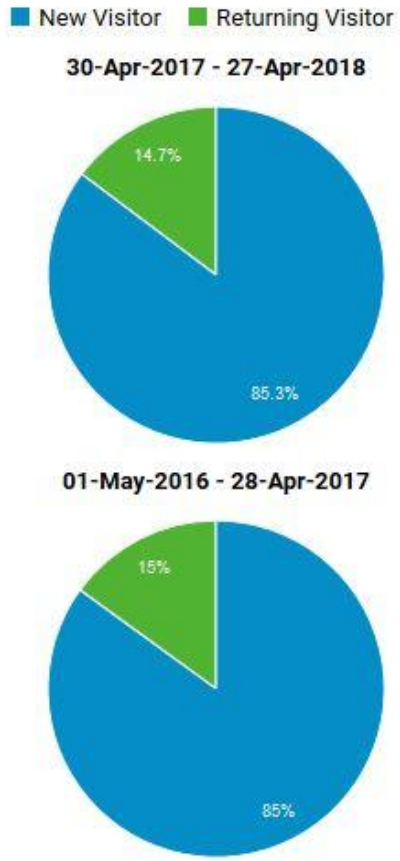
As mentioned in 2017 we had noticed more user communications coming in to enquiries@guidetopharmacology.org, This has steadied to about one a week and they continue to cover a useful spectrum of (mostly minor) fixes that we promptly address.

ENGAGING WITH US

As is implicit from the Social Media section above, it is crucial to extend our external “presence”. 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, new publications, meeting slide sets and blog posts. Note also that each time you either save one of our publications to your own Mendeley or CiteUlike accounts 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 (see below in Portals) notches up for that paper (n.b. we are only advocating professionally considered low-key engagement levels).

THE GUIDE TO PHARMACOLOGY DATABASE (GTOPDB)

GTOPDB WEB SITE ACCESS STATISTICS



Graphs comparing visitors to guidetopharmacology.org for the 12 months from Apr 2017 to Apr 2018, with the previous 12 months.

Monthly statistics	***Apr 2017 - Apr 2018 (previous 12 months)***
Sessions	31,269 (27,503)
Users	20,635 (18,015)
Page views	105,763 (102,768)
Pages / Session	3.38 (3.74)
Avg. Session Duration	00:03:12 (00:03:38)

GTOPDB CONTENT

These database statistics were compiled from our May 9th 2018 release (v2018.2). 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	245
Ligand-gated ion channels	81
Voltage-gated ion channels	144
Other ion channels	52
Enzymes	1200
Transporters	509
Other protein targets	194
Targets with ligand interactions	1719
Targets with quantitative ligand interactions	1467
Targets with approved drug interactions	603
Primary targets with approved drug interactions	316
Total number of targets	**2872**
Ligands	*Number of ligands*
Synthetic organics	6048
Metabolites	584
Endogenous peptides	785
Other peptides including synthetic peptides	1307
Natural products	250
Antibodies	240
Inorganics	37
Approved drugs	1364
Withdrawn drugs	68
Ligands with INNs	2208
Labelled ligands	607
Unique PubChem CIDs (total CID links)	6909 (7109)
Ligands with target interactions	7907
Ligands with quantitative interactions (approved drugs)	6953 (849)
Ligands with clinical use summaries (approved drugs)	2224 (1361)
Total number of ligands (PubChem SIDs)	**9251**
Number of binding constants	47058
Number of binding constants curated from the literature	15851

DOWNLOAD STATISTICS

Yearly period 1st May Year 1 to 30th Apr Year 2.

GOOGLE ANALYTICS COMPARISON OF DOWNLOADS

Event Category: Downloads
Event Label: Downloaded

	Count
2016-2017	2,585
2017-2018	2,887
Change	12%

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

A more specific breakdown is shown here:

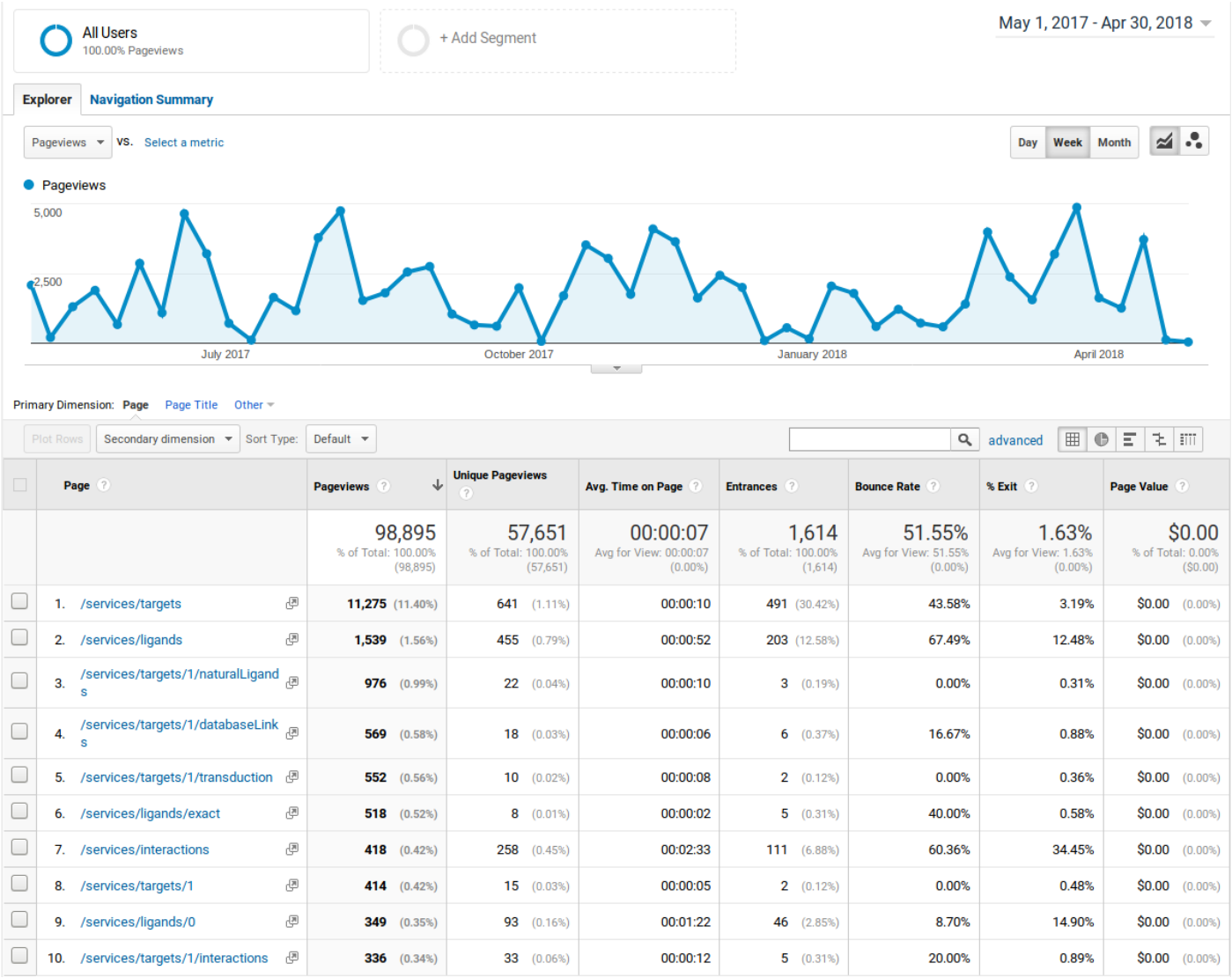
	2016-2017	***2017-2018***	***Change***
Targets CSV file	998	1,047	5%
Interactions CSV file	291	361	24%
Ligands CSV file	240	236	-1%
UniProt Mapping file	170	153	-10%
HGNC mapping file	80	94	18%
Peptides CSV file	90	90	
*PostgreSQL**	158	225	42%
Generic slides (PPT & PDF)	244	222	-9%
Generic poster	113	109	-4%
Other files			
Tutorial	430	515	20%
Terms and Symbols	307	300	-2%

* Total downloads of PostgreSQL database dump files (versions 2016.2-2018.1). The large increase in downloads can possibly be put down to the higher than average number of releases in 2017 (6 in total).

WEB SERVICES

We are now able to report on a full year of web service access statistics. We introduced Google Analytics tracking in our March 2017.2 release. Since these are generally calls made from client computers to our server, they are not recorded in the same way as visits to our website (although you can view the JSON results in a web browser). Therefore, we can't report details on specific users, such as location or number of visits. We can only record the number of hits for each distinct URL.

The image below shows that there were nearly **100,000** total hits over the year. The most popular pages are the target and ligand lists. Unfortunately, it doesn't include information about specific parameters that users can apply to the URLs, such as filters by target or ligand type. So we can't tell if users are loading all targets, or just GPCRs, for example. The most popular target is ID 1 (5-HT1A) and the most popular ligand is ID 1152 (VIP). Perhaps Target ID 1 is popular with people testing out the web services.



Page	Pageviews	Unique Pageviews	Avg. Time on Page	Entrances	Bounce Rate	% Exit	Page Value
	98,895 % of Total: 100.00% (98,895)	57,651 % of Total: 100.00% (57,651)	00:00:07 Avg for View: 00:00:07 (0.00%)	1,614 % of Total: 100.00% (1,614)	51.55% Avg for View: 51.55% (0.00%)	1.63% Avg for View: 1.63% (0.00%)	$0.00 % of Total: 0.00% ($0.00)
1. /services/targets	11,275 (11.40%)	641 (1.11%)	00:00:10	491 (30.42%)	43.58%	3.19%	$0.00 (0.00%)
2. /services/ligands	1,539 (1.56%)	455 (0.79%)	00:00:52	203 (12.58%)	67.49%	12.48%	$0.00 (0.00%)
3. /services/targets/1/naturalLigands	976 (0.99%)	22 (0.04%)	00:00:10	3 (0.19%)	0.00%	0.31%	$0.00 (0.00%)
4. /services/targets/1/databaseLinks	569 (0.58%)	18 (0.03%)	00:00:06	6 (0.37%)	16.67%	0.88%	$0.00 (0.00%)
5. /services/targets/1/transduction	552 (0.56%)	10 (0.02%)	00:00:08	2 (0.12%)	0.00%	0.36%	$0.00 (0.00%)
6. /services/ligands/exact	518 (0.52%)	8 (0.01%)	00:00:02	5 (0.31%)	40.00%	0.58%	$0.00 (0.00%)
7. /services/interactions	418 (0.42%)	258 (0.45%)	00:02:33	111 (6.88%)	60.36%	34.45%	$0.00 (0.00%)
8. /services/targets/1	414 (0.42%)	15 (0.03%)	00:00:05	2 (0.12%)	0.00%	0.48%	$0.00 (0.00%)
9. /services/ligands/0	349 (0.35%)	93 (0.16%)	00:01:22	46 (2.85%)	8.70%	14.90%	$0.00 (0.00%)
10. /services/targets/1/interactions	336 (0.34%)	33 (0.06%)	00:00:12	5 (0.31%)	20.00%	0.89%	$0.00 (0.00%)

Traffic to GtoPdb web services URLs over the past year

GTOPDB TEAM INTERACTIONS

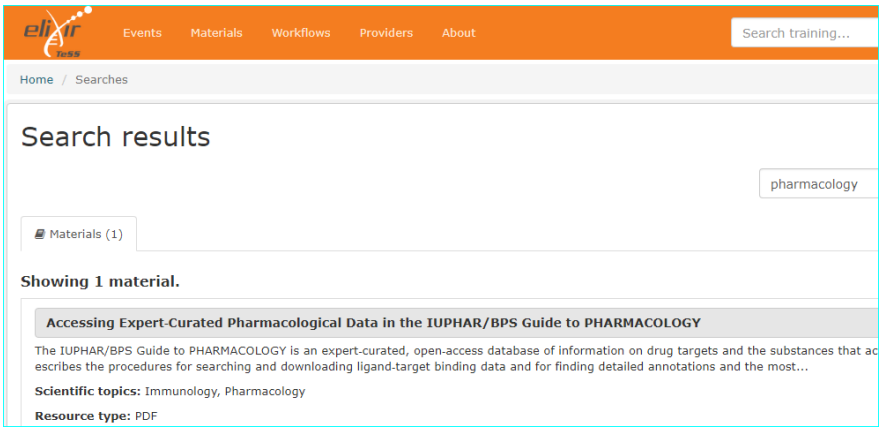
For more details of previous and continuing interactions please see the October 2017 and April 2017 reports. Only significant changes since October are reported below.

GPCRDB

Continuing our long-standing collaborative engagement with the David Gloriam Group, Anthony Davenport and Chris Southan were invited to Copenhagen in Feb 2018 to present at a meeting for the European PhD Training Network to identify selective serotonin receptor 5-HT2A agonists (SAFER) Chris continues to co-supervise one of David's PhD students, Alex Hauser, on his project "Computer-based design of peptide ligands" His 5th 6-monthly report was approved and his publication record with 12 papers indicates impressive progress for entry into his final year. Chris has also been appointed as co-supervisor to a new Copenhagen PhD student, Jens Andreasen, for "Development of a public GPCR ligand resource disseminating and enabling receptor research and drug design". This will enhance the ligand resources recently added to GPCRDB (PMID 29155946). In addition, Simon Harding has been appointed co-supervisor for Christian Munk whose project is on "GPCR protein complex conformations and structural stabilisation in selective signalling". Both these new students also have a previous publication record that will enable them to "hit the ground running" for their studies embedded within the Gloriam Group.

ELIXIR

Engagements continue with this important Europe-wide bioinformatics infrastructure initiative. As reported before, we have an entry in the ELIXIR tools and resources directory as one of the official UK ELIXIR Node Resources and part of the Excelerate initiative. We attend monthly UK node teleconferences and some f2f conferences (listed above) and provide inputs to various strategy documents. We are pleased to note that our latest manuscript is now indexed in the ELIXIR Training Portal (TeSS).



INTEROPERABILITY, RDF AND OPENPHACTS

One of ELIXIR's aims is to promote interoperability and FAIR (Findable, Accessible, Interoperable, Reusable) compliance (see **FAIR** Guiding **Principles** for scientific data management and stewardship. Wilkinson MD et al. Sci Data. (2016)). We have previously reported on our initiatives to increase interoperability of the GtoPdb data, including creating a new RDF version, submitting our ligands to WikiPathways, working with the Bioschemas group to implement Schema.org mark-up (which helps search engines to find and analyse content), and setting up a new NC-IUPHAR Subcommittee on Data Interoperability (chaired by Dr. Alasdair Gray).

Our collaboration with Alasdair Gray, a Linked data and RDF expert from Heriot-Watt University has continued. The aim of this work was to produce an RDF version of the GtoPdb data, focusing on interactions in the first instance. The collaboration was primarily set-up to facilitate eventual loading into the OpenPHACTS API, but RDF is becoming an increasingly important and preferred method of data uptake for direct consumers of our content, including pharmaceutical companies.

GtoPdb currently provides RDF flat files for download, 4 data files in Notation3 (N3) format and 2 metadata files which include a general description of the dataset and specific information on the current version: 2018.2. The metadata have been generated in accordance with the W3C Health Care and Life Sciences Community (HCLS) Profile to ensure FAIR compliance. In the last few months we have established our protocol to update the RDF in line with each database release.

It is still the case that users need to download the flat files and load them into a local triplestore (a special type of database for semantic querying across RDF data). It remains our aim to provide linked data pages for each resource in the RDF data, i.e. the URL used to identify each target, ligand, and interaction in the RDF will become dereferenceable to a specific, new URL on our site. Additionally, we will be providing a SPARQL endpoint with a set of example queries to help exploit the RDF data and enable deeper analysis of the GtoPdb data in conjunction with other linked data datasets. In the future, we plan to provide link-sets that capture the database cross-references contained in the GtoPdb as well as extend coverage of the data.

UNIVERSITY OF EDINBURGH SCHOOL OF INFORMATICS / DATA CITATION PROJECT

The GtoPdb team has been working with Prof Peter Buneman to implement a new method of creating database citations, with the goal of making these readable by online citation aggregators such as Google Scholar (GS). This relies on the assumption that GS and others will pick up citations to documents that look like publication abstracts. The database currently doesn't look like a typical publication, so Peter has created a program which generates reference abstracts from the database content: one per target family, with authors, overview text and a reference list. Each one links back to the family and target database pages it describes. We will publish these on a separate server and monitor whether GS can pick them up. Ultimately, we will change the citations displayed on database pages to link to these abstracts, which will make it easier for users to properly reference the database in their work. The should mean that the authors of the database content will get more recognition for their contributions, and also the authors of the references we choose to include will get a citation.

