NC-IUPHAR

Annual Report

2014/15

IUPHAR

International Union of Basic and Clinical Pharmacology

Background to NC-IUPHAR

NC-IUPHAR was initiated in 1987 at the Xth International Congress of Pharmacology in Sydney. In 1989, the Executive Committee of IUPHAR named Paul Vanhoutte (Hong Kong) as chairman of a revised and enlarged committee, with Michael Spedding (France) as secretary (1990). This committee energetically expanded its activities and the number of subcommittees (to 33), eventually producing the first official compendium on the occasion of the XIIIth International Congress of Pharmacology in Munich in 1998. Robert Ruffolo (USA) was Chairman of NC-IUPHAR from 1998-2002. Michael Spedding became Chairman in 2002 and was elected again in 2006, and assumed the post of Secretary General of IUPHAR in July 2015.

NC-IUPHAR and its partners are developing a knowledge environment that will enable students and scientists in academia and industry, working in areas related to pharmacology and drug/target research, to exploit the full potential of the considerable amount of information on drug action available in the published scientific literature. This knowledge environment will be a valuable tool for basic and clinical scientists seeking new approaches for drug discovery research, and the diagnosis and treatment of disease, and a valuable teaching resource for students of pharmacology and translational medicine.

NC-IUPHAR has the objectives of:

1. Issuing guidelines for the nomenclature and classification of all the (human) biological targets, including all the targets of current and future prescription medicines
2. Facilitating the interface between the discovery of new sequences from the Human Genome Project and the designation of the derived entities as functional biological targets and potential drug targets
3. Designating polymorphisms and variants which are functionally important
4. Developing an authoritative and freely available, global online resource, originally called the IUPHAR database, which is now accessible *via* the IUPHAR/BPS Guide to PHARMACOLOGY web portal (GtoPdb; http://www.guidetopharmacology.org), with a remit to:
    - provide access to data on all known biological targets
    - enable students and scientists in academia and industry, working in areas related to pharmacology and drug/target research, to exploit the full potential of the considerable amount of information on drug action available in the published literature
    - provide an entry point into the pharmacological literature for basic and clinical scientists from other disciplines
    - provide an integrated educational resource with access to high quality training in the principles of basic and clinical pharmacology and techniques
    - foster innovative drug discovery

Outgoing Chairman's statement

2014/15 was another year of remarkable progress for NC-IUPHAR in building our long-term foundations, in line with our strategic objectives. Thanks to the all the attendees at the twice yearly NC-IUPHAR meetings (held alternatively in Edinburgh and Paris), these meetings have been scientifically exciting, administratively effective - and kept to time! The Grant-holders' meetings every two months (held in Edinburgh or by teleconference) have also kept the Wellcome Trust grant on track in terms of fulfillment of the aims and objectives for the development of IUPHAR/BPS Guide to PHARMACOLOGY database (GtoPdb) project.

NC-IUPHAR has grown dramatically in recent years, including increased expert subcommittees, and branching into newer areas that are having a dramatic impact on drug discovery and pharmacology. The immense recent growth of drug target knowledge, including their crystal structures, has been a major support to drug discovery. This includes use of both the NC-IUPHAR classifications and the GtoPdb. We are approaching the point of defining of nearly all potentially druggable sites encoded by the human genome. However, drug discovery success has not grown at the same rate as our knowledge of drug targets. This is partly due to the exponentially-increasing number of drug-related variables as well as a rapidly increasing knowledge of receptor polymorphisms, which may be crucial in disease states, and also contribute to controversy. The highlighting of these variables *via* groups of experts has been shown to be a first step towards controlling them. In the GtoPdb, such identification and highlighting is the result of expert-driven analysis using our (~90) subcommittees.

