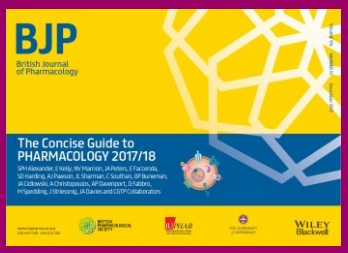
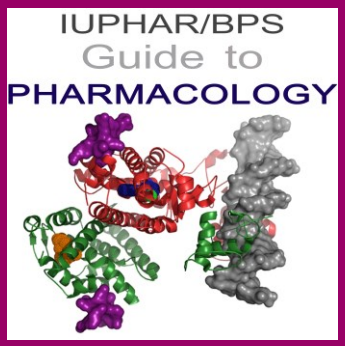
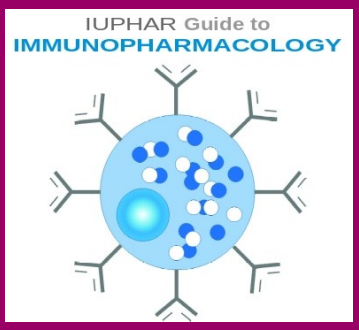
IUPHAR
International Union of Basic and Clinical Pharmacology

BRITISH PHARMACOLOGICAL SOCIETY







IUPHAR/MMV
Guide to MALARIA PHARMACOLOGY

DATABASE Report

October 2018

enquiries@guidetopharmacology.org

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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 Edinburgh in May 2018. Previous reports are online for April 2017, Oct 2017 and May 2018.

We have now reached the end 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.

We again include details on our new Guide to Malaria Pharmacology project. We have 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 May 2018 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 October 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 MAY 2018 AND UPCOMING)

- 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
- 5th European Congress of Immunology, Amsterdam, September 2018, Simon Harding - presented poster on the Guide to IMMUNOPHARMACOLOGY

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 EARLY 2018)

- A new guide to immunopharmacology (2018). Simon D. Harding, Elena Faccenda, Chris Southan, Pasquale Maffia, Jamie A. Davies. Nat. Rev. Immunology (Web Watch). https://doi.org/10.1038/s41577-018-0079-2. Altmetric score of 24 since 16th Oct 2018.
- SynPharm: A Guide to PHARMACOLOGY Database Tool for Designing Drug Control into Engineered Proteins. Sam Ireland, Christopher Southan, Alazne Dominguez, Simon Harding, Joanna Sharman, Jamie Davies. ACS Omega. Jul 31;3(7):7993-8002. PMID: 30087931. The Rx version has garnered 2232, views, 87 downloads and an Altmetic score of 15 since March.
- 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. Jul 31;3(7):8408-8420. PMID:30087946. The Rx version has garnered 466 views and 109 downloads since May 2018.
- 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. PMID:30040201.
- Caveat usor: assessing differences between major chemistry databases. (2018) Chris Southan. ChemMedChem, 13(6):470-481. PMID 29451740 (Gold Open Access)

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 3749 (September 2018), from 3378 in May 2018.

TWITTER

@GuidetoPHARM has just pipped 1,848 tweets, followers have increased to 2186 from 1808 in May 2018 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 @immunopaedia @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 191 followers.

BLOGGING

Our Edinburgh blog (http://blog.guidetopharmacology.org/) is receiving over 750 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. 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

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, Jörg Striessnig, Emma L. Veale & Alastair Mathie, Sadashiva S. Karnik & Kalyan Tirupula, Eamonn Kelly & Katy Sutcliffe, Steve Watterson and Chris Southan (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 2,958 (+171) 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

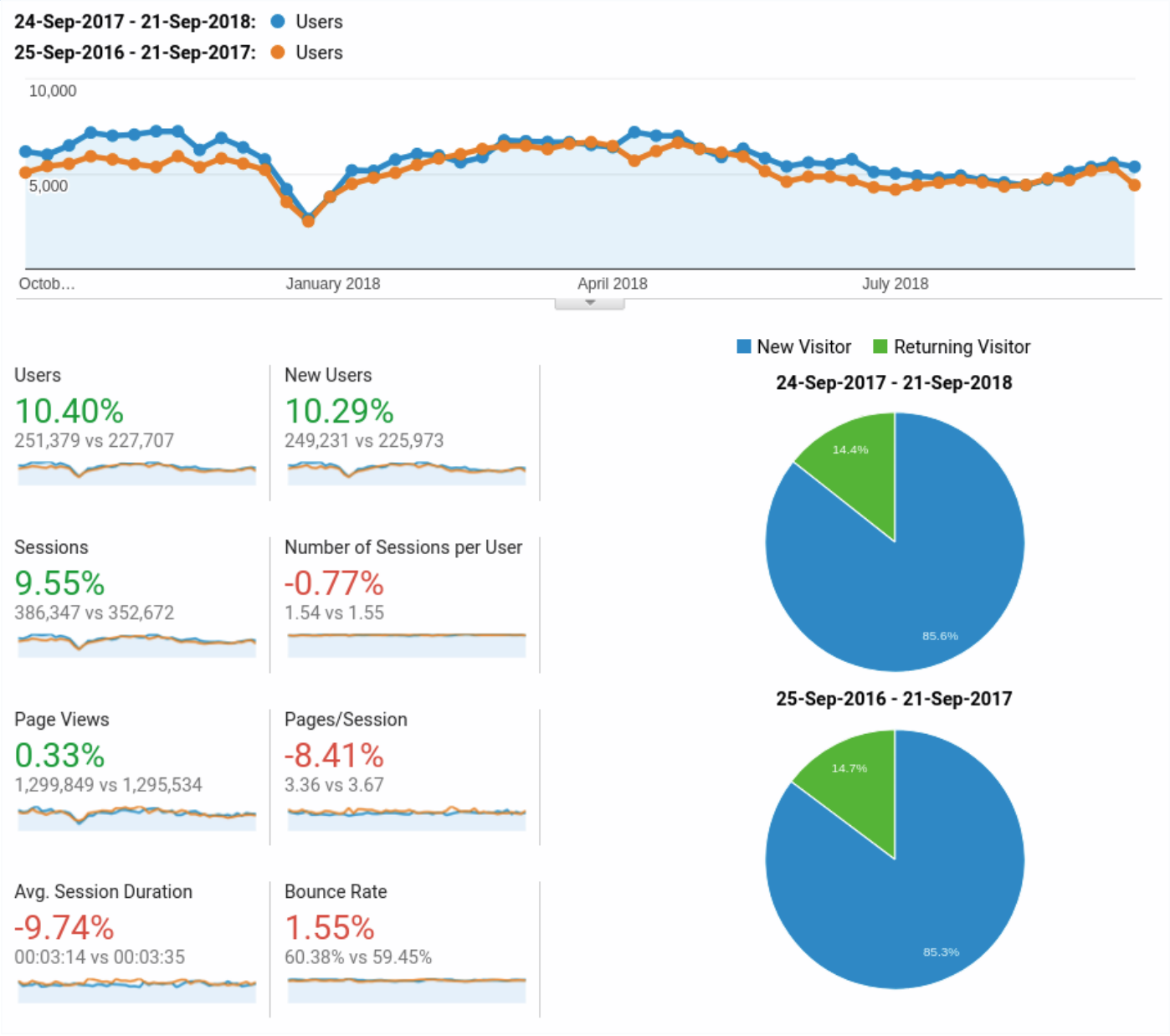
We get a steady stream of user communications coming in to enquiries@guidetopharmacology.org, This is about one a week and they continue to cover a useful spectrum of (mostly minor) fixes that we promptly address.

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).