PUBCHEM

We continue our important interactions with PubChem, including by both mail and TC conversations with Evan Bolton, Paul Theissen and other members of the team. Some of our PubChem ligand content aspects

are outlined in our latest NAR paper PMID 29149325. PubChem have recently piloted a new Classification Browser (https://pubchem.ncbi.nlm.nih.gov/classification/#hid=92) which displays the GtoPdb target hierarchy in a way that allows users to browse our PubChem Substances/Compounds. The GtoPdb target classification is also shown on PubChem Target pages (e.g. HTR1A). Note that PubChem specifically selected us for highlighting in this highly-visible global resource because of our acknowledged quality as a submitter.

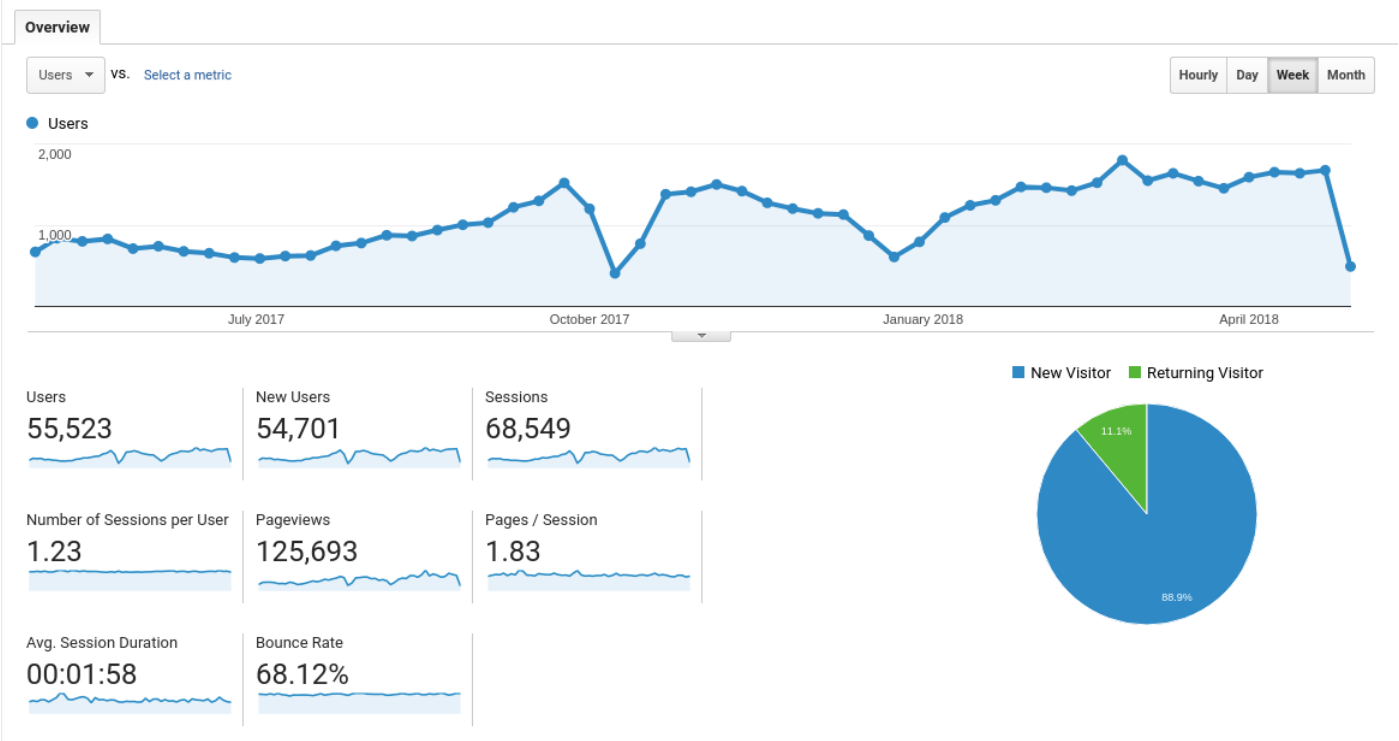
Subsequent to our 2018.2 database release in May we plan to submit new BioAssays to PubChem, following on from a pilot exercise for the 5-HT receptor family in 2015. We will create one Bioassay per protein target ID (i.e. one each per species with activity data at a GtoPdb target). The Bioassays are also shown on Target and Compound pages in PubChem so this will increase exposure of the GtoPdb data.

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*".

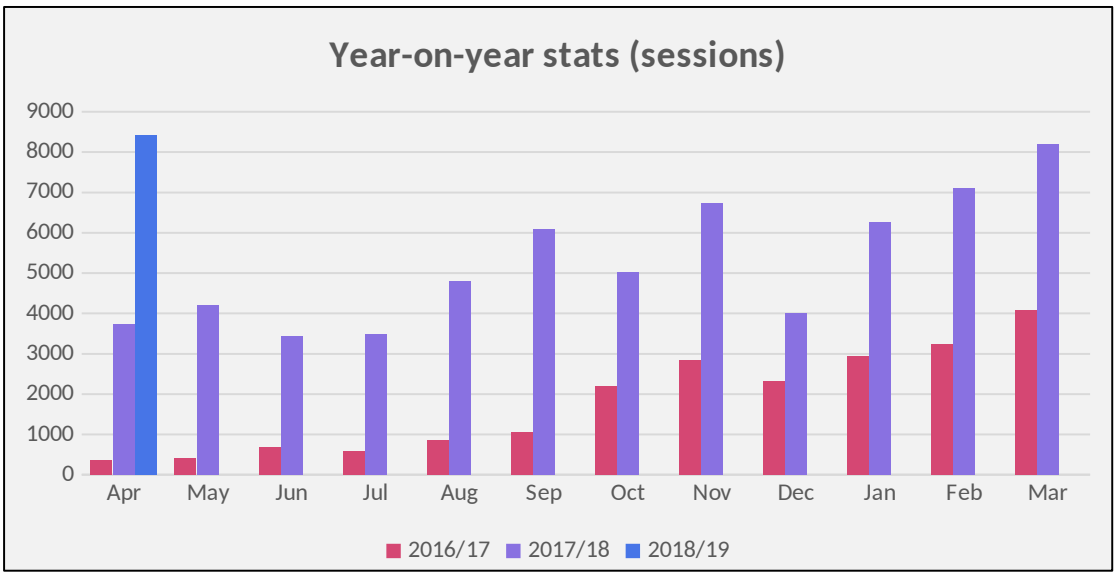
Financial support is in place for one 0.5 FTE for the next ~18 months. This comes from the Chinese, Japanese and Hungarian pharmacological societies.

Site Usage



Google Analytics of access to IUPHAR PEP Website

The analytics output from Google shows that over the last year the site has averaged **~5700 sessions** and over **10,000 page views** per month. Although, as the analytics graph indicates, activity on the site has seen a fairly large increase in the last 6 months. The chart below compares monthly sessions over the lifespan of the resource and highlights the continued increase in visitors to the site.



The average session per month from May-October 2017 was around 4,500 but this has increased to nearly 7,000 between October 2017 and April 2018.

We have noticed relatively high interest in our SlideShare offerings, with >6000 views of our most popular slidesets, and >440 downloads, in the last year.

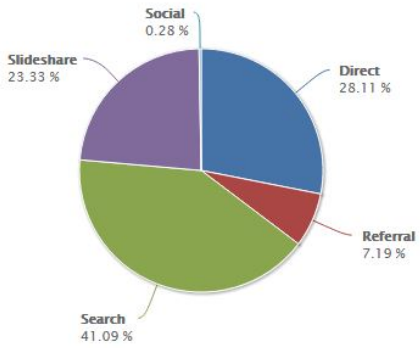
Top content

Name	Views
Drugs acting on the kidney lectures 1 and 2	2,624
Physiology and pharmacology of nausea and emesis 2015 jap	1,328
Introductory receptor pharmacology_2014-15_jap	830
Drugs and blood clotting	682
Autonomic physiology and pharmacology 1 2017 18 jap	597

Top countries

Name	Views
United States	1,542
India	1,006
United Kingdom	480
Australia	231
Pakistan	219

Traffic sources



SlideShare actions

Type	No.
Favorites	42
Comments	0
Downloads	441
Email shares	1

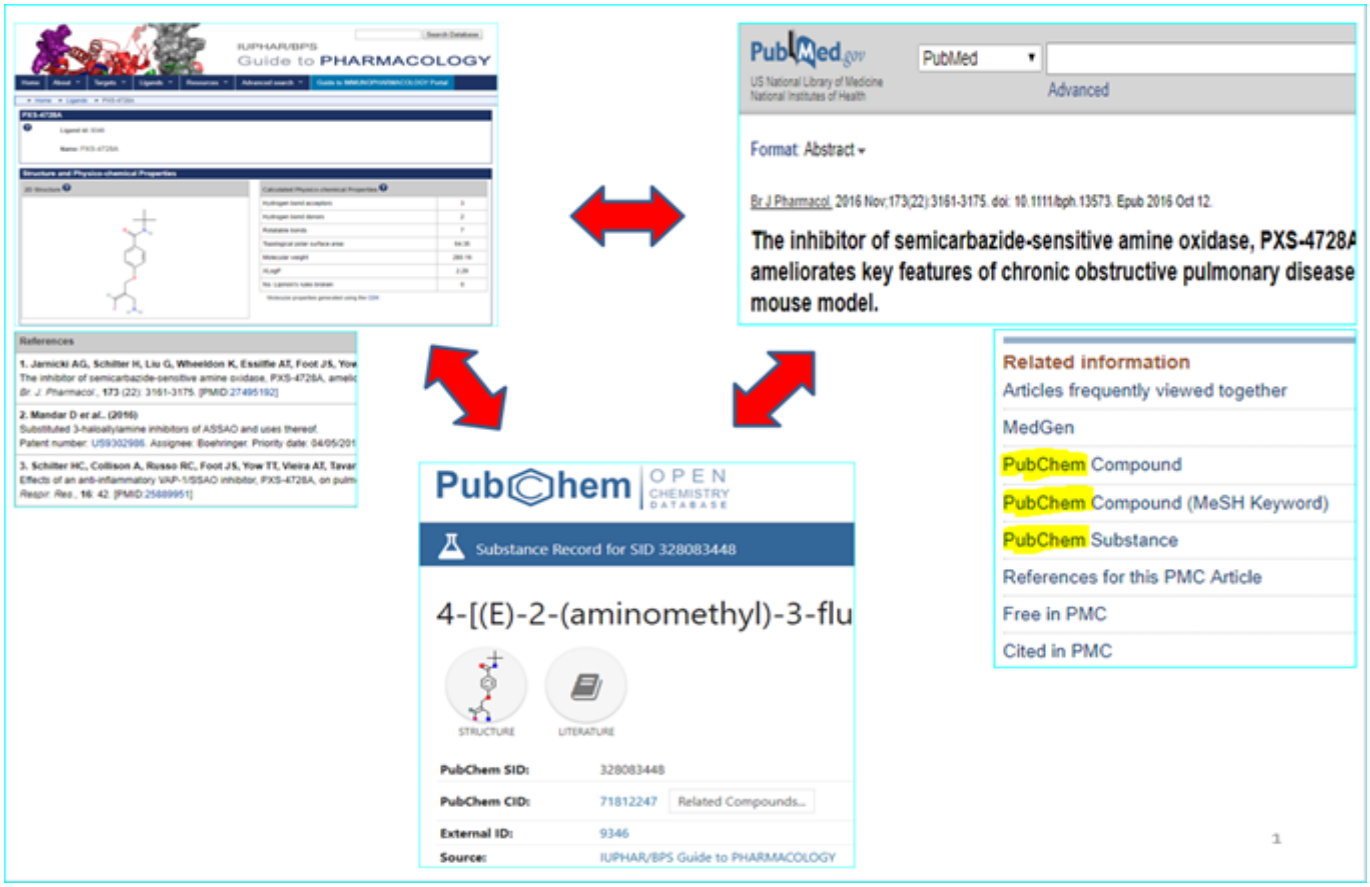
MISCELLANEOUS ENGAGEMENTS

As reported for Oct 2017 Chris Southan is on the SAB for the SGC/Wellcome Chemical Probes Portal, the SAB for BIndingDB and is on the faculty of F1000Prime. Since then he has joined the SAB for the Phyre protein structure prediction server at Imperial College, London (also an ELIXIR-UK Node resource). He has recently joined the Editorial Boards of the Journals ACS Omega and the Wiley/ASPET Pharmacology Research and Perspectives (PR&P).

JOURNAL < - > DATABASE CONNECTIVITY

The current statistics from the entity-linking initiative for the BJP since Oct 2014 and BJCP since Nov 2016, can be counted via the reference citations from our three NAR papers. The results establish that the Journal -> GtoPdb live outlinks (initially as Tables of Links but inline with text since 2017) stand at 1146 (~ 80%) for BJP and 560 (~ 50%) for BJCP papers. Despite this success, there have been occasions when the key compound was not in GtoPdb (i.e. thus could not be linked). In a few cases where the papers were in our capture remit (e.g. for immunopharmacology) we have curated them post-publication so they at least got a database-to-journal reference link. To ameliorate the retrospective “missing key link” problem we have recently instigated a prospective process whereby, on manuscript acceptance followed by their own marking-up of GtoPdb links, authors are advised to alert us directly to key entities that we do not yet have. In appropriate cases we then add these ligands and the new reference. This has the advantages, for both the author and the journal, of not only adding their reference into GtoPdb but also the paper gains PubChem-to-PubMed reciprocal linking derived from our PubChem ligand submissions (see below). Examples from the 2018.2 release include GS-458967 from BJP and esaxerenone from BJCP.

Another important type of connectivity mediated by us (for any journal) can be described as GtoPdb <> PubChem <> PubMed as shown below.