The management structure of NC-IUPHAR and the GtoPdb team, with input from IUPHAR exec, BPS, and input from ASPET, ASCEPT and the Japanese Pharmacological Society, has been functioning extremely well thus far. However, since I have assumed the post of Secretary General of IUPHAR, it is now apparent that the current model involving co-ordination by a single Chair may be too difficult a task in the absence of, essentially, a full-time position dedicated specifically to that role. At my request, a Strategic Review Committee (SRC) was established at the October 2014 NC-IUPHAR meeting held in Paris, with the task of reviewing the current status of NC-IUPHAR and its activities, and recommending a path/model for going forward in terms of management and direction of NC-IUPHAR. The SRC is comprised of Doriano Fabbro (Chair), Arthur Christopoulos, Steve Alexander and Adam Pawson. An initial report with recommendations has been submitted by the SRC to NC-IUPHAR, and further discussions will take place at the April meeting in Edinburgh.

The GtoPdb team consists of five full-time staff with a part-time administrator, thanks to the agreement between IUPHAR, the BPS, the Wellcome Trust and the University of Edinburgh. This has boosted our capacity as evidenced by the expanded number of subcommittees which they are now the nexus of. The database team is efficient, highly motivated, and led by Professor Jamie Davies as the database Principal Investigator at the University of Edinburgh. Our collaboration with the BPS has also produced *The Concise Guide to PHARMACOLOGY*, the successor to the BPS Guide to Receptors and Channels (GRAC). The first edition of the 'Concise Guide' was published in 2013/14, and we are now preparing for the production of the 2015/16 edition due in the autumn. This will be an updated snapshot of the concise target family summaries in the database, published as a series of PDFs as desktop reference guides. This publication has been a major effort of the database team and the 'Concise Guide' Editors. The GtoPdb team have also made significant improvements and enhancements to the web interface and database, which are detailed in this report.

Last July, NC-IUPHAR was extremely well represented at WCP2014 in Cape Town with 7 members presenting inspired plenary lectures, and 14 members speaking in eight symposia. This was a fabulous scientific meeting with excellent organization. We now look forward to WCP2018 in Kyoto (congratulations to the Japanese Pharmacological Society on securing this!) and WCP2022 in Glasgow (congratulations to the BPS on securing this!).

Good health and luck for 2015 ahead.

Michael Spedding
Outgoing Chairman of NC-IUPHAR
Secretary General of IUPHAR

Current and future directions for NC-IUPHAR

NC-IUPHAR is perhaps the most public success of IUPHAR, and is engaged in a major task; to define all the main drug targets encoded by the human genome, and annotate them in a database freely accessible world-wide…and, importantly, link them to therapeutics and pharmacological target validation.

Major efforts continue to define the main variables in drug/receptor interactions including the parameters that can lead to variation in receptor function and pharmacology (*i.e.* biased signalling, splice variation, receptor polymorphisms, hetero-oligomerisation, allosteric modulation, post-translational modification, epigenetic targets, non-coding RNAs, and linkage to multiple signalling cascades). These areas are of great interest because they may considerably expand the repertoire of potential targets for drug development, and are under evaluation by working groups, which will lead to a number of reports about issues which are of crucial importance for pharmacology. All these areas have been or will be worked on for relevance for pharmacology, and additionally may be useful funding application areas to ensure the future sustainability of NC-IUPHAR activities, and the GtoPdb project.

The immense recent growth of knowledge about drug targets, with their crystal structures, has had a dramatic

impact on drug discovery and pharmacology, and importantly, NC-IUPHAR classifications have been widely adopted. In the past year, we have made great strides to proactively include new drug targets in the GtoPdb, and recruit experts to advise on them; to date we have >2700 annotated protein targets in the GtoPdb, with >7500 ligands, including all approved drugs (~1200).

There is growing research interest, academically, clinically and industrially, in the pharmacology of immunity, inflammation and infection in defining the immunological/inflammatory targets in disease states, with their main pharmacology. Within the research community, there is an urgent need for a pre-competitive, unbiased resource that will integrate high-level expertise in immunity, inflammation and infection, pharmacology and medicinal chemistry. At present, immunological and pharmacological knowledge are held by separate communities and the best resources fall short of what is needed. GtoPdb is the best molecular pharmacology database, but is currently limited in the immunity, inflammation and infection area. We have applied to the Wellcome Trust for funding to extend GtoPdb into this arena, and to produce a 'Guide to IMMUNOPHARMACOLOGY'.