GTOPDB WEB SITE ACCESS STATISTICS



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

Monthly statistics	***Sep 2017 - Sep 2018 (previous 12 months)***
Sessions	32,196 (31,269)
Users	20,948 (20,635)
Page views	108,320 (105,763)
Pages / Session	3.36 (3.67)
Avg. Session Duration	00:03:14 (00:03:35)

GTOPDB CONTENT

These database statistics were compiled from our September 19th, 2018 release (v2018.4). 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	1201
Transporters	509
Other protein targets	201
Targets with ligand interactions	1734
Targets with quantitative ligand interactions	1482
Targets with approved drug interactions	610
Primary targets with approved drug interactions	319
Total number of targets	**2880**
Ligands	*Number of ligands*
Synthetic organics	6180
Metabolites	584
Endogenous peptides	787
Other peptides including synthetic peptides	1313
Natural products	256
Antibodies	248
Inorganics	37
Approved drugs	1386
Withdrawn drugs	69
Ligands with INNs	2242
Labelled ligands	610
Unique PubChem CIDs (total CID links)	7023 (7224)
Ligands with target interactions	8047
Ligands with quantitative interactions (approved drugs)	7080 (868)
Ligands with clinical use summaries (approved drugs)	2289 (1383)
Total number of ligands (PubChem SIDs)	**9405**
Number of binding constants	47420
Number of binding constants curated from the literature	16213

DOWNLOAD STATISTICS

Yearly period 20th Sep Year 1 to 20th Sep Year 2.

GOOGLE ANALYTICS COMPARISON OF DOWNLOADS

Event Category: Downloads
Event Label: Downloaded

	Count
2016-2017	2,576
2017-2018	2,971
Change	15%

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:

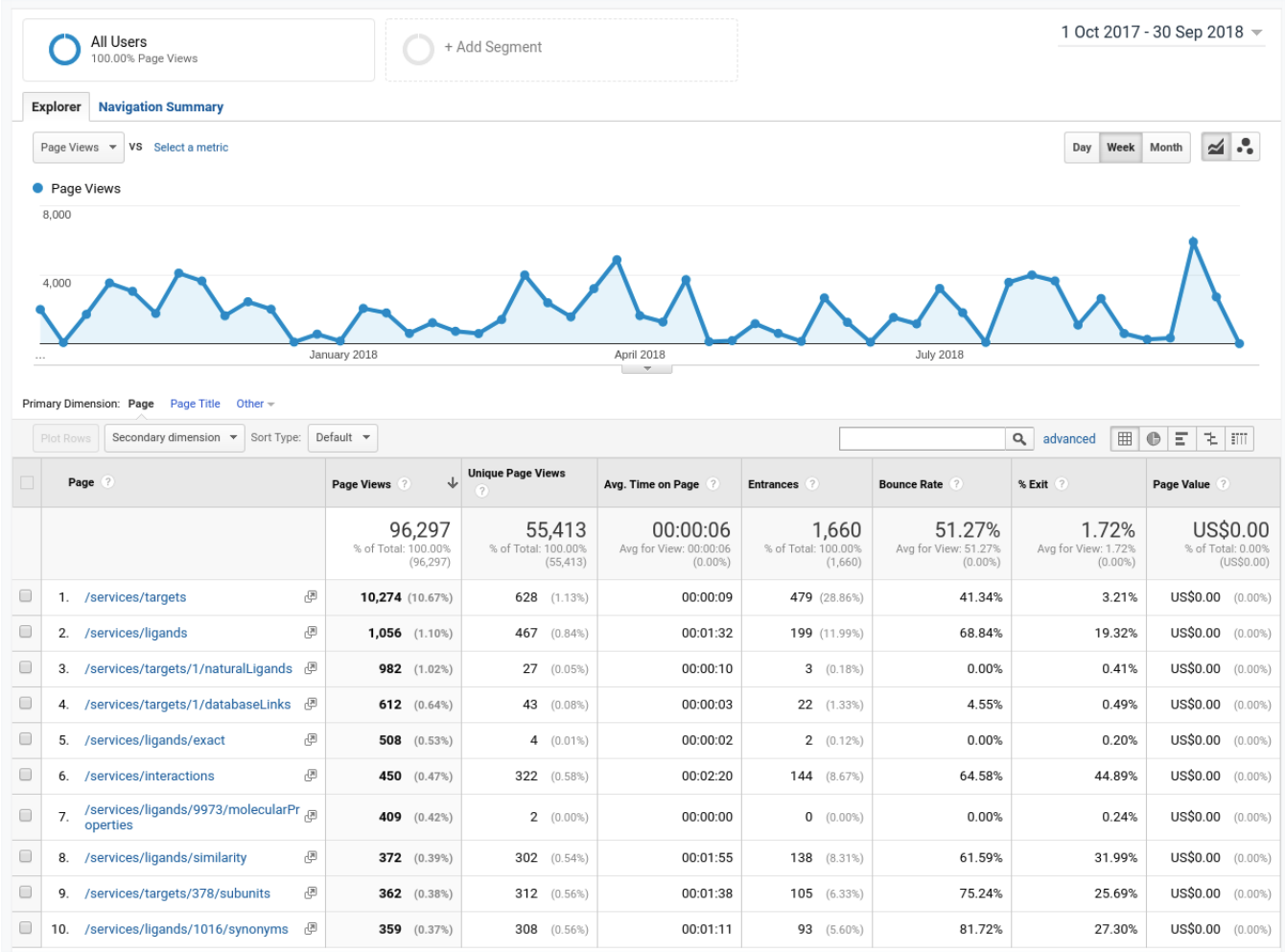
	2016-2017	***2017-2018***	***Change***
Targets CSV/TSV file	1007	1123	12%
Interactions CSV/TSV file	295	338	15%
Ligands CSV/TSV file	250	254	2%
UniProt Mapping file	167	148	-11%
HGNC mapping file	80	94	18%
Peptides CSV file	101	100	no change
*PostgreSQL**	160	227	41%
Generic slides (PPT & PDF)	210	223	6%
Generic poster	107	99	-7%
Other files			
Tutorial	430	515	20%
Terms and Symbols	307	300	-2%

* Total downloads of PostgreSQL database dump files (versions 2016.4-2018.3). A higher number of downloads is likely in this calendar year due to release coinciding with our bi-annual NAR paper.

WEB SERVICES

Tracking of our web-services has been in place 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'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	Page Views	Unique Page Views	Avg. Time on Page	Entrances	Bounce Rate	% Exit	Page Value
	96,297 % of Total: 100.00% (96,297)	55,413 % of Total: 100.00% (55,413)	00:00:06 Avg for View: 00:00:06 (0.00%)	1,660 % of Total: 100.00% (1,660)	51.27% Avg for View: 51.27% (0.00%)	1.72% Avg for View: 1.72% (0.00%)	US$0.00 % of Total: 0.00% (US$0.00)
1. /services/targets	10,274 (10.67%)	628 (1.13%)	00:00:09	479 (28.86%)	41.34%	3.21%	US$0.00 (0.00%)
2. /services/ligands	1,056 (1.10%)	467 (0.84%)	00:01:32	199 (11.99%)	68.84%	19.32%	US$0.00 (0.00%)
3. /services/targets/1/naturalLigands	982 (1.02%)	27 (0.05%)	00:00:10	3 (0.18%)	0.00%	0.41%	US$0.00 (0.00%)
4. /services/targets/1/databaseLinks	612 (0.64%)	43 (0.08%)	00:00:03	22 (1.33%)	4.55%	0.49%	US$0.00 (0.00%)
5. /services/ligands/exact	508 (0.53%)	4 (0.01%)	00:00:02	2 (0.12%)	0.00%	0.20%	US$0.00 (0.00%)
6. /services/interactions	450 (0.47%)	322 (0.58%)	00:02:20	144 (8.67%)	64.58%	44.89%	US$0.00 (0.00%)
7. /services/ligands/9973/molecularProperties	409 (0.42%)	2 (0.00%)	00:00:00	0 (0.00%)	0.00%	0.24%	US$0.00 (0.00%)
8. /services/ligands/similarity	372 (0.39%)	302 (0.54%)	00:01:55	138 (8.31%)	61.59%	31.99%	US$0.00 (0.00%)
9. /services/targets/378/subunits	362 (0.38%)	312 (0.56%)	00:01:38	105 (6.33%)	75.24%	25.69%	US$0.00 (0.00%)
10. /services/ligands/1016/synonyms	359 (0.37%)	308 (0.56%)	00:01:11	93 (5.60%)	81.72%	27.30%	US$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.