The temporal sequence for the navigable links is as follows: We curate the ligand and primary references (e.g. a J.Med.Chem.), one of which includes the quantitative interaction data (under the “Biological activity” tab). The entry may accrue additional key references for both in vivo progression (e.g. a BJP paper) and later a clinical report (e.g. a BJCP paper). When the GtoPdb release first containing that ligand is submitted to PubChem it then acquires “our” Substance Identifier (SID). At the same time we submit the references for that ligand listed in the SID (and refreshed for new references in later releases). The NCBI Entrez system then generates PubMed links between the SID structure (as well as the CID) and any of the PMIDs we submit. As can be seen in the diagram above these processes result in a “virtuous circle” (indicated by the reciprocal red arrows) that users of either of the three entry points (GtoPdb, PubChem and PubMed) can navigate. Importantly ourselves, the journals and the authors benefit from the increasing traffic that goes around these links. We can select the headline statistics for SID > PubMed links (each of which have a PubChem link) as follows

1. Our 9251 SIDs link to 9833 PMIDs from the GtoPdb ligand references
2. Of these 1076 are J.Med.Chem papers
3. 379 are from BJP
4. 165 are from Nature

5. 18 are from BJCP
6. 10 are from PR&P

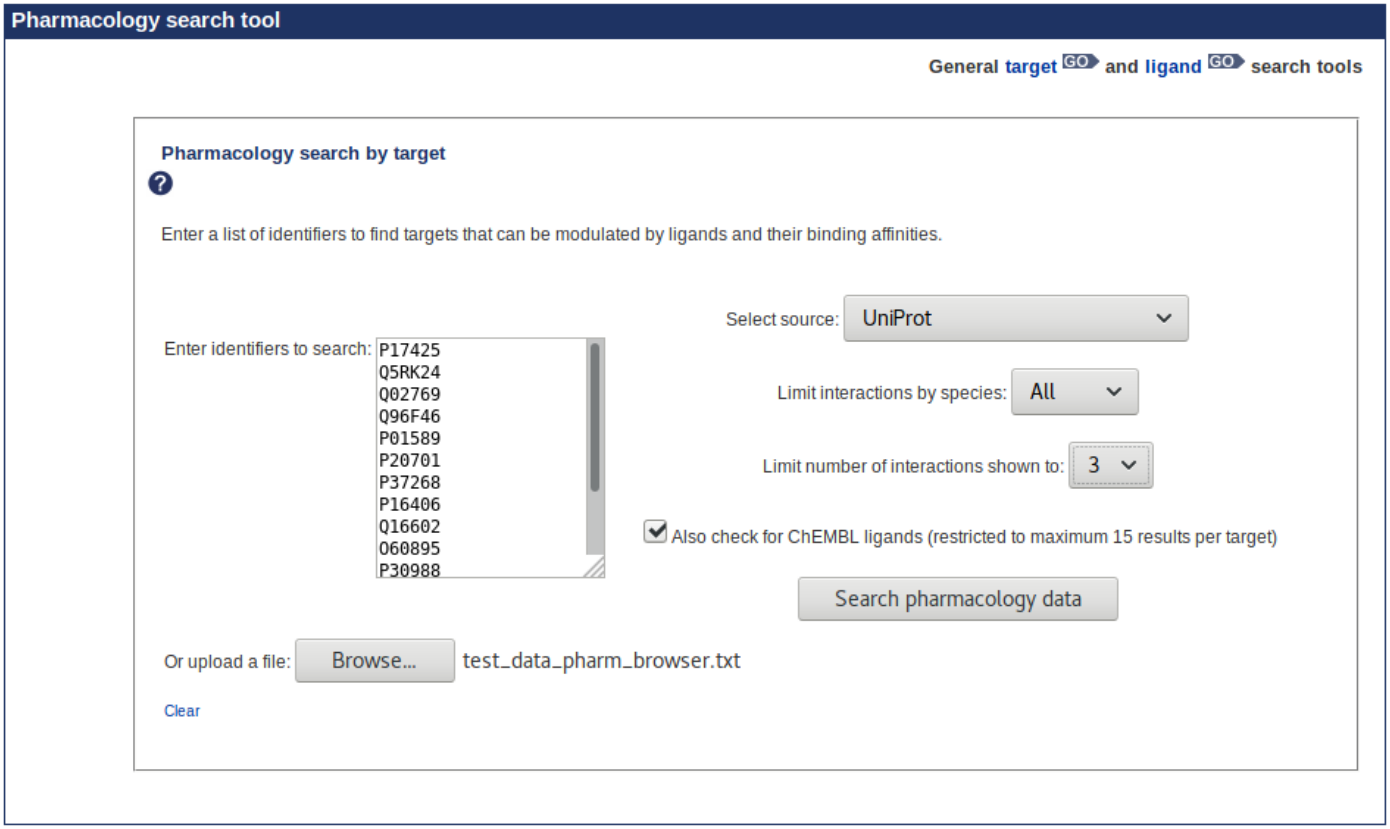
The figures above can be broken down by CID distributions. The rankings are similar but note that some of our 240 antibodies will have SID-only links (n,b, the above represent a different type of connectivity to the Wiley outlinks but may occasionally intersect for the same BJP or BJCP paper).

NEW GTOPDB WEBSITE FEATURES (SINCE OCT 2017)

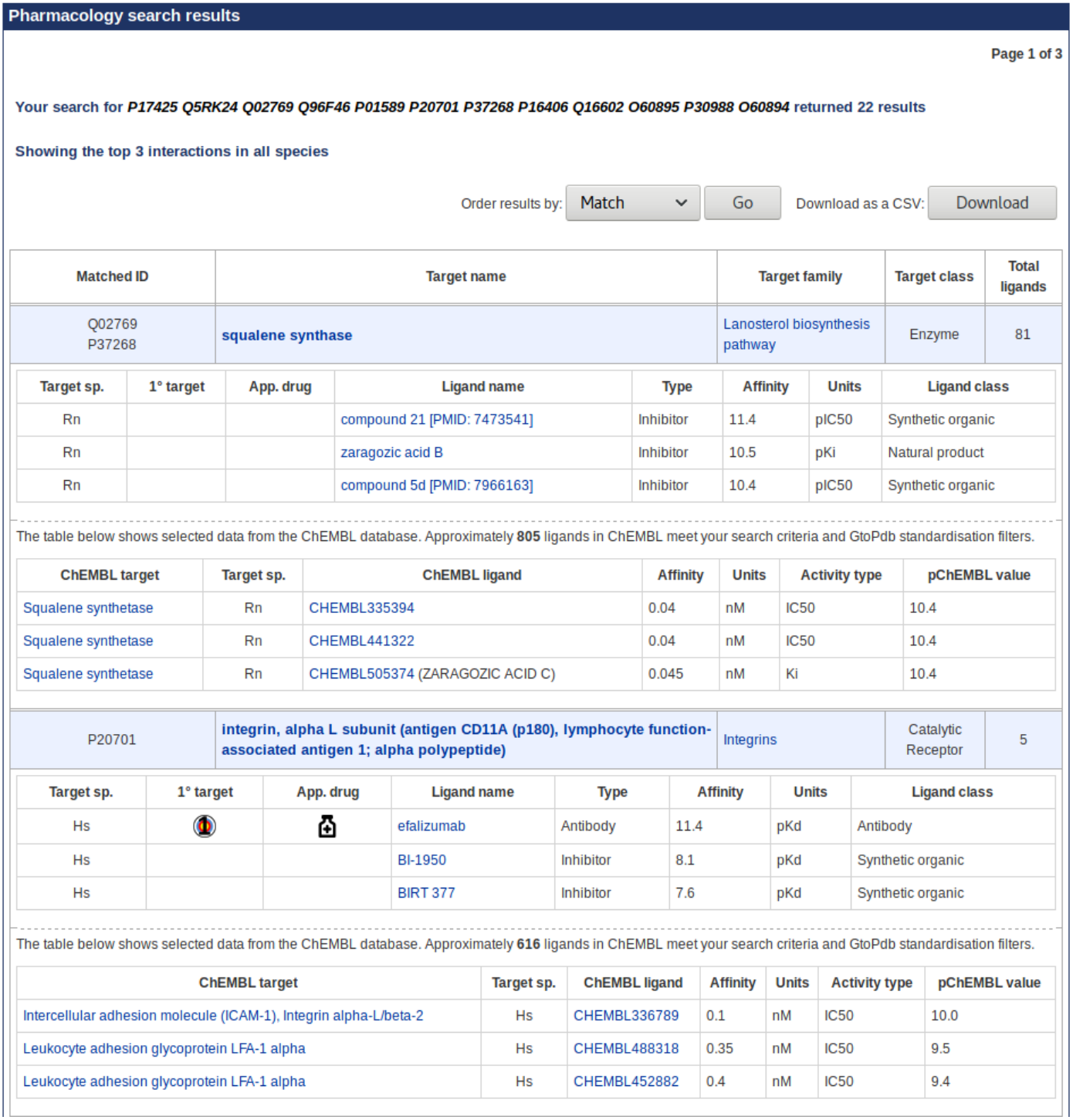
PHARMACOLOGY SEARCH TOOL

A new feature of the GtoPdb site is a Pharmacology Search tool, available under the Advanced Search menu. This tool allows users to upload a list of gene/protein Ids and find out if they are targeted by ligands. The figures below show the upload page, and a sample of the results. Users can limit by target species and the number of interactions shown (the default is 5).

Users can also now choose to include a search of the ChEMBL database (version 23 at the time of writing) in their results. We have taken a subset of the most relevant ligands in ChEMBL and made these available for searching (up to 15 interactions can be shown per target). Where possible we normalise the recorded ChEMBL activity types to one of the GtoPdb activity types (Ki, IC50 etc) and we display both the raw data and the pChEMBL value (a calculated -log value).



Pharmacology search tool with a file uploaded containing a list of UniProt accessions



Pharmacology search results

Page 1 of 3

Your search for ***P17425 Q5RK24 Q02769 Q96F46 P01589 P20701 P37268 P16406 Q16602 O60895 P30988 O60894*** returned 22 results

Showing the top 3 interactions in all species

Order results by: Match Go Download as a CSV: Download

Matched ID	Target name	Target family	Target class	Total ligands
Q02769 P37268	squalene synthase	Lanosterol biosynthesis pathway	Enzyme	81

Target sp.	1° target	App. drug	Ligand name	Type	Affinity	Units	Ligand class
Rn			compound 21 [PMID: 7473541]	Inhibitor	11.4	pIC50	Synthetic organic
Rn			zaragozic acid B	Inhibitor	10.5	pKi	Natural product
Rn			compound 5d [PMID: 7966163]	Inhibitor	10.4	pIC50	Synthetic organic

The table below shows selected data from the ChEMBL database. Approximately **805** ligands in ChEMBL meet your search criteria and GtoPdb standardisation filters.

ChEMBL target	Target sp.	ChEMBL ligand	Affinity	Units	Activity type	pChEMBL value
Squalene synthetase	Rn	CHEMBL335394	0.04	nM	IC50	10.4
Squalene synthetase	Rn	CHEMBL441322	0.04	nM	IC50	10.4
Squalene synthetase	Rn	CHEMBL505374 (ZARAGOZIC ACID C)	0.045	nM	Ki	10.4

P20701	integrin, alpha L subunit (antigen CD11A (p180), lymphocyte function-associated antigen 1; alpha polypeptide)	Integrins	Catalytic Receptor	5

Target sp.	1° target	App. drug	Ligand name	Type	Affinity	Units	Ligand class
Hs			efalizumab	Antibody	11.4	pKd	Antibody
Hs			BI-1950	Inhibitor	8.1	pKd	Synthetic organic
Hs			BIRT 377	Inhibitor	7.6	pKd	Synthetic organic

The table below shows selected data from the ChEMBL database. Approximately **616** ligands in ChEMBL meet your search criteria and GtoPdb standardisation filters.

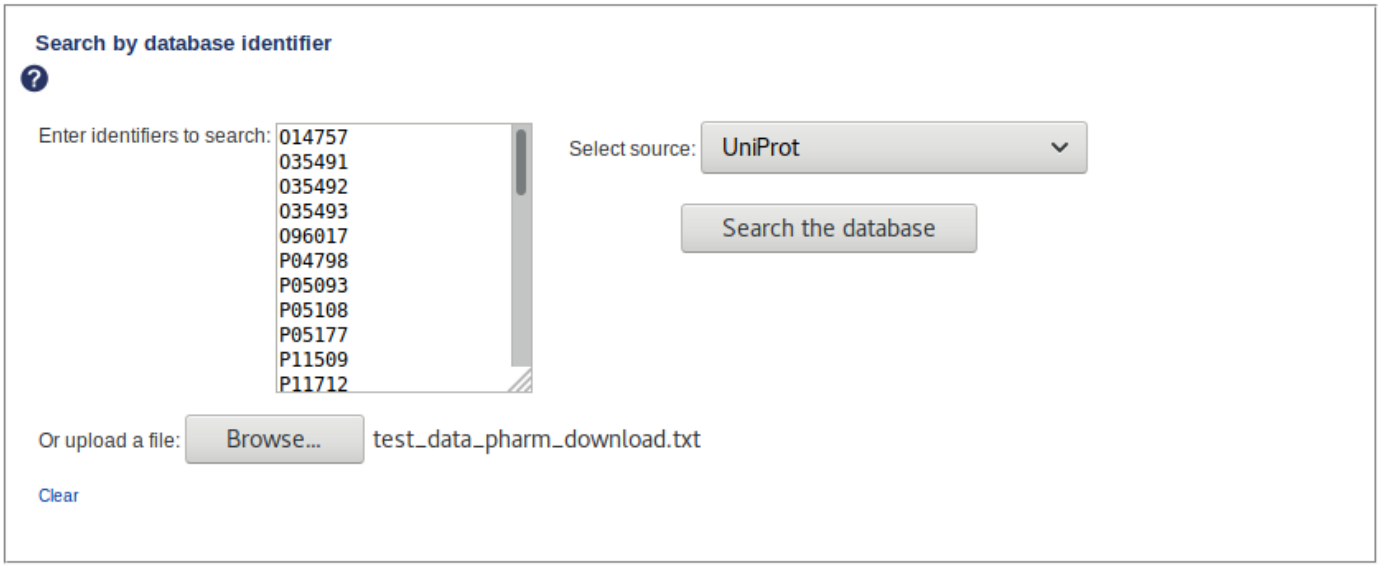
ChEMBL target	Target sp.	ChEMBL ligand	Affinity	Units	Activity type	pChEMBL value
Intercellular adhesion molecule (ICAM-1), Integrin alpha-L/beta-2	Hs	CHEMBL336789	0.1	nM	IC50	10.0
Leukocyte adhesion glycoprotein LFA-1 alpha	Hs	CHEMBL488318	0.35	nM	IC50	9.5
Leukocyte adhesion glycoprotein LFA-1 alpha	Hs	CHEMBL452882	0.4	nM	IC50	9.4

Pharmacology Search results page showing the top two targets. By default, targets are ordered by the total number of ligands that matched the search criteria (in this case for both GtoPdb and ChEMBL). They can also be ordered alphabetically.

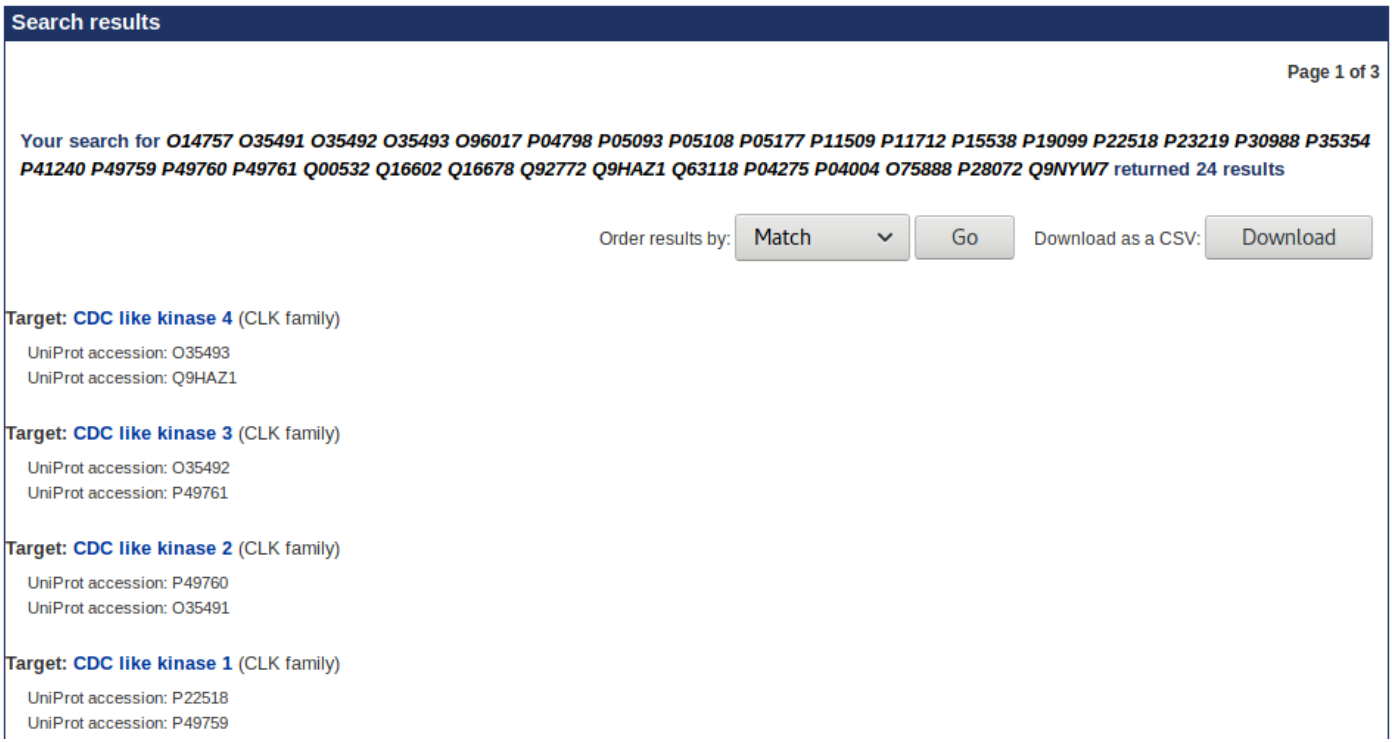
EXTENSIONS TO THE DATABASE SEARCH FEATURES

We have implemented a feature to allow users to upload a file or paste in a list of target or ligands IDs (e.g. UniProtKB Acc, Ensembl Gene Id, PubChem CID) and find matching GtoPdb entries. This is shown in the first image below.

We also now provide a “Download as CSV” option on search results pages (targets, ligands and the Pharmacology Search) - look for the “Download” button at the top right of the page. The downloadable CSV file provides additional information on the targets, ligands and families that were returned in the search results.