We have also applied for funding for a COST Action in neuropharmacology/neuroimmunology. This is partly as a result of our collaboration with the European College of Neuropsychopharmacology (ECNP) and members of the Nomenclature Task Force for drugs in psychiatry. There is a long way to go but, as a first strategic step, we are collating the drugs in development for Alzheimer's and several examples (in conjunction with ECNP) in psychiatry, data trawling, and linking with expert subcommittees. Thus, we would not only be able to regroup targets by type, but also by therapeutic indication. This would be of great use to patient groups.

An exciting challenge on the not too distant horizon is our 'One Health' Initiative; *One Biology, One Health, One Medicine: An Integrated Database for the Pharmacological Action of Drugs in Humans, Domestic Animals and Model Organisms*. We will be submitting an application to the BBSRC for funding to drive this initiative in due course. We are moving towards encouraging our subcommittees of experts to include information on translational pharmacology on drug targets. We will also be extending GtoPdb into the area of stem cell pharmacology (a database linking stem cell science with expertly curated pharmacological knowledge), and also into the critically important arena of environmental pharmacology (a database that provides comprehensive information on defined and emerging pesticide risks, including their affinities and potency in identified species). However, given the current budgetary climate (see Appendix V: Funds available as of 31st March 2015**), this is all reliant on funding, which we are vigorously pursuing.

Finally, working with the University of Edinburgh Drupal Website Service, and with funding from ASPET, Simon Maxwell has spearheaded the development of the IUPHAR/ASPET Pharmacology Education Project, an education portal that will be closely linked with the GtoPdb. It will provide access to high quality training in the principles and techniques of basic and clinical pharmacology.

Organisation of NC-IUPHAR

Core committee

The core committee of NC-IUPHAR is listed in Appendix I. The biannual core NC-IUPHAR meetings are themed and we have established an alliance with the Japanese Pharmacology Society who pay the travel for two members*, but who are invited according to the meeting themes.

Corresponding Members

In order to broaden the expertise of the core committee, the number of corresponding members (see Appendix I) has been further increased, to include 7 new members: David Gloriam (University of Copenhagen and GPCRDB, Denmark), Gillian Gray (University of Edinburgh, UK), Bong-Kiun Kaang (Seoul National University, Korea), Stefan Knapp (Structural Genomics Consortium, UK), Margaret (Mandy) MacLean (University of Glasgow, UK), Fiona Marshall (Heptares, UK) and Georg Terstappen (AbbVie, Germany). Corresponding members attend selected meetings of NC-IUPHAR and are invited according to the meeting themes. They include representatives of the major pharmaceutical companies.

Evolving Pharmacology Group

Anthony Davenport leads a group which monitors the 'de-orphanisation' of GPCRs and evolving pharmacology of

drug targets in general. Particularly important and timely breakthroughs are included in the Hot Topics section of the database along with email alerts.

Clinical Translational Pharmacology Group

In order to provide advice on the translational aspects of drug target pharmacology, a subgroup (see Appendix I) of clinical pharmacologists (core member, Sir Colin Dollery) discuss how best to respond to the wishes of our clinical colleagues and to translate activity at drug target sites to clinical efficacy.

Subcommittees

Chairpersons (see Appendix II) propose a list of experts, ratified by NC-IUPHAR, to ensure adequate representation of the field. The chairperson of each subcommittee plays a critical role co-ordinating the actions of the subcommittee, organising meetings, finalising documents and the website pages. However, we encourage postdocs to join the subcommittee, as chairs simply do not have enough time to fill in the various template fields - postdocs can therefore get publication credits, and several NC-IUPHAR publications have become citation classics. The h-index of NC-IUPHAR is >74. The subcommittees meet to establish consensus on classification, and to ensure that the NC-IUPHAR guidelines are complied with. We now have more >90 subcommittees (see Appendix II).

Publications and Outreach

Recent publications

NC-IUPHAR has built its reputation on the basis of its published articles with nomenclature recommendations which are adopted worldwide. NC-IUPHAR has an h-Index of 74 for articles which carry the badge IUPHAR. NC-IUPHAR has a longstanding, formal collaboration with ASPET and *Pharmacological Reviews*, and the official nomenclature reports are published in the journal. In addition, our collaboration with the BPS has led to the publication of a series of general 'state-of-the-field' review articles (alongside database updates) in the *British Journal of Pharmacology*.