ELIXIR

Engagements continue with this important Europe-wide bioinformatics infrastructure initiative. As reported before, we have an entry in the ELIXIR bio-tools directory as one of the official UK ELIXIR Node Resources and part of the Excelerate initiative. We attend the ELIXIR All-Hands Meeting held in June in Berlin and will be represented at the November UK All-Hands Meeting.

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.

We continue to keep the RDF version of the Guide to Pharmacology up-to-date at each release. These are 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: 2018.4. The metadata have been generated in accordance with the W3C Health Care and Life Sciences Community (HCLS) Profile to ensure FAIR compliance.

We have been exploring the implementation of a SPARQL endpoint and plan to use LodeStar as the web-application layer on top of the triple store. This will provide a graphical frontend to the RDF data and allow control over SPARQL queries and provide the data in a human-readable format.

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 have been submitting new BioAssays to PubChem, following on from a pilot exercise for the 5-HT receptor family in 2015. At this point all of our BioAssays have been submitted, following a re-generation step to improve the structure/content of the XML. We can report a good working relationship with Ben Shoemaker at PubChem who has been helpfully overseeing the upload of the assays. The Bioassays are also shown on Target and Compound pages in PubChem so this will increase exposure of the GtoPdb data.

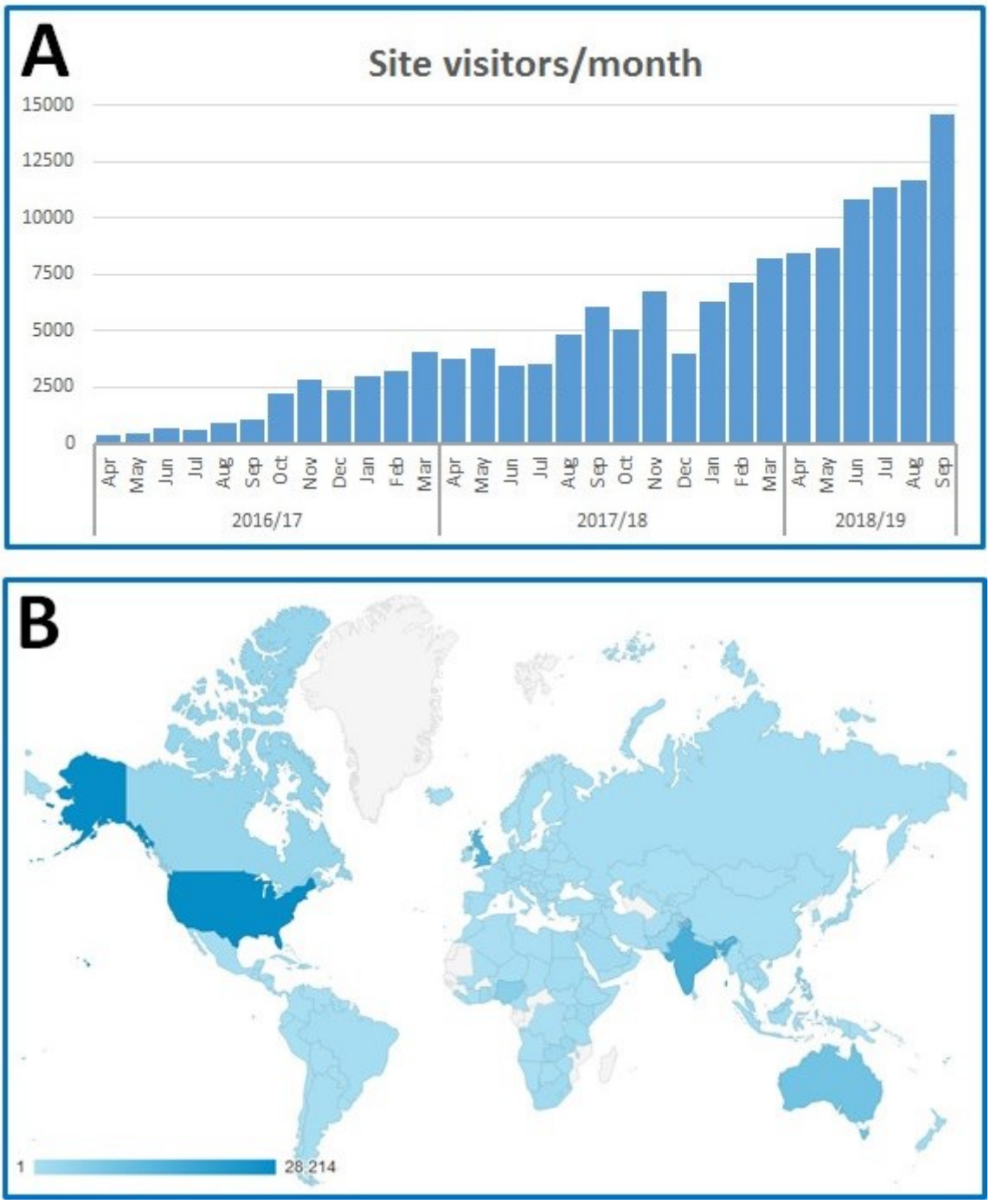
IUPHAR PHARMACOLOGY EDUCATION PROJECT (PEP)

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 ~12 months. This comes from the Chinese, Japanese and Hungarian pharmacological societies.

Site Usage

The figure below shows month to month data from Google Analytics of the recorded PEP user sessions (Panel A) and the global distribution of users (Panel B), from April 2016 when the PEP was launched up to the most current data. User sessions are continuing to grow, and in September 2018 we saw our highest traffic yet at almost 15,000 sessions.



Google Analytics of access to IUPHAR PEP Website

We have noticed relatively high interest in our SlideShare offerings. We currently have 19 slide sets posted, and data analytics has recorded almost 11,000 views of our most popular slidesets, and ~900 downloads, in the last year.

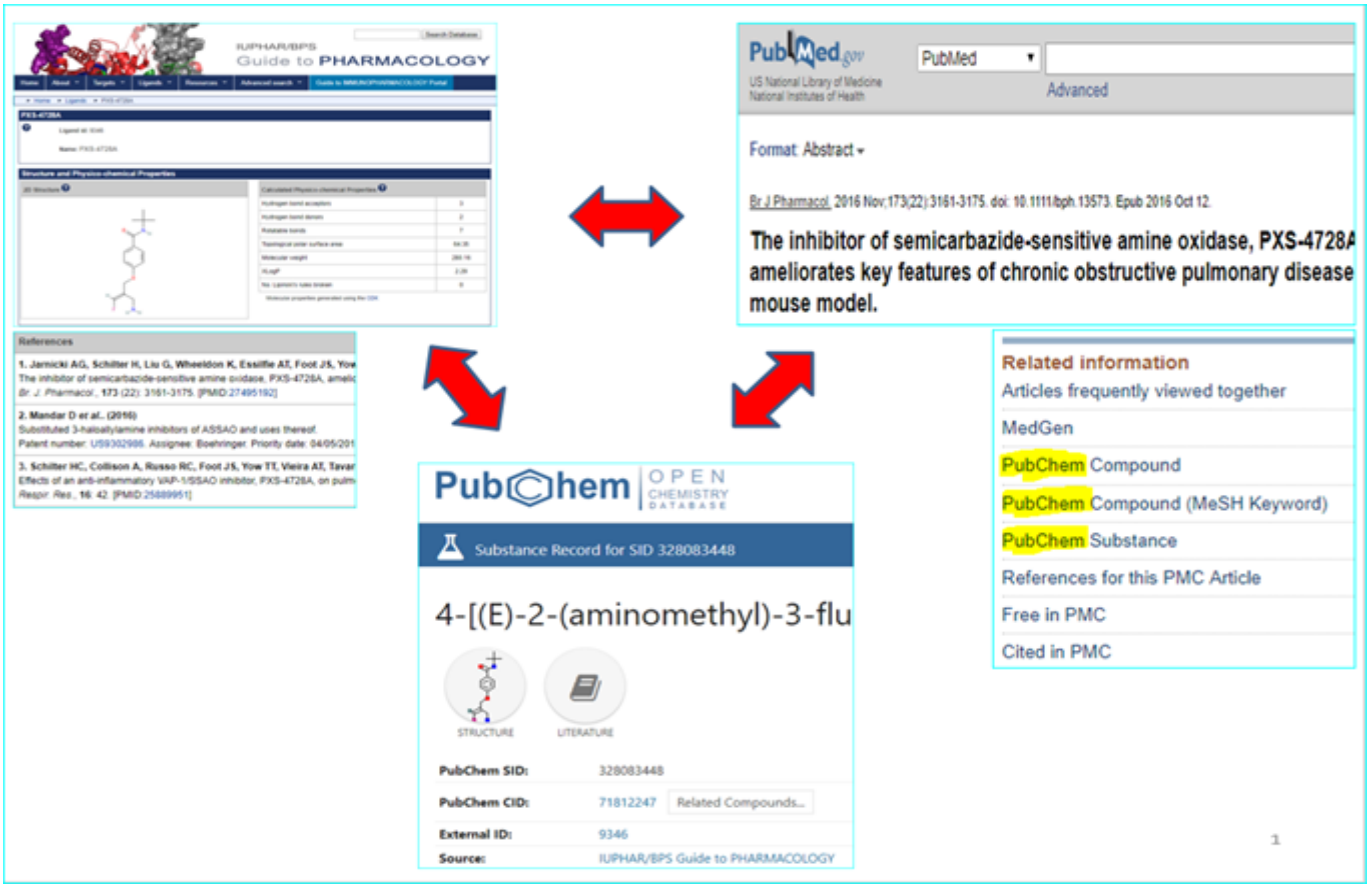
In November 2018, the PEP team had a 'Practice article' entitled 'The IUPHAR Pharmacology Education Project' accepted for publication in the journal Clinical Pharmacology & Therapeutics. This is due for publication in a themed issue in early 2019. We also submitted a short article that reports on PEP activities at WCP2018 for inclusion in IUPHAR's Pharmacology International newsletter.