Target search page showing a file of UniProt accessions uploaded



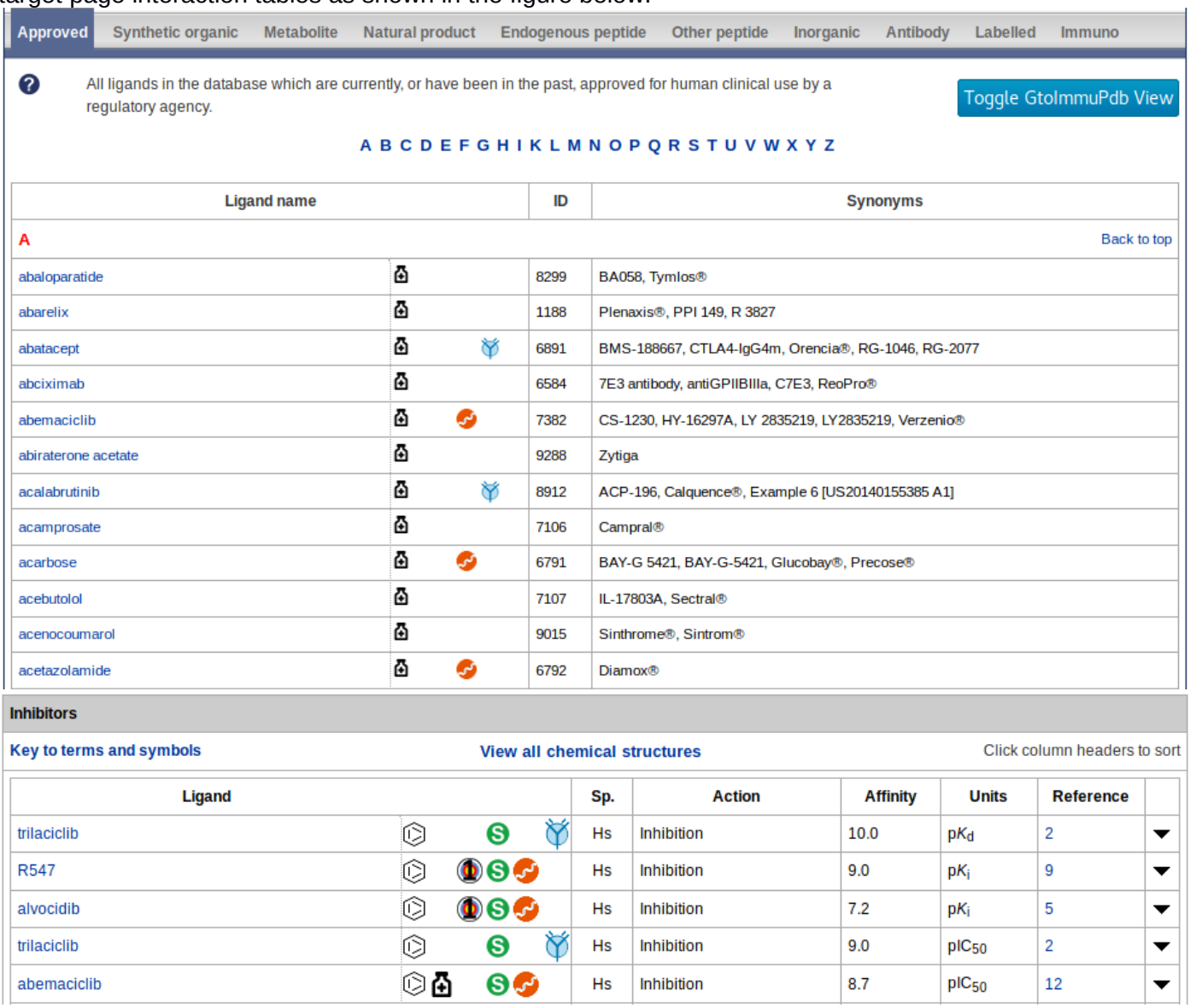
Target search results page showing the Download as CSV button in the top right

	A	B	C	D	E	F	G	H	I	J
1	entity_type	gtopdb_id	name	ab	sys	url	class	families	uniprot_accessions	gene_symbols
2	Target	1993	CDC like kinase 4	CLK4		http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1993	Enzyme	CLK family	Human:Q9HAZ1|Mouse:O35493	Human:CLK4|Mou
3	Target	1992	CDC like kinase 3	CLK3		http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1992	Enzyme	CLK family	Human:P49761|Mouse:O35492|Rat:Q63117	Human:CLK3|Mou
4	Target	1991	CDC like kinase 2	CLK2		http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1991	Enzyme	CLK family	Human:P49760|Mouse:O35491	Human:CLK2|Mou
5	Target	1990	CDC like kinase 1	CLK1		http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1990	Enzyme	CLK family	Human:P49759|Mouse:P22518	Human:CLK1|Mou
6	Target	47	calcitonin receptor-like receptor			http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=47	GPCR	Calcitonin receptors	Human:Q16602|Mouse:Q9R1W5|Rat:Q63118	Human:CALCRL|M
7	Target	2407	proteasome subunit beta 6			http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2407	Enzyme	T1: Proteasome	Human:P28072|Mouse:Q60692|Rat:P28073	Human:PSMB6|M
8	Target	659	TAS2R1			http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=659	GPCR	Taste 2 receptors	Human:Q9NYW7	Human:TAS2R1
9	Target	1326	CYP2C9			http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1326	Enzyme	CYP2 family	Human:P11712	Human:CYP2C9
10	Target	1321	CYP2A6			http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1321	Enzyme	CYP2 family	Human:P11509	Human:CYP2A6
11	Target	1320	CYP1B1			http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1320	Enzyme	CYP1 family	Human:Q16678|Mouse:Q64429|Rat:Q64678	Human:CYP1B1|M
12	Target	1319	CYP1A2			http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1319	Enzyme	CYP1 family	Human:P05177|Mouse:P00186|Rat:P04799	Human:CYP1A2|M
13	Target	1318	CYP1A1			http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1318	Enzyme	CYP1 family	Human:P04798|Mouse:P00184|Rat:P00185	Human:CYP1A1|M
14	Target	1361	CYP17A1			http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1361	Enzyme	CYP11, CYP17, CYP19, CYP20 and CYP21	Human:P05093|Mouse:P27786|Rat:P11715	Human:CYP17A1|
15	Target	1360	CYP11B2	Aldost		http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1360	Enzyme	CYP11, CYP17, CYP19, CYP20 and CYP21	Human:P19099|Mouse:P15539|Rat:P30099|R	Human:CYP11B2|
16	Target	1359	CYP11B1			http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1359	Enzyme	CYP11, CYP17, CYP19, CYP20 and CYP21	Human:P15538|Rat:P15393	Human:CYP11B1|
17	Target	1358	CYP11A1			http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1358	Enzyme	CYP11, CYP17, CYP19, CYP20 and CYP21	Human:P05108|Mouse:Q9QZ82|Rat:P14137	Human:CYP11A1|
18	Target	1983	cyclin dependent kinase like 2	CdkL2		http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1983	Enzyme	Cyclin-dependent kinase-like (CDKL) family	Human:Q92772|Mouse:Q9QUK0|Rat:Q5XIT0	Human:CDKL2|Mo
19	Target	1982	cyclin dependent kinase like 1	CdkL1		http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1982	Enzyme	Cyclin-dependent kinase-like (CDKL) family	Human:Q00532|Mouse:Q8CEQ0|Rat:Q66HE7	Human:CDKL1|Mo
20	Target	43	CT receptor			http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=43	GPCR	Calcitonin receptors	Human:P30988|Mouse:Q60755|Rat:P32214	Human:CALCR|Mo
21	Target	1994	C-terminal Src kinase	CSK		http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1994	Enzyme	Csk family	Human:P41240|Mouse:P41241|Rat:P32577	Human:CSK|Mous
22	Target	1376	COX-2			http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1376	Enzyme	Cyclooxygenase	Human:P35354|Mouse:Q05769|Rat:P35355	Human:PTGS2|Mo
23	Target	1375	COX-1			http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1375	Enzyme	Cyclooxygenase	Human:P23219|Mouse:P22437|Rat:Q63921	Human:PTGS1|Mo
24	Target	1988	checkpoint kinase 2	Chk2		http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1988	Enzyme	RAD53 family|CHK1 subfamily	Human:O96017|Mouse:Q9Z265	Human:CHEK2|Mo
25	Target	1987	checkpoint kinase 1	Chk1		http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1987	Enzyme	CHK1 subfamily	Human:O14757|Mouse:O35280|Rat:Q91ZN7	Human:CHEK1|Mo

Section of the downloaded results file

NEW ICONS ON LIGAND TABLES

Two new icons have been added to the ligand list: one (a magenta circle with a white mosquito) indicates the antimalarial ligands (see below section on the Guide to Malaria Pharmacology). The other (an orange circle with a white alpha helix) indicates ligands with entries in the PDB. This icon is also displayed on target page interaction tables as shown in the figure below.



The new PDB ligand icon is an orange circle with a white helix. Top image: the full ligand list. Bottom image: the inhibitor list on a target page.

DISEASE LIST AND SUMMARY PAGES

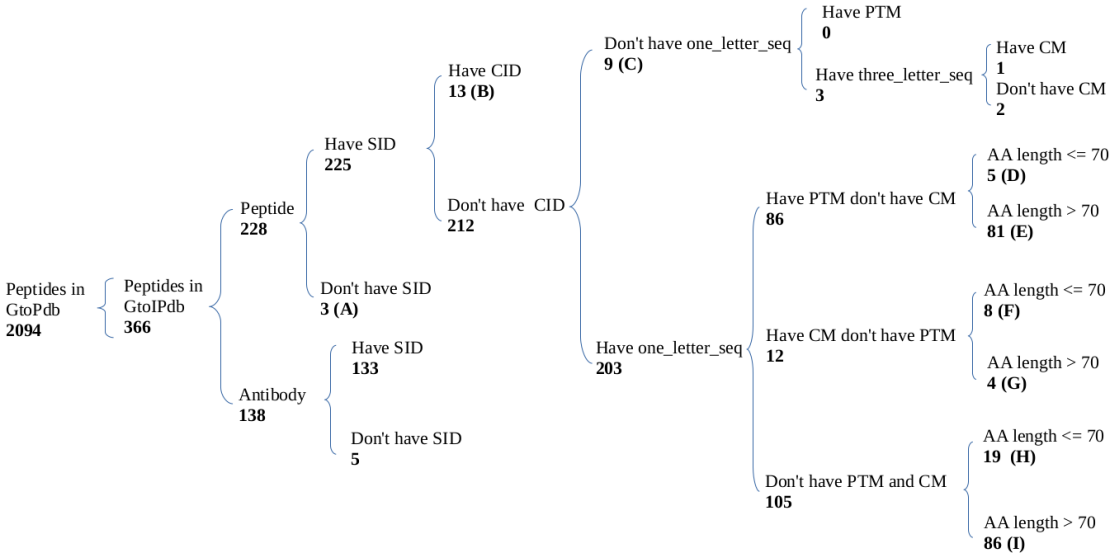
This work is discussed in detail under the Guide to Immunopharmacology section below, but it is also relevant to the core GtoPdb site. A new disease list is available from the main menu bar and each disease name links to a specific disease summary page. Disease pages include a summary of the disease data in GtoPdb including any synonyms, database links (OMIM, Orphanet and Disease Ontology) and links to target pathophysiology/mutation tables (and, via GtoImmuPdb, links to drugs/ligands). Work is currently underway to add a categorisation of diseases to aid navigation, based on the Disease Ontology.

MSC PROJECT ON PEPTIDE STRUCTURES

We currently have an MSc Drug Discovery & Translation student, Lin Yikai, working on a summer project investigating the GtoPdb peptide ligand structures and finding ways of converting these into standardised specifications, e.g. SMILES, HELM, InChI, IUPAC. There are a number of possible outcomes.

- If we can convert smaller peptides (<70 AA, 1000 atoms) to SMILES using the SugarNSplice software (SnS), and submit these to PubChem, they will create new CIDs from our SID structures.
- The first stage is establishing what's in GtoPdb and defining different sets of peptides, e.g. those with FASTA sequences and no PTMs that can be converted to SMILES, those with non-standard AAs that aren't recognised by SnS, etc.
- Focus on immuno-relevant peptides initially
- Other possible outcomes: extend existing curation procedure, enhance website with new data types, add new structural search tools including BLAST and possibly SMILES-based searching for small or modified peptides.
- Compare GtoPdb peptides with those in other databases e.g. PubChem and ChEMBL.

Lin's initial piece of work has been to analyse what data the GtoPdb currently holds on peptides, focussing on a subset that are flagged as relevant to immunopharmacology in the first instance. This early work has yielded the graph shown below that gives a breakdown of the immuno-peptides, identifying those with sequences, modifications, CIDs and length under 70 residues.



Graph illustrating the breakdown of peptides (of immune relevance) in GtoPdb

OTHER WORK

Updates on other ongoing new website features discussed at the October 2017 meeting in Paris are:

- **Converting to HTTPS:** Using HTTPS (secure connection) on websites is becoming increasingly important (browsers and search engines are starting to warn users when they access an insecure site). JS has been working with UofE Information Services to obtain security certificates from JISC which will allow us to install HTTPS on our web server. This is currently undergoing testing and we hope will be completed soon.
- **Upgrading our server software**: Our server software has now been upgraded to recent versions of Java and Tomcat (the web server). The switch-over was done in December 2017 and went very smoothly (there was no downtime for the public site). We still need to upgrade the Operating System and the PostgreSQL database application, both of which are now at EOL (end of life) stage, meaning they are no longer supported. This is likely to mean some downtime but we have yet to discussed this possibility with IS and make detailed plans.
- **Creating a mobile application for the GtoPdb and CGTP**: There has been enthusiasm over the years for developing a mobile application for GtoPdb and/or the CGTP. Feedback so far is that this should concentrate on the CGTP information, and that there is a commercial incentive for BPS/Wiley to progress with this.

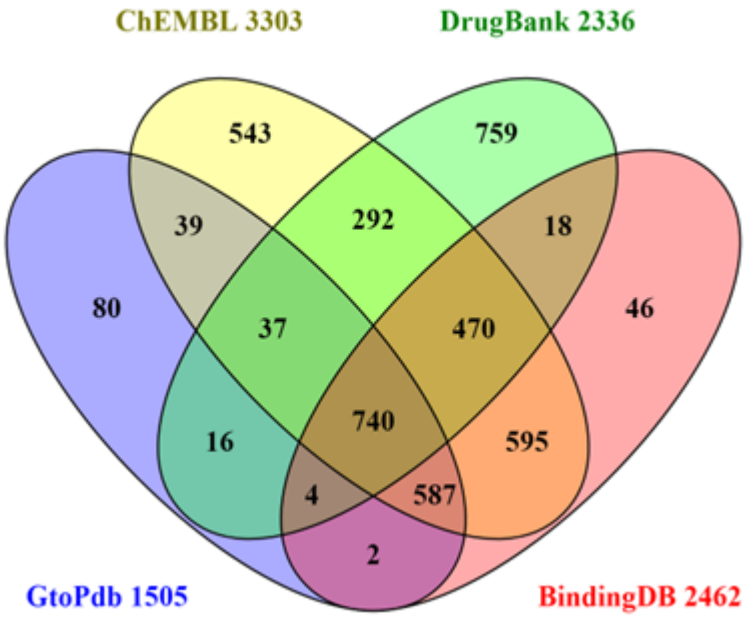
GTOPDB ENTITY GROWTH

Growth rates over the span of the previous Wellcome Trust grant are documented in earlier reports and our 2016 and 2018 NAR papers. Notwithstanding, it is important to note that the staff changes associated with the new Wellcome grant resulted in the loss of one curatorial FTEs from the team as a whole, plus the effective transfer of two FTEs to GtoImmuPdb. We consequently cannot sustain the previous overall growth rate (*i.e.* 2013-15 below). While the subcommittees have submitted Concise Guide updates, most new entities are being added *via* the population of GtoImmuPdb. However, significant curation effort goes towards tagging pre-existing targets and ligands with GtoImmuPdb relevant comments and new references.

	Oct 2013	***Oct 2015***	***April 2016***	***Oct 2016***	***Apr 2017***	***Oct 2017***	***May 2018***
Target protein IDs	2485	2761	2775	2794	2808	2825	2872
Ligands total	6064	8024	8400	8674	8872	8978	9251
Approved drugs	559	1233	1273	1291	1322	1334	1364
Antibodies	10	138	172	205	212	223	240
Peptides	1776	1981	2007	2039	2063	2079	2092
Synthetic small molecules	3504	5055	5363	5563	5729	5807	6048
PubChem SIDs	3107	8024	8328	8674	8831	8978	9251
PubChem CIDs	2694	6057	6163	6337	6813	6822	7109
Binding constants	41076	44691	45534	45908	46287	46488	47058
References	21774	27880	29247	30251	31239	31733	33245

GTOPDB TARGET UPDATES (SINCE OCTOBER 2017)

- **GPCRs:** 5-Hydroxytryptamine receptors, ACKR3 (Chemokine receptors), Adenosine receptors, Adrenoceptors, Cannabinoid receptors, Complement peptide receptors, D2 receptor, Ghrelin receptor, Glucagon receptors, GPR35 (Class A Orphans), Histamine receptors, Lysophospholipid (LPA) receptors, Lysophospholipid (S1P) receptors, Opioid receptors, Opsin receptors have been added as a new family, Prostanoid receptors, Vasopressin and oxytocin receptors
- **NHRs:** Mineralocorticoid receptor, Peroxisome proliferator-activated receptors
- **Ion channels:** Aquaporins (received 14/2/2018), Nav1.5, P2X receptors, Transient Receptor Potential channels, Voltage-gated calcium channels
- **Enzymes:** Cyclin-dependent kinase (CDK) family, Cyclooxygenase, Mitogen-activated protein kinases (MAP kinases), NADPH oxidases, Nitric oxide synthases, Phosphodiesterases, 3′,5′-cyclic nucleotide (PDEs)
- **Transporters:** ABCB subfamily, ABCC subfamily, ATP-binding cassette transporter family, Monoamine transporter subfamily, Organic anion transporters (OATs), SLC22 family of organic cation and anion transporters
- **Other protein targets:** Heat Shock Proteins
- **New targets:** 1.-.-.- Oxidoreductases | 2.3.2.27 RING-type E3 ubiquitin transferase | 2.7.1.40 Pyruvate kinases | 3.2.1.- Glycosidases | Antimalarial targets | Antimalarial targets | BTB (POZ) domain containing TFs | CD molecules | Chitinase-like proteins | Chitinases | Forkhead box TFs | GDNF receptor family | Heat shock proteins | Hydrolases | Immunoglobulin C1-set domain-containing proteins | Immunoglobulin C2-set domain-containing proteins | Immunoglobulin like domain containing proteins | Immunoglobulin-like family of IL-1 receptors | NADPH oxidases | Neuropilins and Plexins | NFkB regulators | Opsin receptors | Orai channels | Other anti-infective targets | Other immune checkpoint proteins | Protein tyrosine phosphatases | STAT transcription factors | Tumour-associated antigens | UDP glucuronosyltransferases (UGT)
- **Relative target growth and coverage:** This can be assessed by comparing our own UniProt Human Swiss-Prot cross-references (for targets with quantitative interactions) against the other major chemogenomic resources that also have such cross-references, DrugBank, BindingDB and ChEMBL(23). The April 2018 updates are shown below.



Note that our total has broken 1500 data-supported druggable targets for the first time and we have 80 targets not in the other three databases. Our 2018.2 release should add a number of new targets but the cross-references will be updated with the next UniProt release in June 2018. The intersects and differences in the above figure are complex but note that the DrugBank apparently large unique content includes interaction inferences based on literature co-occurrence rather than data-supported mechanism of action. There is a slow increase in the 4-way consensus to 740 over the 2017 figures but up from 568 in 2016. For more details see this slideshare set.

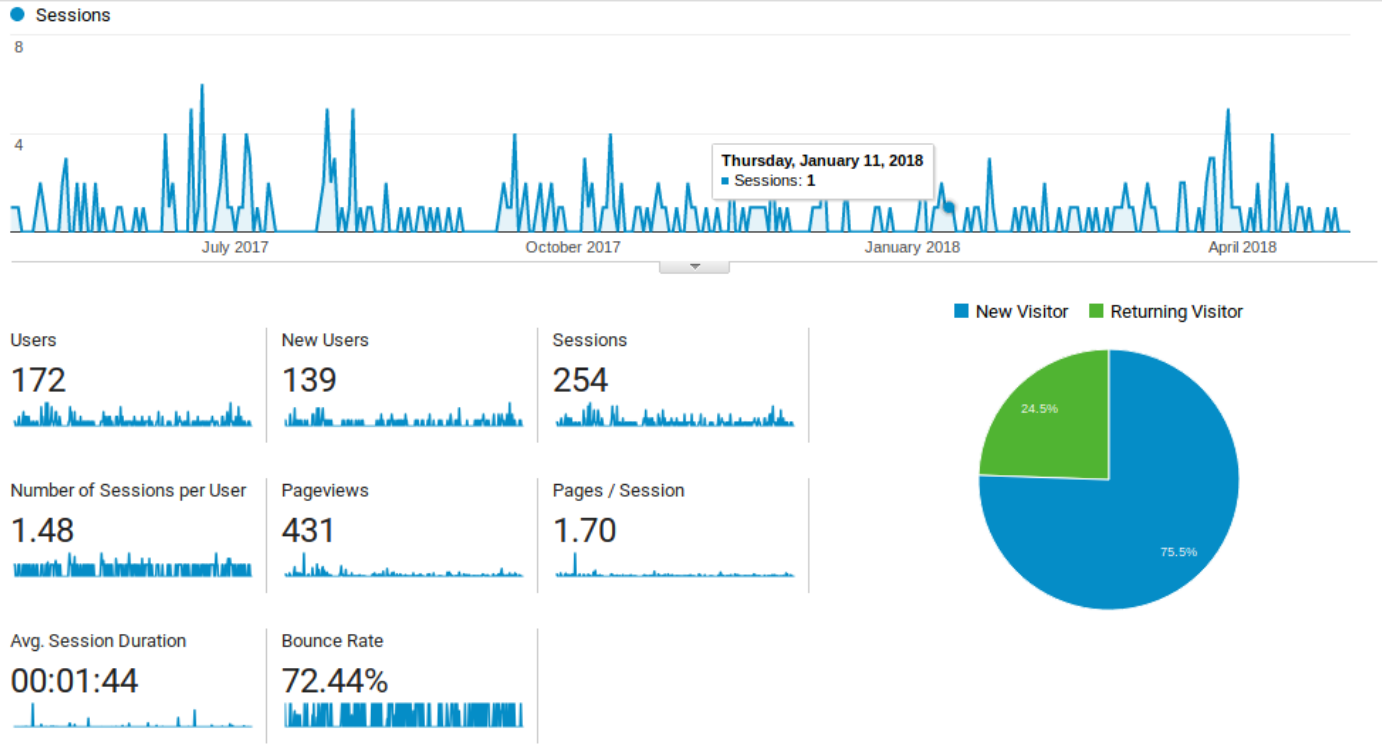
GTOPDB AND GTOIMMUPDB PUBCHEM STATS

Our PubChem statistics for 2017.5 have been described in our 2018 NAR paper (see Fig.3 in PMID 29149325). The general distribution pattern will be similar for 2018.2 but the selected highlights for numerical updates (with 2017.5 in brackets) are as follows (n.b. because the NCBI Entrez system suffers from constitutive overload the links below may time out but should eventually return the result).

1. Substances (SID) that we submit to PubChem (refreshing previous submissions) are up to 9251 (8978).
2. Those that have defined chemical structures are merged into 6969 (6822) Compound Identifiers, CIDs (i.e. small molecules and moderate peptides)
3. The select "IUPHAR/BPS Guide to PHARMACOLOGY"[SourceName] AND approved [Comment] now retrieves 1457 SIDs (1417) .
4. Of these 1278 (1247) have CIDs (use the “Find Related Data” operator and select “same CIDs”.
5. Of our SIDs, 993 are tagged in GtoImmuPdb and 258 of these are approved drugs
6. Of our CIDs 628 are tagged in GtoImmuPdb
7. We have 1675 (1595) structures that ChEMBL23 does not have, 5451 not in DrugBank and 5540 not in DrugCentral.
8. 95 (326) structures unique to us as a source. The reason for the drop here is that many of our previously novel SIDs now have CIDs.

SYNPHARM: A NEW DATABASE OF SMALL MOLECULES AND THEIR DRUG-RESPONSIVE PROTEIN SEQUENCES LINKED TO GTOPDB

For a detailed description of SynPHARM please see the October 2016 report or the website: http://synpharm.guidetopharmacology.org/. It is a database of drug-responsive protein sequences derived from GtoPdb interaction data. A paper describing SynPHARM has been submitted (see above publication list and also the pre-print server ChemRxiv). The figure below shows the SynPHARM access statistics for the past year. About 12% of the hits come from Edinburgh, many of which are likely to be from our team or local UofE SynthSys institute colleagues. A further 6% are from London, which likely represents visits from Sam Ireland, the original developer of SynPHARM, who has now moved to London.



Demographics
Language
Country
City
System
Browser
Operating System

	City	Users	% Users
1.	Edinburgh	21	11.73%
2.	(not set)	13	7.26%
3.	London	12	6.70%
4.	Tunis	11	6.15%
5.	Beijing	5	2.79%
6.	Cambridge	4	2.23%

SynPharm access statistics for the past year

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 Pub Med 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 and HSD 0000-0002-9262-8318.

Below are the May 2018 live bibleometic updates compared to the Oct 2017 metrics. These are given with EPMC links which have the advantage over PubMed of directly generating a citation ranking for any set (but with significantly lower citation rates than PubMed, Google Scholar or WOS).

- Database team member cumulative co-authored publications have increased from 153 to 164 (this is a PubMed query that not so easy to do in EPMC).

- IUPHAR reviews in BJP are up by one to 25.
- IUPHAR Pharmacological Reviews also notched up by one to 93.
- The BJP “Concise Guide” sets from 2013 and 2015 added up to 17 with the 2017/18 set now taking us to 26 papers.
- Our publications in the NAR Database issues have notched up from five to six
- We continue to get high citation rates in our NAR and Concise Guide articles because the BJP and BJCP selected these as reference citations for the GtoPdb outlinks. These are topped by our NAR 2016 entry (PMID 24234439) with 675 citations, overtaking the 2014 paper (PMID 24234439) that reached 574.
- The “Concise Guide” citations are currently led by 2015/16: Enzymes (PMID 26650445) at 463 closely followed by 2013/14: G protein-coupled receptors (PMID 24517644) at 445.
- The overall citation performance of our papers resulted in team members JLS., EF. and AJP, along IUPHAR co-authors, SPHA and MS, being listed in the Clavariate 2017 ranking of Highly Cited Researchers.
- The Altmetric rankings for all our OA papers are now indexed in ScienceOpen. Presciently, in the context of our new Antimalarial project, the highest ranked paper (PMID 27800551) with our affiliation happens to be a 2016 antimalarial paper with MMV co-authors which has reached 204. Not unexpectedly, the Concise Guides are also well ranked with the 2015/16: Overview (PMID 26650438) coming in at 53. This puts it in the top 5% of all research outputs scored by Altmetric (substantially due our own, the BPS and BJP twitter pushes). Coming in as our fastest climber it was gratifying to see another BJP team publication “Is systems pharmacology ready to impact upon therapy development?”(PMID 28910500) hit a respectable 31 after only 6 months.

THE GUIDE TO IMMUNOPHARMACOLOGY DATABASE (GTOIMMUPDB)

GTOIMMUPDB WEB INTERFACE AND DATABASE DEVELOPMENT STATUS

The first public beta-release of GtoImmuPdb was made in May 2017 (GtoImmuPdb beta v1.0) and followed in August with the GtoImmuPdb beta-release v2.0. Since we have made a third beta-release (GtoImmuPdb beta v3.0), in March 2018, and this section of the report covers the major development contained in that release. Full technical details on the development progress of GtoImmuPdb can be found on our blog.

As a reminder, GtoImmuPdb is an extension of GtoPdb and its development has 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 involves 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).

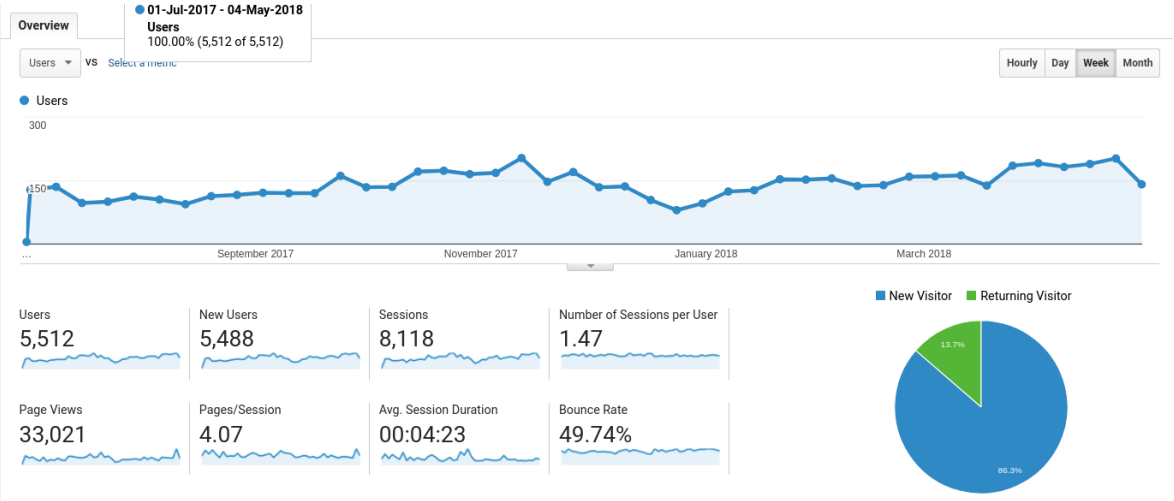
In earlier releases our focus was on incorporating process and cell type data, both of which were entirely new data types to the database. In GtoImmuPdb beta v3.0 the focus shifted to associating immunological disease data to existing targets and ligands. GtoPdb already contains disease data related to pathophysiology and mutations, so this extension sought to integrate disease association of immunological relevance to the existing GtoPdb data, ultimately leading to the development of disease summary pages that cut across both GtoPdb and GtoImmuPdb.

GTOIMMUPDB USER TESTING

During July 2017, a user-testing exercise was undertaken to gather feedback on the GtoImmuPdb v1.0 beta-release. This was fairly successful and after the GtoImmuPdb v3.0 release we have undertaken to repeat this process. This will hopefully inform further development towards the end of the project in October 2018. We have aimed to get more immunology-based researchers to test the site by reaching out to several of the British Society for Immunology regional groups in addition to members of the IUPHAR ImmuPhar Section.

GTOIMMUPDB ANALYTICS

Google Analytics have been in place on the GtoImmuPdb code since July 2017 to tracks users who specifically access the www.guidetoimmunopharmacology.org URL. In the 10-month period since then ~185 session have been recorded on GtoImmuPdb each week. This is an increase on ~140 sessions-per-week recorded in the first 3-months on analytics starting.