JOURNAL < - > DATABASE CONNECTIVITY ***(SAME AS MAY 2018 REPORT)***

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).

IMMUNOPAEDIA

We have recently begun to build links with Immunopaedia, an open-access online platform freely available for learning and teaching immunology. The resource aims to improve engagement between core immunology and clinical practice, and it is the official International Union of Immunological Societies (IUIS) learning site. Immunopaedia provides clinical case studies to help highlight immunological concepts, online course to support teaching and learning in immunology, and it provides information on treatment and diagnostics on infectious diseases.

During our Immunopharmacology Meeting in October 2018 we heard a presentation from Prof. Clive Gray (founder) and held discussion on establishing links between Immunopaedia and the Guide to Pharmacology. To date, Immunopaedia have implement links from some case stduies into GtoPDb target and ligand pages. We intend to put in place links from our target and ligand pages back into Immunopaedia and are holding discussions on the best way to do this.

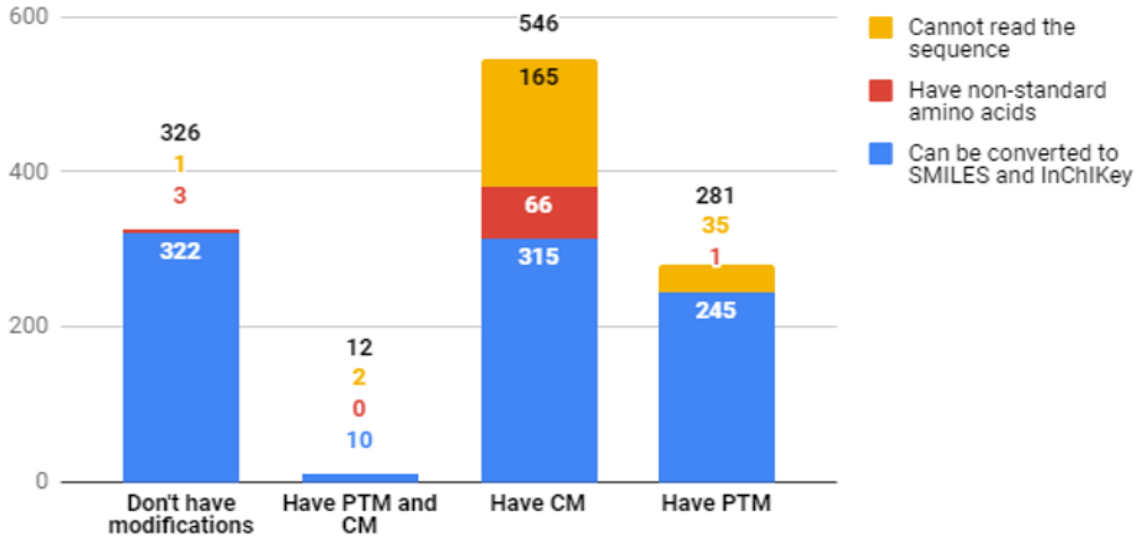
NEW GTOPDB WEBSITE FEATURES (SINCE MAY 2018)

MSC PROJECT ON PEPTIDE STRUCTURES

A MSc Drug Discovery & Translation student, Lin Yikai, worked 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 project explored the following:

- Using the Sugar and Splice (S&S) software (NextMove) to convert our smaller peptides (<70 AA, 1000 atoms) to SMILES and submit these to PubChem, thereby creating CIDs from our SID structures.
- Initially we tried to establish what is 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.
- Future outcomes: extend our 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.

Lin submitted her project dissertation in August 2018. The pipelines she developed for peptide sequence to SMILEs conversion are very useful and will become part of our standard procedure when curating peptides in future. In the analysis of the existing peptide structures in GtoPdb the work provided some interesting information. Here the breakdown of peptides based on whether their sequences have chemical or post-translational modification (which make them more difficult to convert).



The distribution of different subsets of peptides in GtoPdb

OTHER WORK

Updates on other ongoing new website features 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.
- **Update CDK libraries**: We routinely use the Chemistry Development Kit (CDK) to calculate physio-chemical properties of ligands. We have update the libraries we use to the latest version (CDK 2.2) and have re-calculated all ligand properties using these libraries.
- **Switch to using Chemicalize Pro (ChemAxon)**: The GtoPdb website uses the ChemAxon's Marvin JS web-based editor for drawing chemical structures (for subsequent site search). Until now this had required a non-commercial license. By using Chemicalize Pro this drawing tool can be integrated into our site with simple HTML and JS API can handle different functions for exporting/improting molecules and control other events).

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. While the subcommittees have submitted Concise Guide updates, most new entities have been 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***	***Sep 2018***
Target protein IDs	2485	2761	2775	2794	2808	2825	2872	2880
Ligands total	6064	8024	8400	8674	8872	8978	9251	9405
Approved drugs	559	1233	1273	1291	1322	1334	1364	1386
Antibodies	10	138	172	205	212	223	240	248
Peptides	1776	1981	2007	2039	2063	2079	2092	2100
Synthetic small molecules	3504	5055	5363	5563	5729	5807	6048	6180
PubChem SIDs	3107	8024	8328	8674	8831	8978	9251	9405
PubChem CIDs	2694	6057	6163	6337	6813	6822	7109	7224
Binding constants	41076	44691	45534	45908	46287	46488	47058	47426
References	21774	27880	29247	30251	31239	31733	33245	34382

GTOPDB TARGET UPDATES (SINCE MAY 2018)

GPCRs:
Adenosine receptors
Chemokine receptors
Cholecystokinin receptors
Dopamine receptors
Ghrelin receptors
Opioid receptors
GPR55 receptors
Cannabinoid receptors
GPR88
GPR119
Opioid receptors
Free fatty acid receptors
Apelin receptor
Endothelin receptors

NHRs:
Retinoic acid receptor
Peroxisome proliferator-activated receptors
Liver X receptor-like receptors
Retinoic acid-related orphans
3-Ketosteroid receptors

Channels:
Transient Receptor Potential channels
Voltage-gated sodium channels
Orai channels
Voltage-gated potassium channels