Access statistics for GtoImmuPdb (July 2017-April 2018)

The majority of users accessing GtoImmuPdb have come from the USA and UK, together accounting for nearly 36% of all traffic to the site. This is down from 46% in the first 3-months, indicating an increase in the diversity of regions accessing GtoimmuPdb. The countries with the next highest users accessing

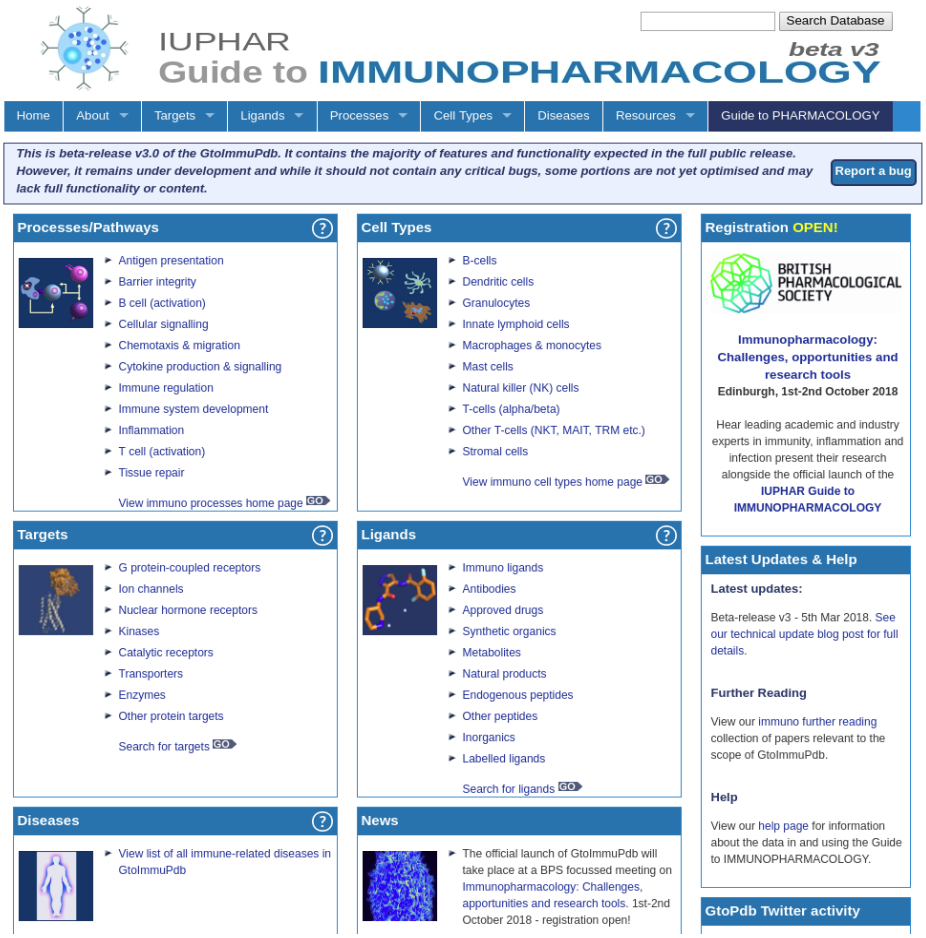
	Country	Users	% Users
1.	United States	1,215	21.95%
2.	United Kingdom	795	14.36%
3.	China	419	7.57%
4.	India	306	5.53%
5.	Germany	244	4.41%
6.	Japan	231	4.17%
7.	Mexico	188	3.40%
8.	Spain	154	2.78%
9.	France	145	2.62%
10.	Brazil	136	2.46%

GtoImmuPdb are China (8%), India (6%), Germany (4%) and Japan (4%).

The top ten countries ordered by number of sessions accessing GtoImmuPdb between July 2017 and April 2018

GTOIMMUPDB PORTAL AND SEARCHING

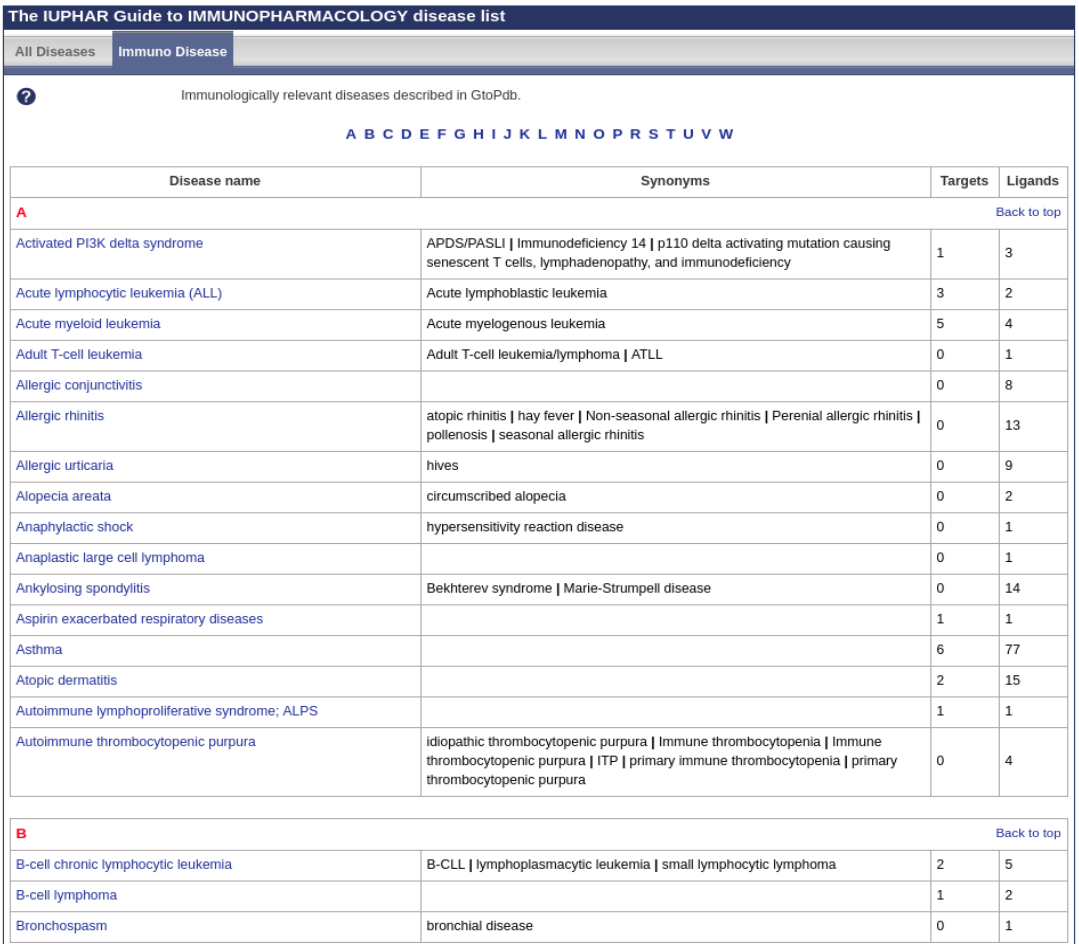
Minor change to the portal in the last 6 months include a re-organisation of the panels to place updates and news in the upper right. This is a better placement for announcements, such as the October, BPS Immunopharmacology Meeting. A new ‘Diseases’ menu item helps support navigation to this data type.



The GtoImmuPdb beta v3.0 portal

DISEASE DATA

As already mentioned the major new development for GtoImmuPdb has been changes to the way disease associations are presented. Previously, the target-disease and ligand-disease associations had been displayed separately. It made sense to consolidate the data into a single list of diseases and a series of detailed disease summary pages. These now contain all the curated information in GtoPdb about a disease. This work was done in conjunction with the Guide to PHARMACOLOGY (GtoPdb) development, as GtoPdb already contains information on target pathophysiology and mutations relating to specific diseases.



The IUPHAR Guide to IMMUNOPHARMACOLOGY disease list

All Diseases | Immuno Disease

Immunologically relevant diseases described in GtoPdb.

A B C D E F G H I J K L M N O P R S T U V W

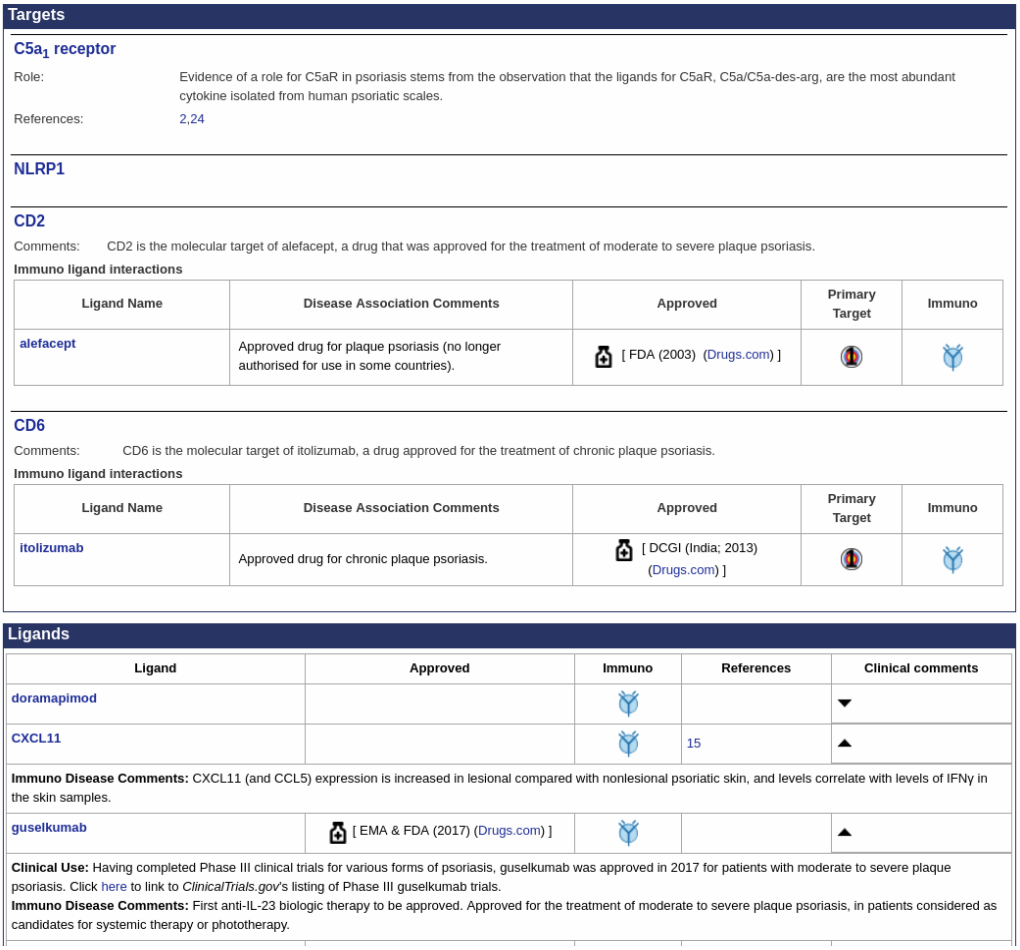
Disease name	Synonyms	Targets	Ligands
A			Back to top
Activated PI3K delta syndrome	APDS/PASLI | Immunodeficiency 14 | p110 delta activating mutation causing senescent T cells, lymphadenopathy, and immunodeficiency	1	3
Acute lymphocytic leukemia (ALL)	Acute lymphoblastic leukemia	3	2
Acute myeloid leukemia	Acute myelogenous leukemia	5	4
Adult T-cell leukemia	Adult T-cell leukemia/lymphoma | ATLL	0	1
Allergic conjunctivitis		0	8
Allergic rhinitis	atopic rhinitis | hay fever | Non-seasonal allergic rhinitis | Perenial allergic rhinitis | pollenosis | seasonal allergic rhinitis	0	13
Allergic urticaria	hives	0	9
Alopecia areata	circumscribed alopecia	0	2
Anaphylactic shock	hypersensitivity reaction disease	0	1
Anaplastic large cell lymphoma		0	1
Ankylosing spondylitis	Bekhterev syndrome | Marie-Strumpell disease	0	14
Aspirin exacerbated respiratory diseases		1	1
Asthma		6	77
Atopic dermatitis		2	15
Autoimmune lymphoproliferative syndrome; ALPS		1	1
Autoimmune thrombocytopenic purpura	idiopathic thrombocytopenic purpura | Immune thrombocytopenia | Immune thrombocytopenic purpura | ITP | primary immune thrombocytopenia | primary thrombocytopenic purpura	0	4
B			Back to top
B-cell chronic lymphocytic leukemia	B-CLL | lymphoplasmacytic leukemia | small lymphocytic lymphoma	2	5
B-cell lymphoma		1	2
Bronchospasm	bronchial disease	0	1

The GtoPdb Disease List page. Alphabetical list of diseases with associated data in GtoPdb.

The new disease list page, accessed from a new menu-bar item, lists all diseases with curated data in GtoPdb/GtoImmuPdb. A convenient alphabetical list of diseases, with links to the disease summary pages, synonyms and counts of associated targets and ligands. Our longer-term aim is to provide several disease categories to make finding diseases of interest easier. We will use the Disease Ontology to underpin disease categorisation. This will enables us to provide a more broad categorisation in the GtoPdb view, but a higher resolution view for the GtoImmuPdb. At present though, there is a single ‘Immuno Diseases’ category for diseases that are relevant to immunology, and/or are associated to targets and ligands of immunological-relevance.

Being able to search via disease names and synonyms is also in the pipeline.

The disease summary pages have been designed to display all pathophysiology, mutation and immunopharmacology data curated in GtoPdb and GtoImmuPdb in one place. The detailed information on each target gives a summary of any curated pathophysiology data, including the role of the target along with information on drugs and their therapeutic use and side effects. If any mutation data is available this is indicated. The target information also shows any specific immunopharmacology comments and ligands for which there is interaction data where the ligand is also associated with the disease.



Targets

$C5a_1$ receptor

Role: Evidence of a role for C5aR in psoriasis stems from the observation that the ligands for C5aR, C5a/C5a-des-arg, are the most abundant cytokine isolated from human psoriatic scales.

References: 2,24

NLRP1

CD2

Comments: CD2 is the molecular target of alefacept, a drug that was approved for the treatment of moderate to severe plaque psoriasis.

Immuno ligand interactions

Ligand Name	Disease Association Comments	Approved	Primary Target	Immuno
alefacept	Approved drug for plaque psoriasis (no longer authorised for use in some countries).	[FDA (2003) (Drugs.com)]		

CD6

Comments: CD6 is the molecular target of itolizumab, a drug approved for the treatment of chronic plaque psoriasis.

Immuno ligand interactions

Ligand Name	Disease Association Comments	Approved	Primary Target	Immuno
itolizumab	Approved drug for chronic plaque psoriasis.	[DCGI (India; 2013) (Drugs.com)]		

Ligands

Ligand	Approved	Immuno	References	Clinical comments
doramapimod				
CXCL11			15	
Immuno Disease Comments: CXCL11 (and CCL5) expression is increased in lesional compared with nonlesional psoriatic skin, and levels correlate with levels of IFNγ in the skin samples.				
guselkumab	[EMA & FDA (2017) (Drugs.com)]			
Clinical Use: Having completed Phase III clinical trials for various forms of psoriasis, guselkumab was approved in 2017 for patients with moderate to severe plaque psoriasis. Click here to link to *ClinicalTrials.gov*'s listing of Phase III guselkumab trials. **Immuno Disease Comments:** First anti-IL-23 biologic therapy to be approved. Approved for the treatment of moderate to severe plaque psoriasis, in patients considered as candidates for systemic therapy or phototherapy.				

Disease Summary page for Psoriasis: Snapshot of target and ligands data associated to Psoriasis

The ligand section lists all ligands associated to the disease and includes information on whether the ligand is an approved drug, immunopharmacology comments and clinical use information. Comments fields have been place in expandable sections (hidden by default) as in several cases the list of associated ligands is quite long. Ligand names link back to ligand summary pages to provided more details.

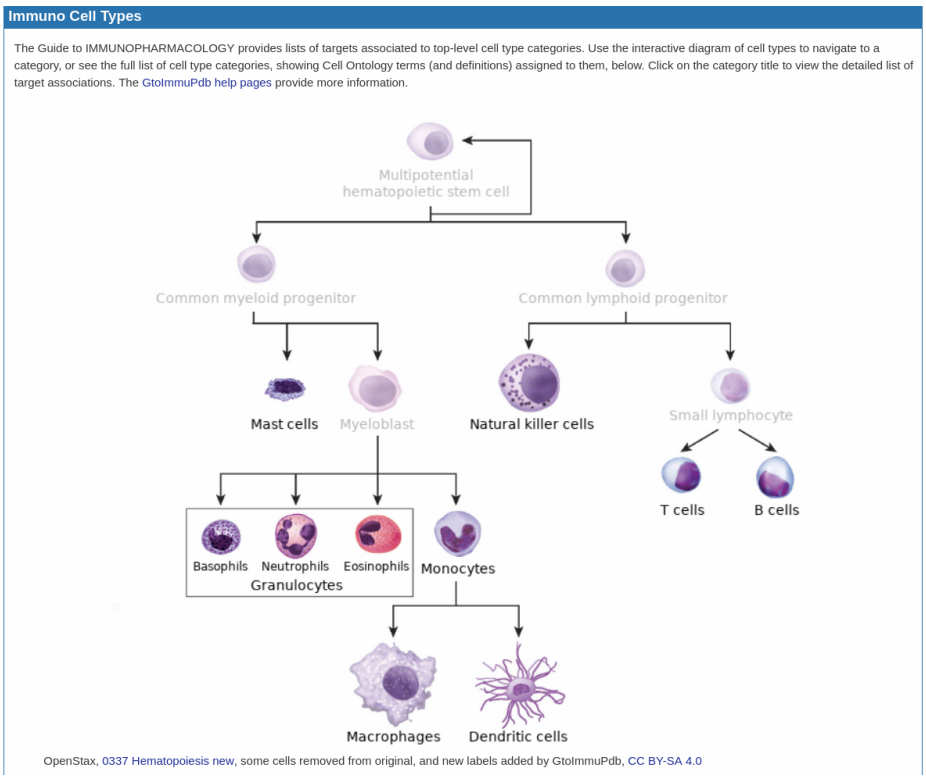
Diseases with most association to targets	
Rheumatoid arthritis	11
Asthma	6
Osteoarthritis	5
Psoriasis	2
Multiple sclerosis	2
Behcet syndrome	2
Graft versus host disease	2
Acute myeloid leukemia	2
Acute lymphocytic leukemia (ALL)	2
Irritable bowel syndrome	2

Diseases with most associations to ligands	
Rheumatoid arthritis	123
Asthma	77
Psoriasis	54
Chronic obstructive pulmonary disease	42
Crohn's disease	26
Osteoarthritis	24
Systemic lupus erythematosus	23
Ulcerative colitis	20
Psoriatic arthritis	16
Atopic dermatitis	15
Ankylosing spondylitis	14
Dermatitis	14
Allergic rhinitis	13
Relapsing-remitting multiple sclerosis	12
Graft versus host disease	11

These table give a fair rough overview of the disease with the most target and ligand associations in GtoImmuPdb.

GRAPHICAL BROWSING

GtoImmuPdb has been exploring different ways for users to explore and browse data, one of which is via the use of graphics and images. We took an tree diagram of immune system cell types from Wikimedia Commons and adapted it to show the cell types for which we have data. The image was re-labelled and an image map produced to make it interactive and a way to browse to different data types. This currently being tested.

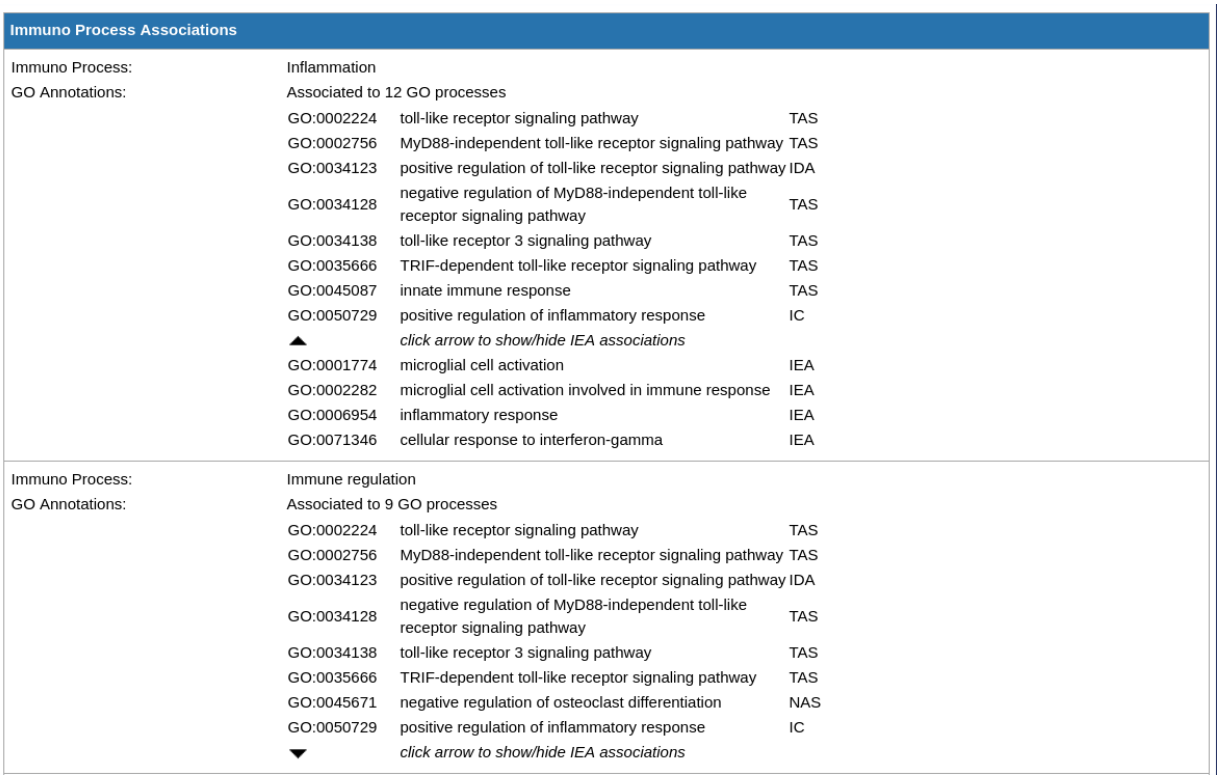


IMMUNO PROCESS DATA

Curations has continued on associating our target to imunological process. The table below summarises the unique target (UniProtKB) annotated to each category and the total target-GO annotations.

Process Category	*GtoPdb Human UniProtKB*	*Target-GO annotations*
Barrier integrity	46	59
Inflammation	605	1372
Antigen presentation	169	242
T cell (activation)	185	384
B cell (activation)	149	245
Immune regulation	461	1190
Tissue repair	20	20
Immune system development	227	398
Cytokine production & signalling	452	1152
Chemotaxis & migration	243	423
Cellular signalling	465	1145

Adjustments have been made to the way process association data is presented, making use of the fact that we capture GO evidence codes for all associations. On the target detailed view page, the section on process associations only shows GO terms associated to the target if they have a GO evidence code other than ‘IEA’ (inferred by electronic annotation). The IEA evidence is the only evidence used by GO that “is assigned by automated methods, without curatorial judgement”. As such we hide these by default (but users can expand the section to see them). On the process association page, the IEA terms are show, but italicised, to emphasise this difference.



Immuno Process Associations			
Immuno Process:	Inflammation		
GO Annotations:	Associated to 12 GO processes		
	GO:0002224	toll-like receptor signaling pathway	TAS
	GO:0002756	MyD88-independent toll-like receptor signaling pathway	TAS
	GO:0034123	positive regulation of toll-like receptor signaling pathway	IDA
	GO:0034128	negative regulation of MyD88-independent toll-like receptor signaling pathway	TAS
	GO:0034138	toll-like receptor 3 signaling pathway	TAS
	GO:0035666	TRIF-dependent toll-like receptor signaling pathway	TAS
	GO:0045087	innate immune response	TAS
	GO:0050729	positive regulation of inflammatory response	IC
	▲	*click arrow to show/hide IEA associations*	
	GO:0001774	microglial cell activation	IEA
	GO:0002282	microglial cell activation involved in immune response	IEA
	GO:0006954	inflammatory response	IEA
	GO:0071346	cellular response to interferon-gamma	IEA
Immuno Process:	Immune regulation		
GO Annotations:	Associated to 9 GO processes		
	GO:0002224	toll-like receptor signaling pathway	TAS
	GO:0002756	MyD88-independent toll-like receptor signaling pathway	TAS
	GO:0034123	positive regulation of toll-like receptor signaling pathway	IDA
	GO:0034128	negative regulation of MyD88-independent toll-like receptor signaling pathway	TAS
	GO:0034138	toll-like receptor 3 signaling pathway	TAS
	GO:0035666	TRIF-dependent toll-like receptor signaling pathway	TAS
	GO:0045671	negative regulation of osteoclast differentiation	NAS
	GO:0050729	positive regulation of inflammatory response	IC
	▼	*click arrow to show/hide IEA associations*	

Modification to show/hide GO associations with IEA evidence

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	33
T cells	CL:0000789 alpha-beta T cell CL:0000815 regulatory T cell CL:0000911 effector T cell	47
Dendritic cells	CL:0000451 dendritic cell	32
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	3
Macrophages & monocytes	CL:0000235 macrophage CL:0000576 monocyte	43
Granulocytes	CL:0000094 granulocyte	37
Natural killer cells	CL:0000623 natural killer cell	20
Mast cells	CL:0000097 mast cell	28
Innate lymphoid cells	CL:0001065 innate lymphoid cell	2
Stromal cells	CL:0000499 stromal cell	0

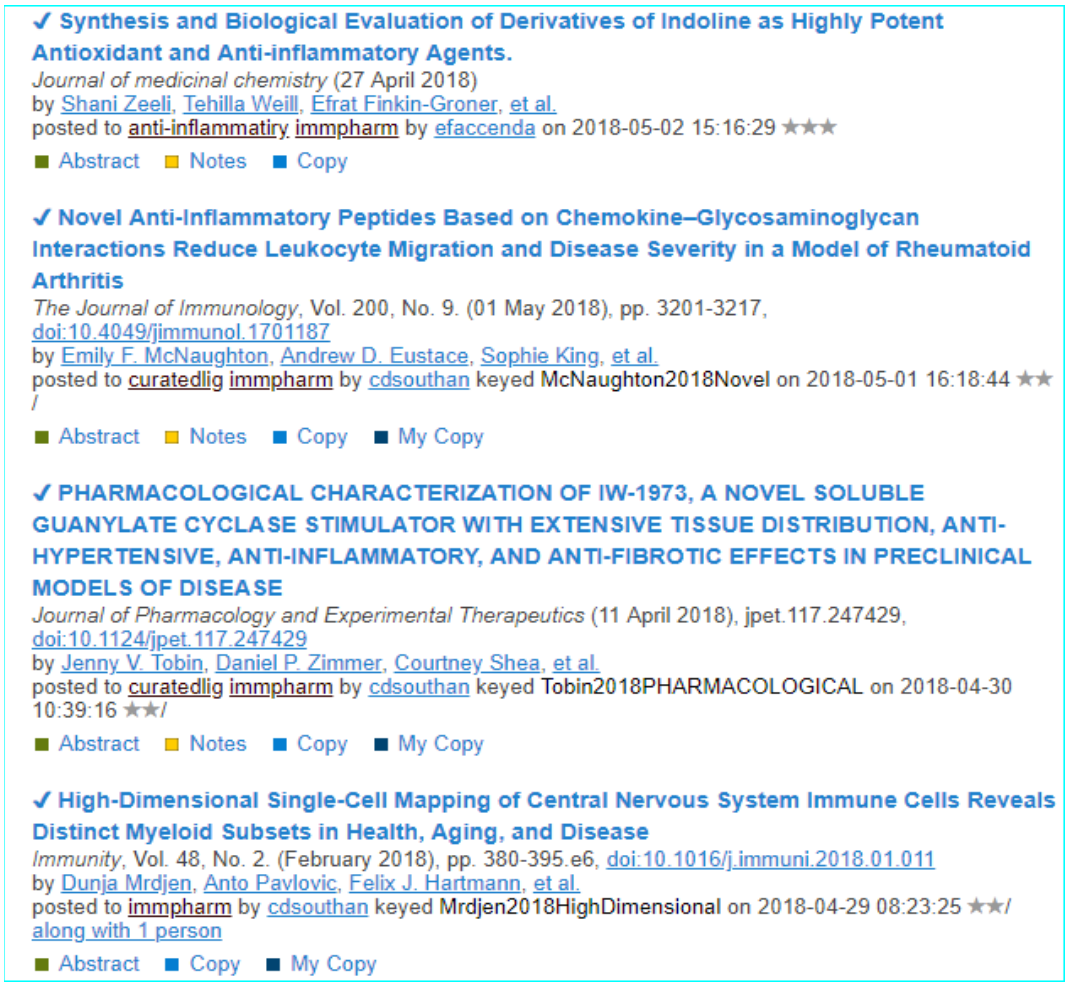
GTOIMMUPDB TARGET AND LIGAND CURATION STATUS

GTOIMMUPDB CURATION STATS

- 525 targets tagged as in GtoImmuPdb:
  - 145 catalytic receptors
  - 168 enzymes
  - 94 gpcrs
  - 17 voltage-gated ion channels
  - 87 other proteins
  - 7 nuclear hormone receptors
  - 5 transporters
  - 3 ligand-gated ion channels
- 993 ligands tagged as in GtoImmuPdb:
  - 589 synthetic organic
  - 138 antibodies
  - 228 peptides
  - 26 metabolite
  - 11 natural products
  - 1 inorganic
- Detailed lists on:
  - www.guidetoimmunopharmacology.org/immuno/immunoHelpPage.jsp

SEARCHING, COLLATION, AND ALERTING

The different strategies explored to retrieve papers have already been described in the Oct 2017 report. The distribution of journal titles has not significantly shifted since then, although the number of curated papers has gone up. The curation team have now collated 921 publications in In CiteUlike, tagged as immphar". A recent selection is shown below.



✓ **Synthesis and Biological Evaluation of Derivatives of Indoline as Highly Potent Antioxidant and Anti-inflammatory Agents.**
Journal of medicinal chemistry (27 April 2018)
by Shani Zeeli, Tehilla Weill, Efrat Finkin-Groner, et al.
posted to anti-inflammatiry immpharm by efaccenda on 2018-05-02 15:16:29 ★★★
■ Abstract ■ Notes ■ Copy

✓ **Novel Anti-Inflammatory Peptides Based on Chemokine–Glycosaminoglycan Interactions Reduce Leukocyte Migration and Disease Severity in a Model of Rheumatoid Arthritis**
The Journal of Immunology, Vol. 200, No. 9. (01 May 2018), pp. 3201-3217, doi:10.4049/jimmunol.1701187
by Emily F. McNaughton, Andrew D. Eustace, Sophie King, et al.
posted to curatedlig immpharm by cdsouthan keyed McNaughton2018Novel on 2018-05-01 16:18:44 ★★/
■ Abstract ■ Notes ■ Copy ■ My Copy

✓ **PHARMACOLOGICAL CHARACTERIZATION OF IW-1973, A NOVEL SOLUBLE GUANYLATE CYCLASE STIMULATOR WITH EXTENSIVE TISSUE DISTRIBUTION, ANTI-HYPERTENSIVE, ANTI-INFLAMMATORY, AND ANTI-FIBROTIC EFFECTS IN PRECLINICAL MODELS OF DISEASE**
Journal of Pharmacology and Experimental Therapeutics (11 April 2018), jpet.117.247429, doi:10.1124/jpet.117.247429
by Jenny V. Tobin, Daniel P. Zimmer, Courtney Shea, et al.
posted to curatedlig immpharm by cdsouthan keyed Tobin2018PHARMACOLOGICAL on 2018-04-30 10:39:16 ★★/
■ Abstract ■ Notes ■ Copy ■ My Copy

✓ **High-Dimensional Single-Cell Mapping of Central Nervous System Immune Cells Reveals Distinct Myeloid Subsets in Health, Aging, and Disease**
Immunity, Vol. 48, No. 2. (February 2018), pp. 380-395.e6, doi:10.1016/j.immuni.2018.01.011
by Dunja Mrdjen, Anto Pavlovic, Felix J. Hartmann, et al.
posted to immpharm by cdsouthan keyed Mrdjen2018HighDimensional on 2018-04-29 08:23:25 ★★/
along with 1 person
■ Abstract ■ Copy ■ My Copy

We use a variety of tags for our own triage in addition to adding pre-curation (e.g. PubChem IDs and patent numbers) and post curation notes (including to curated ligands). All our tagging and notes (yellow squares) are open. The papers are split between those from which targets and or ligands eventually get extracted

into GtoImmuPdb or are put into the general reading list (e.g. the last paper on the list above). We follow Twitter feeds from Immune Regulation News , Human Immune News British Society for Immunology, Edinburgh Centre for Inflammation Research as well as journals such as Nature Immunology and Journal of Immunology. As a custom alerting strategy this gives a good balance of specificity against recall. We also run a high-recall multi-term query in PubMed but since this comes in a ~ 5000 references a month this is intersected with selected journals such as J.Med Chem and BJP.

THE GUIDE TO MALARIA PHARMACOLOGY PROJECT

INTRODUCTION

As we have already mentioned at the beginning of our report, the Guide to Malaria Pharmacology (GtoMPdb) is a recently initiated project that is funded by the Medicines for Malaria Venture (MMV). We are developing this resource as an extension to the existing Guide to PHARMACOLOGY (GtoPdb), with the aim of providing optimised access to the data in GtoPdb for the malaria research community.