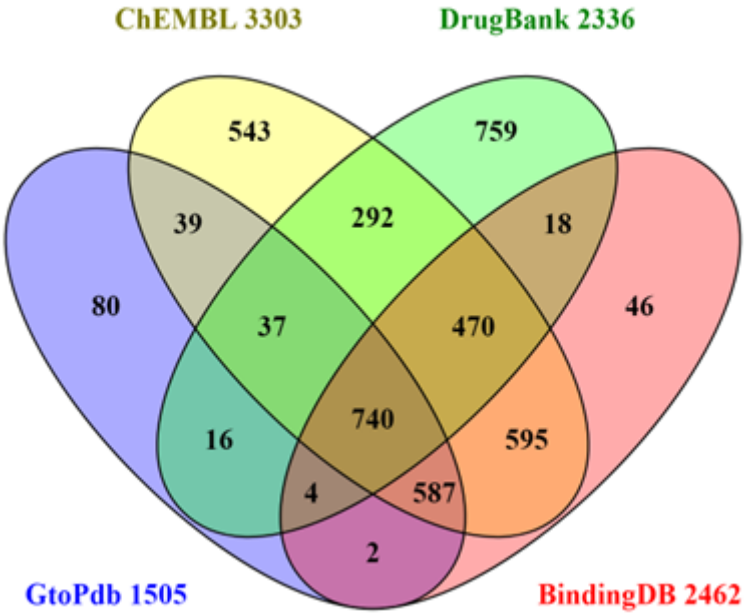
Enzymes:
Guanylyl cyclases (GCs)
Janus kinase (JakA) family
Mitogen-activated protein kinases (MAP kinases)
Nitric oxide synthases
Hydrolases
Janus kinase (JakA) family
Tec family
2.3.2.13 Transglutaminases
1.-.-.- Oxidoreductases
Ceramide turnover
Eicosanoid turnover
Cyclin-dependent kinase (CDK) family
Protein kinase C (PKC) family
AMPK subfamily
Polo-like kinase (PLK) family
Bromodomain kinase (BRDK) family

Catalytic Receptors:
Natriuretic peptide receptor family

Transporters:
ABCG subfamily
Monoamine transporter subfamily
SLC6 neurotransmitter transporter family

Others:
CD molecules
Nuclear export proteins
Aryl hydrocarbon receptor complex
EF-hand domain containing proteins
CD molecules, Immunoglobulin like domain containing proteins
Kelch-like proteins

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.



Our total broke 1500 data-supported druggable targets for the first time in May 2018 and we have 80 targets not in the other three databases (as of May 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

The stats for the 2018.4 release (with 2018.2 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).

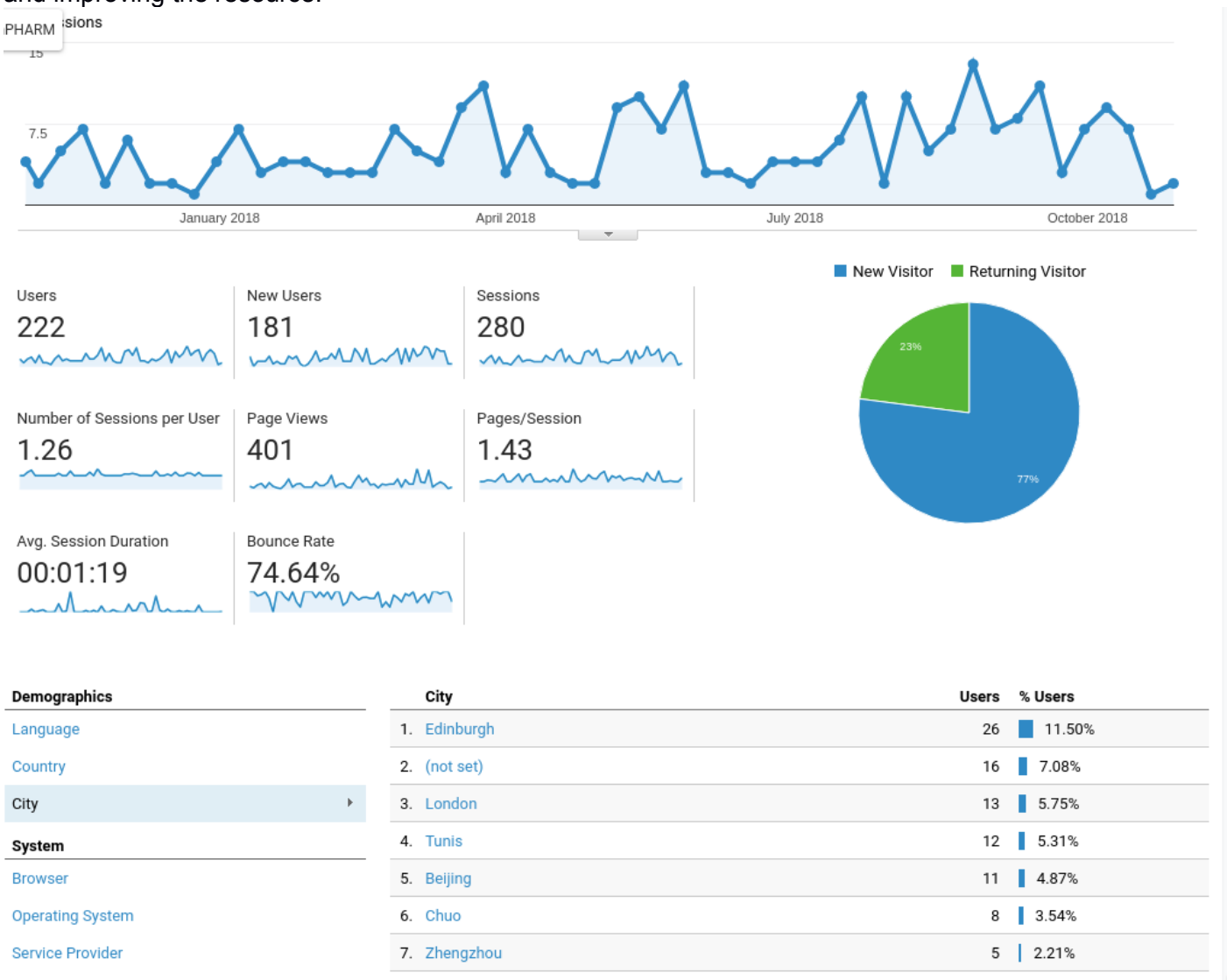
1. Substances (SID) that we submit to PubChem (refreshing previous submissions) are up to 9251 (8978).
2. Those that have defined chemical structures are merged into 6969 (6822) Compound Identifiers, CIDs (i.e. small molecules and moderate peptides)
3. The select "IUPHAR/BPS Guide to PHARMACOLOGY"[SourceName] 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 published: Ireland et al. (2018) SynPharm: A Guide to PHARMACOLOGY Database Tool for Designing Drug Control into Engineered Proteins. ACS Omega. Jul 31;3(7):7993-8002. PMID: 30087931. The figure below shows the SynPHARM access statistics for the past year. About 12% of the hits come from Edinburgh (same as previous report), 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.

Our intention is to try and increase our engagement with UofE SynthSys members to assessing, testing and improving the resource.



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 SDH 0000-0002-9262-8318.

Below are the November 2018 live bibleometic updates compared to the May 2018 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 164 to 169 (this is a PubMed query that not so easy to do in EPMC).
- IUPHAR reviews in BJP are remain level at 25.
- IUPHAR Pharmacological Reviews is now at 103.
- 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 remains at 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 684 citations, overtaking the 2014 paper (PMID 24234439) that reached 591.
- The "Concise Guide" citations are currently led by 2015/16: Enzymes (PMID 26650445) at 488 closely followed by 2013/14: G protein-coupled receptors (PMID 24517644) at 448.
- 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 203. 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 30 after only 6 months.

THE GUIDE TO IMMUNOPHARMACOLOGY DATABASE (GTOIMMUPDB)

GTOIMMUPDB WEB INTERFACE AND DATABASE DEVELOPMENT STATUS

In October 2018 we officially launched the IUPHAR Guide to IMMUNOPHARMACOLOGY, have made the first public release back in June 2018. 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).