EXPERT ADVISORY COMMITTEE (EAC)

A new committee of experts is required for this project and the core membership for this has been appointed. A meeting with Dr David Cavanagh has already taken place and we expect to begin active consultation with the full committee during the next six-month period.

COMMITTEE MEMBERSHIP:

Professor Alexandra Rowe
Institute of Immunology and Infection Research, University of Edinburgh

Dr David Cavanagh
Institute of Immunology and Infection Research, University of Edinburgh

Professor Matthew Todd
School of Chemistry, University of Sydney

Dr Chris Swain
Cambridge MedChem Consulting, Cambridge

Professor Mark Coster
Griffith Institute for Drug Discovery (GRIDD), Griffith University

Professor Michael Pollastri
Department of Chemistry & Chemical Biology, Northeastern University.

Professor Laurent Rénia
Executive Director Singapore Immunology Network (SIgN), Agency for Science, Technology, and Research (A*STAR)

Professor Elizabeth A. Winzeler
University of California Health Sciences Center for Immunology, Infection and Inflammation, UC San Diego.

TARGET AND LIGAND CURATION

CURATION SUMMARY

Initial curation effort focused on collating a list of clinical and investigational antimalarial drugs together with a list of molecular targets with relevance to malaria. This information was used to search GtoPdb for existing coverage and to select and curate a small number of further ligands and targets. Please note that the ligands and targets added during the GtoMPdb project (highlighted in blue in the tables below) are available on our development site and we intend to make this data public during the next database release.

GtoPdb antimalarial ligands: table includes pre-existing entries and those added as part of the GtoMPdb project (highlighted in turquoise).

GtoPdb:Ligand ID	GtoPdb:Ligand Name
2342	quinidine
2510	quinine
4252	mefloquine
4800	pyrimethamine
5535	chloroquine
6464	doxycycline
7198	hydroxychloroquine
9644	DSM265
9647	Compound 34c
9648	BRD3444
9676	proguanil
9695	atovaquone
9708	OSM-S-38
9721	cipargamin
9722	tafenoquine
9723	(+)-SJ733
9726	MMV048
9737	DDD498
9739	fosmidomycin
9740	P218

GtoPdb *P. falciparum* targets: table includes pre-existing entries and those added as part of the GtoMPdb project (highlighted in turquoise).

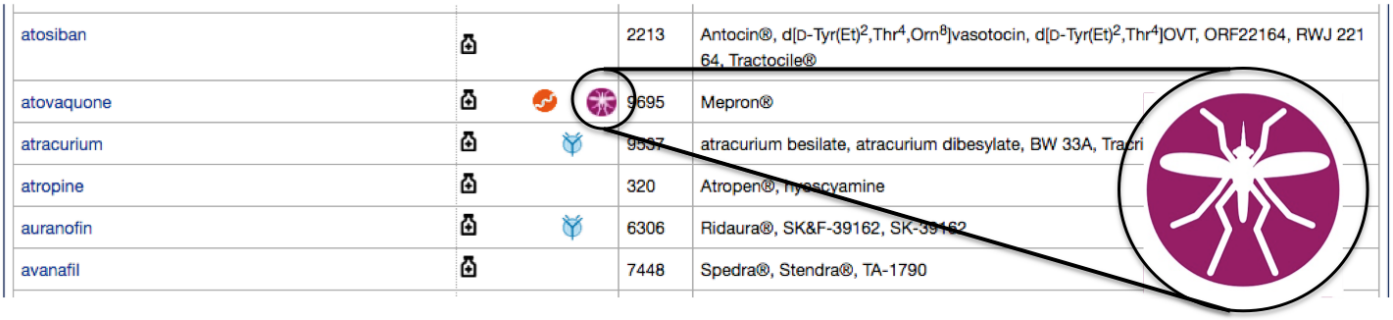
GtoPdb:Target ID	GtoPdb:Target Name
2949	PfDHODH
2954	PfcPheRS
2955	PfNMT
2971	PfATP4
2972	PfP14K
2975	PfeEF2
2980	PfDXR
2981	PfDHFR-TS

COLLECTING AND PRIORITISING CONTENT

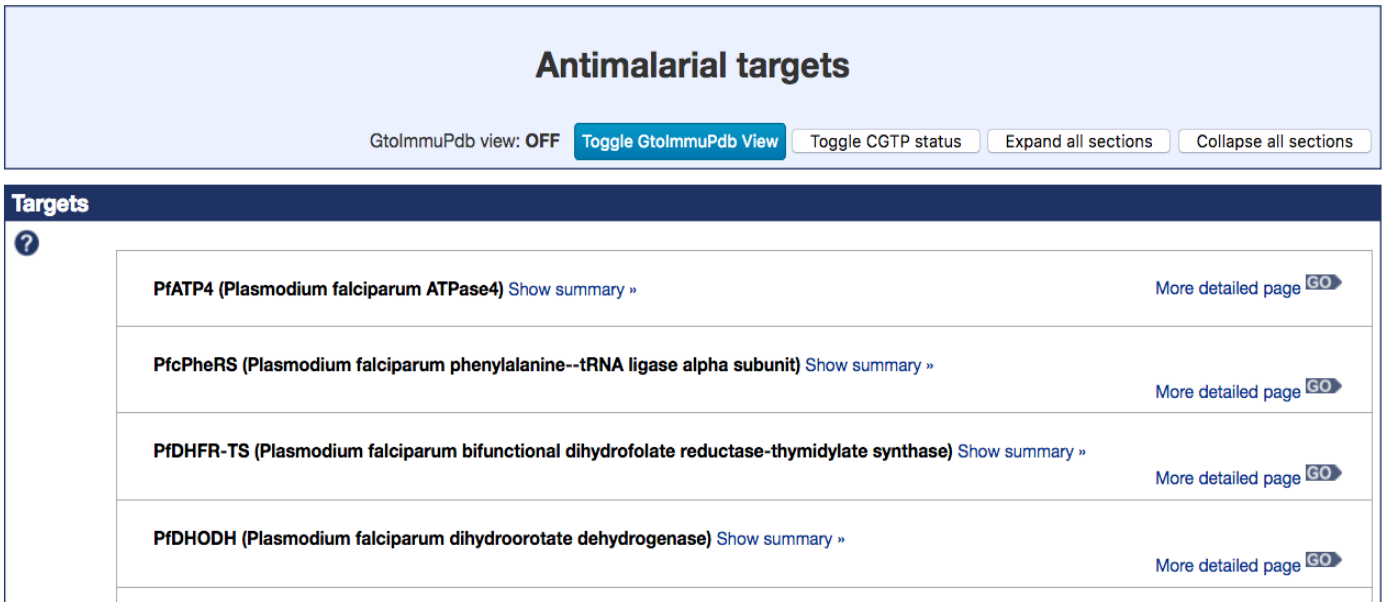
The curation team use a similar strategy to the one employed by GtoImmuPdb and described in our previous reports. In CiteUlike, we have collected 174 publications that we have tagged with antimalarial specific tags (antimalarial, antimalarial_targets, antimalarial_notarget). In addition, MMV are in the process of providing a list of targets and ligands that are of high priority and we will continue to build on this list with the advice of both MMV and our EAC.

WEB INTERFACE AND DATABASE DEVELOPMENT

Following consultation with MMV, we have made a number of changes to the database structure and the web interface to improve both capture and presentation of antimalarial metadata. For example, we have tagged all antimalarial ligands in GtoPdb with a Malaria Project tag and this is now being used to display a new antimalarial icon on the ligand list page. We have also created a new “Antimalarial targets” subfamily as part of the existing “Anti-infective targets” family.



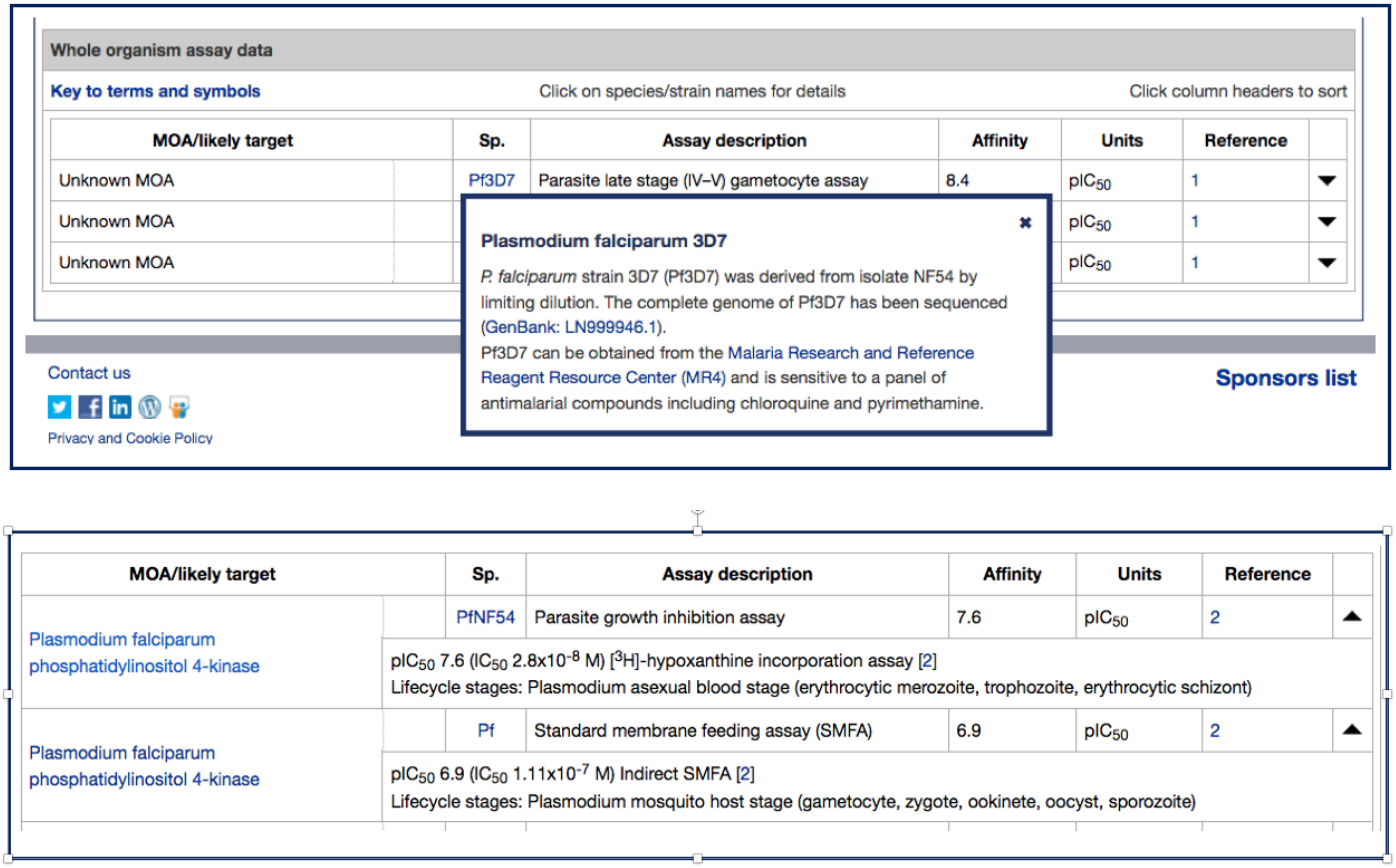
Icon indicating that a ligand has antimalarial activity



New Antimalarials targets subfamily

To fully describe the activity and target interactions of antimalarial compounds requires the display of additional information some of which is specific for the malaria parasite. A number of improvements are available on our development site (password protected, example ligands cipargamin and DDD498) and are under review by MMV. We hope to make these updates public during the next database release.

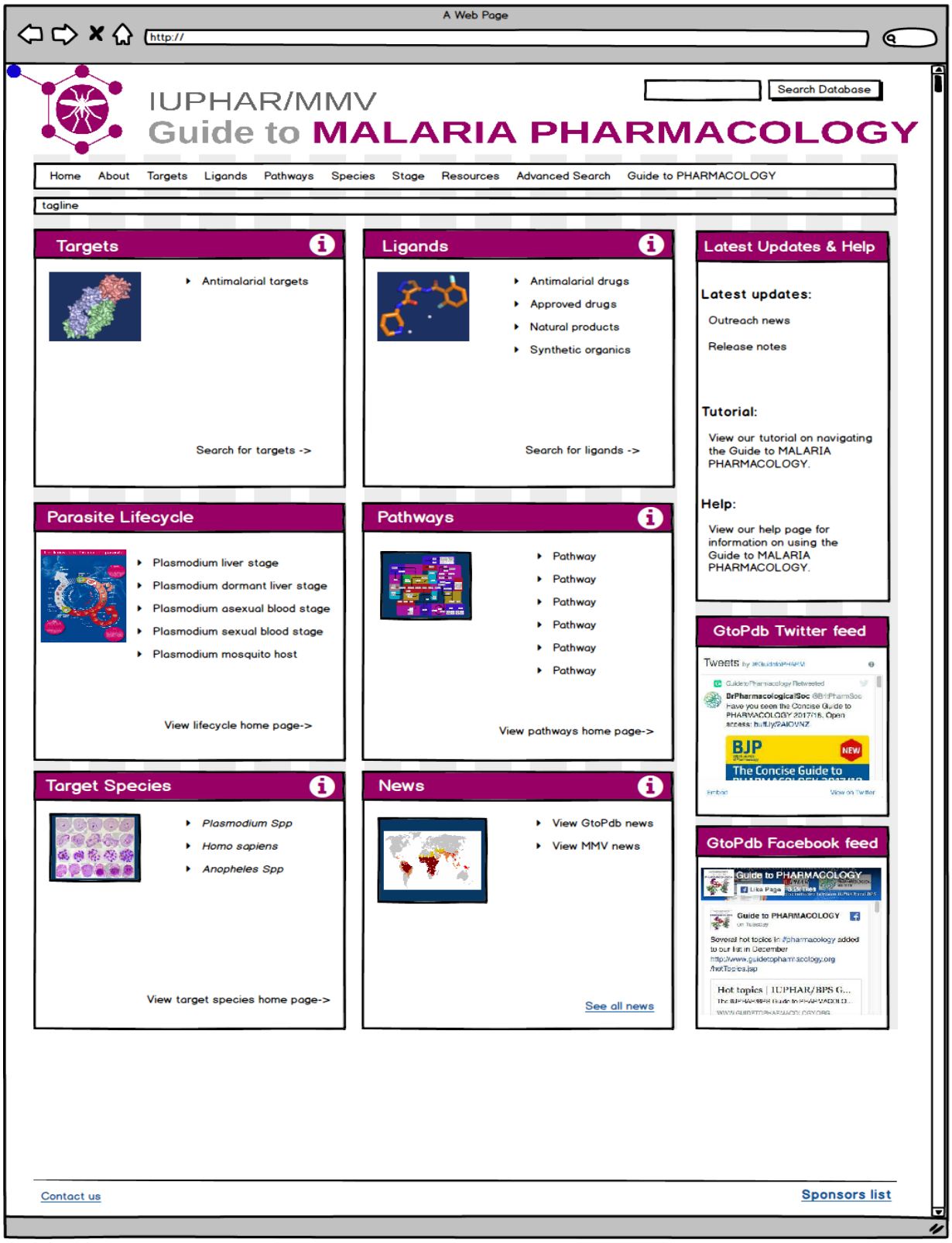
- Many antimalarial compounds have a poorly understood mechanism of action and an unknown molecular target and we have extended the interactions table and updated the web interface to accommodate this.
- A new “whole organism” assay type has been introduced to capture data from the whole cell assays used routinely in antimalarial drug discovery.
- Information about the *Plasmodium* lifecycle activity of a ligand can now be stored in the database and is available from the interactions table.
- Details about the *Plasmodium* species/strain can be stored in the database and displayed using a pop-up window that has been added to the interactions table.



Development site: information about *Plasmodium* species/strain (top panel of image) and lifecycle stage (bottom panel) is now available on the relevant ligand and target pages. The top panel also illustrates the new whole organism assay type and unknown MOA.

PORTAL DESIGN

The GtoMPdb will require a dedicated portal, providing access to the data in GtoPdb and optimized for those involved in malaria research. We are in the early design phase for this aspect of the project: a draft wireframe of the homepage has been prepared (please see figure on following page) and initial feedback has been received from MMV. This draft, draws on our experience from developing the GtoImmuPdb portal, providing a number of tailored search options in addition to the existing ligand and target searches available on the GtoPdb.



Draft wireframe of GtoMPdb homepage