IMMUNOPHARMACOLOGY: CHALLENGES, OPPORTUNITIES AND RESEARCH TOOLS

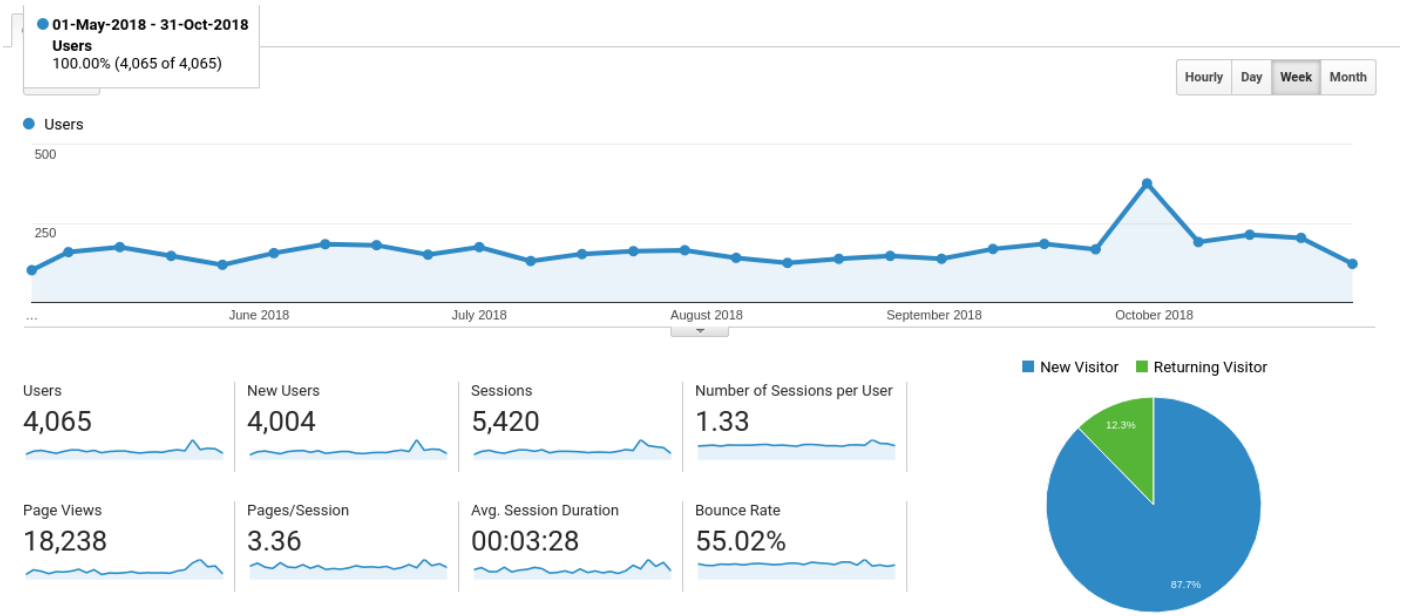
At the beginning of October 2018 we held a meeting in Edinburgh focussed on the launch of the IUPHAR Guide to IMMUNOPHARMACOLOGY. Invited speakers contributed to productive discussions on the varying challenges and opportunities in immunopharmacology research.

We have collated the presentations and written a detailed meeting report which are available on the website. Here is a direct download of the the Meeting Report (PDF).

The meeting included Prof. Tracy Hussell delivering the Anthony Harmar Memorial Lecture, details of which are given in a dedicated blog post.

GTOIMMUPDB ANALYTICS

Our analytics over the last 7 months show an average of 775 session per month. From the grpah below you can see the spike in usage that conincided with the offical launch of GtoImmuPdb during our Ocotber Immunopharmacology Meeting.



Access statistics for GtoImmuPdb (May 2018-October 2018)

The majority of users accessing GtoImmuPdb have come from the USA and UK, together accounting for nearly 37% 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 GtoImmuPdb are China (8%), India (6%) and Japan (5%),

	Country	Users	% Users
1.	United States	1,120	27.44%
2.	United Kingdom	403	9.87%
3.	China	316	7.74%
4.	India	250	6.12%
5.	Japan	215	5.27%
6.	Germany	144	3.53%
7.	France	127	3.11%
8.	Brazil	120	2.94%
9.	Spain	116	2.84%
10.	Mexico	84	2.06%

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

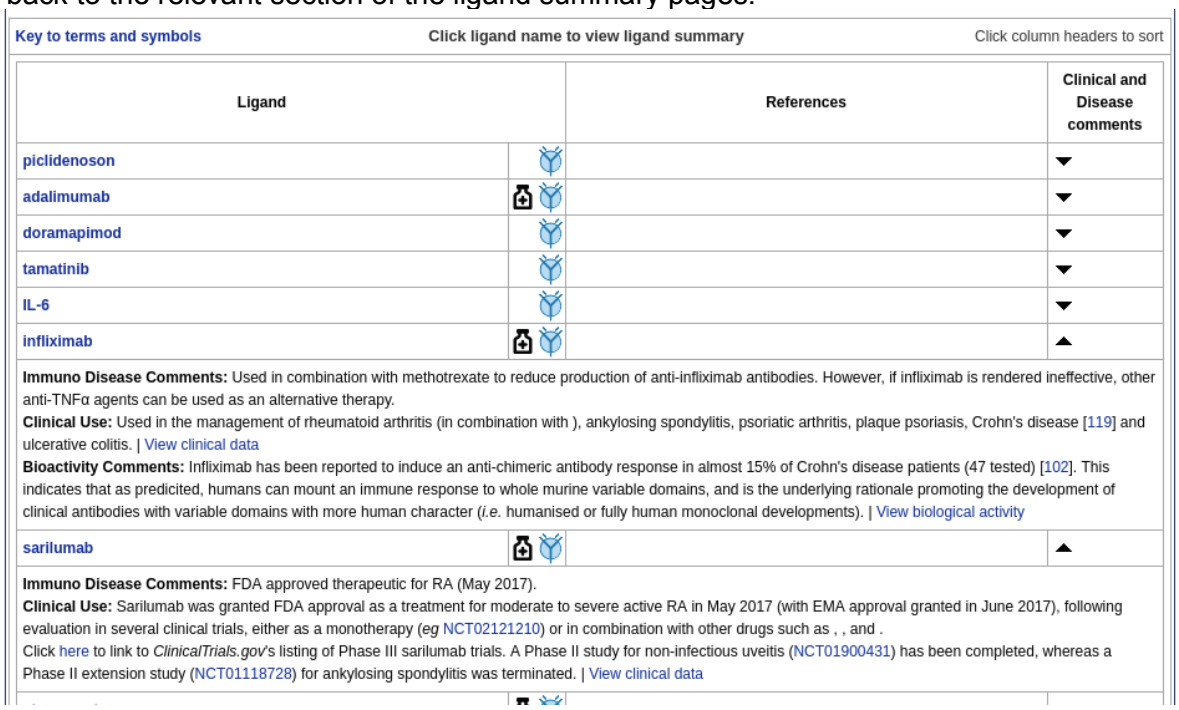
GTOIMMUPDB PORTAL AND SEARCHING

No major changes to the portal have been made in the last 6-months, with the exception of including tutorial videos under the help icon links.

The GtoImmuPdb portal, October 2018; Showing pop-up help with tutorial videos

DISEASE DATA

Our work on the presentation of disease data has been extended to incorporate addition ligand comments on the disease summary pages. Both clinical use and bioactivity comments are now included and these also link back to the relevant section of the ligand summary pages.



Key to terms and symbols | Click ligand name to view ligand summary | Click column headers to sort

Ligand	References	Clinical and Disease comments
piclidenoson		▼
adalimumab		▼
doramapimod		▼
tamatinib		▼
IL-6		▼
infliximab		▲

Immuno Disease Comments: Used in combination with methotrexate to reduce production of anti-infliximab antibodies. However, if infliximab is rendered ineffective, other anti-TNFα agents can be used as an alternative therapy.
Clinical Use: Used in the management of rheumatoid arthritis (in combination with), ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, Crohn's disease [119] and ulcerative colitis. | View clinical data
Bioactivity Comments: Infliximab has been reported to induce an anti-chimeric antibody response in almost 15% of Crohn's disease patients (47 tested) [102]. This indicates that as predicited, humans can mount an immune response to whole murine variable domains, and is the underlying rationale promoting the development of clinical antibodies with variable domains with more human character (*i.e.* humanised or fully human monoclonal developments). | View biological activity

sarilumab		▲

Immuno Disease Comments: FDA approved therapeutic for RA (May 2017).
Clinical Use: Sarilumab was granted FDA approval as a treatment for moderate to severe active RA in May 2017 (with EMA approval granted in June 2017), following evaluation in several clinical trials, either as a monotherapy (*eg* NCT02121210) or in combination with other drugs such as , , and .
Click here to link to *ClinicalTrials.gov*'s listing of Phase III sarilumab trials. A Phase II study for non-infectious uveitis (NCT01900431) has been completed, whereas a Phase II extension study (NCT01118728) for ankylosing spondylitis was terminated. | View clinical data

Ligands section of Rheumatoid Arthritis disease summary page. Showing that clinical use and bioactivity comments have been incorporated.

We have also now completely incorporated disease terms and data into the site search mechanisms. This includes being able to find diseases through the site-wide search.

Disease Associations to Targets and Ligands: Disease with most associations			
Disease	**Targets**	**Disease**	**Ligands**
Rheumatoid arthritis	11	Rheumatoid arthritis	125
Asthma	6	Asthma	77
Osteoarthritis	5	Psoriasis	56
Acute myeloid leukemia	3	Chronic obstructive pulmonary disease	42
Psoriasis	2	Crohn's disease	26
Irritable bowel syndrome	2	Osteoarthritis	25
Acute lymphocytic leukemia (ALL)	2	Systemic lupus erythematosus	23
Behcet syndrome	2	Ulcerative colitis	21
Multiple sclerosis	2	Psoriatic arthritis	16
		Atopic dermatitis	15
		Dermatitis	14
		Ankylosing spondylitis	14
		Allergic rhinitis	13
		Relapsing-remitting multiple sclerosis	12
		Chronic lymphocytic leukemia	11
		Allergic urticaria	9
		Allergic conjunctivitis	8
		Inflammatory bowel disease 1; IBD1	8
		Graft versus host disease	7
		non-Hodgkin lymphoma	7

These table give an overview of the diseases with the most target and ligand associations in GtoImmuPdb.

IMMUNO PROCESS DATA

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	47	63
Inflammation	630	1434
Antigen presentation	178	260
T cell (activation)	195	418
B cell (activation)	156	261
Immune regulation	481	1252
Tissue repair	21	21
Immune system development	240	428
Cytokine production & signalling	504	1347
Chemotaxis & migration	266	491
Cellular signalling	480	1177

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	47
T cells	CL:0000789 alpha-beta T cell CL:0000815 regulatory T cell CL:0000911 effector T cell	69
Dendritic cells	CL:0000451 dendritic cell	37
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	53
Granulocytes	CL:0000094 granulocyte	40
Natural killer cells	CL:0000623 natural killer cell	22
Mast cells	CL:0000097 mast cell	37
Innate lymphoid cells	CL:0001065 innate lymphoid cell	2
Stromal cells	CL:0000499 stromal cell	1

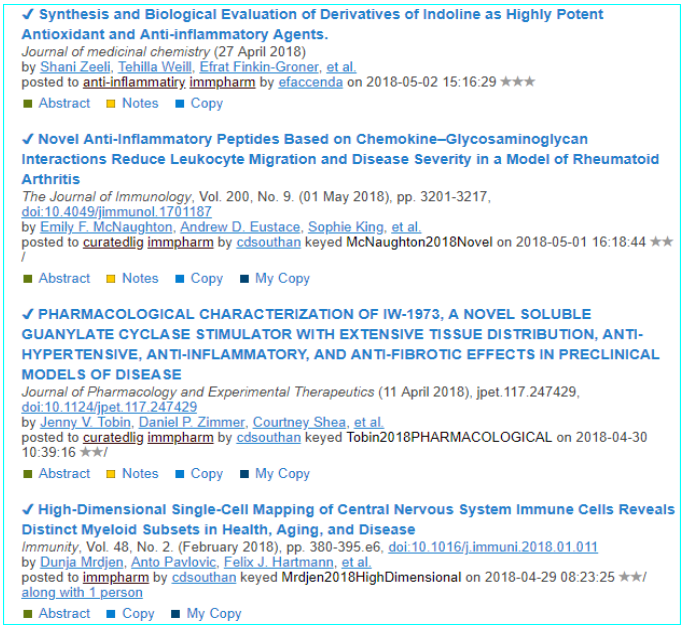
GTOIMMUPDB TARGET AND LIGAND CURATION STATUS

GTOIMMUPDB CURATION STATS

- 568 targets tagged as in GtoImmuPdb:
  - 145 catalytic receptors
  - 183 enzymes
  - 98 gpcrs
  - 24 voltage-gated ion channels
  - 93 other proteins
  - 8 nuclear hormone receptors
  - 9 transporters
  - 8 ligand-gated ion channels
- 1068 ligands tagged as in GtoImmuPdb:
  - 640 synthetic organic
  - 146 antibodies
  - 236 peptides
  - 34 metabolite
  - 11 natural products
  - 1 inorganic
  - 236 Approved drugs
- Detailed lists on:
  - www.guidetoimmunopharmacology.org/immuno/immunoHelpPage.jsp

SEARCHING, COLLATION, AND ALERTING ***(SAME AS MAY 2018 REPORT)***

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 ~950 publications in In CiteUlike, tagged as immphar". A recent selection is shown below.



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 for the malaria research community to the data in GtoPdb. In this section of the report we will provide an update on the curation effort and also describe progress on development of the GtoMPdb portal.

TARGET AND LIGAND CURATION

CURATION SUMMARY

The number of ligands in the public database with antimalarial activity has continued to increase and we have also added to the number of *P. falciparum* targets.

- 41 ligands tagged as in GtoMPdb:

  http://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=999

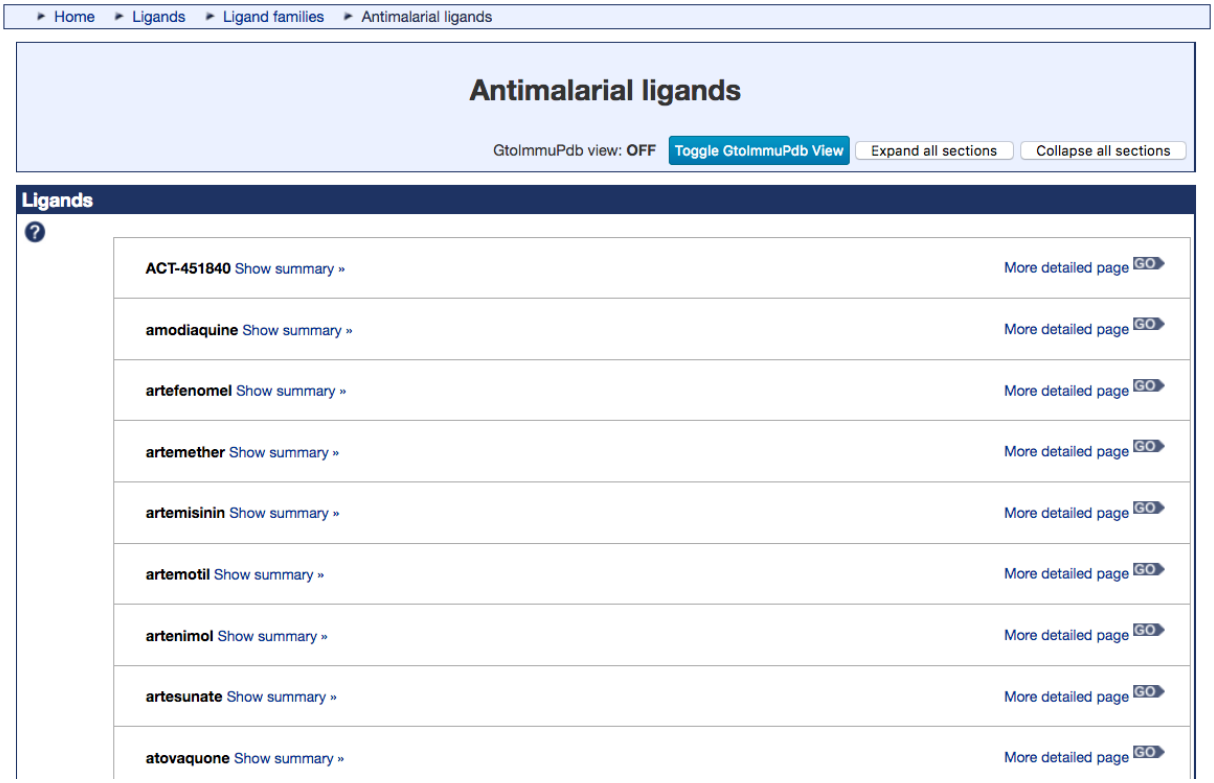
- 9 targets tagged as in GtoMPdb:
  http://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=970

COLLECTING AND PRIORITISING CONTENT

The curation team use a similar strategy to the one employed by GtoImmuPdb and described in our previous reports. We have continued to add to CiteUlike, collecting 195 publications that we have tagged with antimalarial specific tags (antimalarial, antimalarial_targets). In addition, MMV have provided 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 expert advisory committee (EAC).

WEB INTERFACE AND DATABASE DEVELOPMENT

In the May 2018 report we described a number of changes to the database structure and the web interface that were necessary for the capture and presentation of antimalarial data. Although this completed the major part of the required development, we have continued to implement improvements: including updating the web interface to help surface antimalarial ligands by introducing an 'Antimalarial ligands' subfamily and providing an 'antimalarial' tab on the ligand list page (both updates are illustrated below).
In addition, we have put in place the ability to tag both targets and ligands of relevance to malaria and provide curatorial comments. These comments surface on the website (development site only) and are incorporated into the site search.



The IUPHAR/BPS Guide to PHARMACOLOGY complete ligand list

Approved | Syn. organic | Metabolite | Nat. product | Endogenous peptide | Other peptide | Inorganic | Antibody | Labelled | Immuno | **AntiMal**

Toggle GtoImmuPdb View

A B C D E F H K L M O P Q S T

Ligand name	ID	Synonyms
A		Back to top
ACT-451840	10022	ACT451840, Actelion-451840
amodiaquine	10018	Alphaquine®, Amdaquine®, Amoquin®, Camoquin®, Flavoquine®
artefenomel	9971	OZ439
artemether	9955	β-artemether, beta-artemether
artemisinin	9954	
artemotil	9958	β-arteether
artenimol	9957	DHA, dihydroartemisinin, GNF-Pf-5634
artesunate	9956	
atovaquone	9695	Mepron®
azithromycin	6510	
B		Back to top
BRD3444	9648	

PORTAL DESIGN

In the May report we also described the requirement for a dedicated portal for the GtoMPdb, that would provide access to the data in GtoPdb and be optimised for those involved in malaria research. Development of this portal has been the major focus over the summer months and an alpha-release (v1.0) has been deployed to our development site. We have received initial comments from MMV and we are preparing to gather further feedback from MMV, our EAC and the wider research community.

HOMEPAGE

The GtoMPdb homepage has been designed to provide tailored routes into browsing the antimalarial data, in addition to the existing ligand and target browse/search functionality available on the GtoPdb. For the alpha-release we have developed customised views of the data that include parasite lifecycle and target species activity, with access from either the menu-bar or panels on the homepage.

GtoMPdb homepage (alpha-release v1.0)

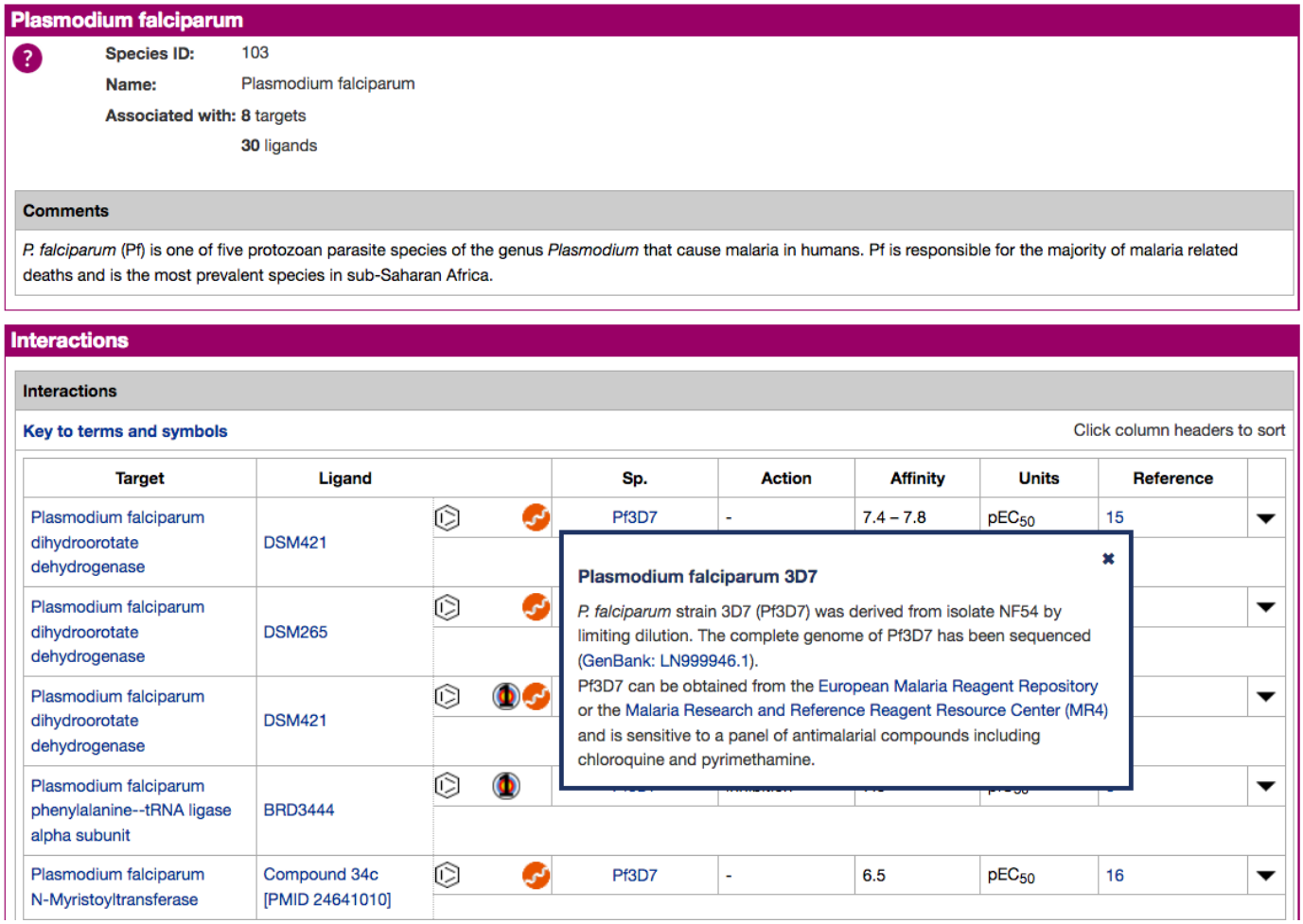
PARASITE LIFECYCLE ACTIVITY DATA

The GtoMPdb uses a set of top-level *Plasmodium* lifecycle stages (collective categories for one or more developmental forms of the parasite) against which interactions in the database can be annotated and which form the basis of organising, navigating and searching for parasitic lifecycle activity.
We have developed a new Parasite Lifecycle homepage that provides a short introduction and links to additional pages for each of the top-level lifecycle stages. These in turn contain a more detailed description and a table of interactions for that lifecycle stage.

Parasite Lifecycle homepage with links to individual lifecycle pages

TARGET SPECIES

The Target Species homepage provides a short description for *Plasmodium* species that are of clinical or research importance. It also includes a resource section and links to individual pages for species that have annotated interactions in the database. The figure below illustrates an example of an individual species page. The interactions table displays affinity data for the species but also provides additional details, when available, for the strain used. We will continue to develop this page and are in the process of replacing the 'Comments' section with a more detailed 'Description' field.



Individual Target Species page for *P. falciparum* showing interaction data and an example of the pop-up strain window