Eight NC-IUPHAR nomenclature reports (see Appendix III) have appeared in *Pharmacological Reviews* (Editor, Eliot Ohlstein) so far during the 2014/15 period, reflecting the activity of NC-IUPHAR. In addition, 12 NC-IUPHAR commissioned reviews for the *British Journal of Pharmacology* (Editor-in-Chief, Ian McGrath) have recently been accepted (see Appendix III).

During the second half of 2014, Adam Pawson and the Press Editors at the *British Journal of Pharmacology* started implementing links directly from all published review articles (starting initially with the IUPHAR reviews) and research articles to GtoPdb entries. All articles (since ~August 2014) now include a 'Table of links' beneath the abstract listing all targets and ligands in the article with hyperlinks to the corresponding entries in the GtoPdb, thus allowing readers instant access to the wealth of information contained in the database.

Newsletter

The biannual NC-IUPHAR newsletter continues to be distributed in the spring and autumn, through a mailing list (using MailChimp - Email Marketing and Email List Manager software) comprising all IUPHAR member societies, NC-IUPHAR subcommittees and collaborators, pharmacology departments worldwide, and database users who have signed-up to receive news alerts; and was made available for download from GtoPdb homepages. The newsletter was also advertised on social media and the RSS feed.

GtoPdb team representation of NC-IUPHAR at conferences and meetings

The activities of NC-IUPHAR have been promoted by NC-IUPHAR representatives at the following conferences and meetings during the past year:

- The 7th International Biocuration Conference (International Society for Biocuration), Toronto, April 2014; Helen Benson
- Computational Challenges in Data Citation workshop, Philadelphia, April 2014; Joanna Sharman;
- The GLISTEN Barcelona GPCR Spring Conference 2014, GPCRDB Satellite Workshop, Barcelona, April 2014; Joanna Sharman
- BioIT World, Boston, April 2014; Christopher Southan

- Presentation at the Department of Drug Design and Pharmacology, Faculty of Health And Medical Sciences, University of Copenhagen, May 2014; Christopher Southan
- SULSA Synthetic Biology Meeting, Edinburgh, June 2014; Adam Pawson and Jamie Davis
- International Conference on Chemical Structures (ICCS/GCC), June 2014, Noordwijkerhout; Christopher Southan
- World Congress of Pharmacology 2014, Cape Town, South Africa, July 2014; Adam Pawson and Christopher Southan
- Quantitative nutrition and metabolism, University of Reading; Contacts made include Marcus Tindall (Reading) who is setting up a consortium on systems pharmacology, September 2014; Helen Benson
- Web services workshop; Nijmegen, The Netherlands, September 2014; Joanna Sharman
- GLISTEN/GPCRDB Budapest 2014 Conference, Budapest, October 2014; Adam Pawson
- Clinical Genomes Scotland Meeting, Edinburgh, October 2014; Joanna Sharman
- Pharmacology 4th year honours tutorial session on databases and GtPdb demo, October 2014; Helen Benson and Elena Faccenda
- RSC CICAG What's in a Name meeting, RSC, London, October 2014; Elena Faccenda
- BPS Pharmacology 2014 meeting, London, December 2014
- 88th annual meeting of the Japanese Pharmacological Society, Nagoya, March 2015; Adam Pawson
- In addition, we have also had representation at many other meeting by members of NC-IUPHAR

Upcoming:

- BNA2015: Festival of Neuroscience, Edinburgh, April 2015; Adam Pawson, Helen Benson, Elena Faccenda
- BPS Focused Meeting, April 2015, Edinburgh, GtoPdb team
- Joint ASCEPT-BPS Scientific Meeting, Hong Kong, May 2015; Adam Pawson
- 23rd Annual International Conference on Intelligent Systems for Molecular Biology and the 14th European Conference on Computational Biology, Dublin, July 2015; Joanna Sharman
- American Chemical Society Meeting, Boston, August 2015; Christopher Southan
- In addition, we will also have representation at Experimental Biology 2015 (San Diego), Physiology 2015 (London), and others thanks to our partnership with BPS

Social media and Wikipedia

We use social media sites to further the outreach of GtoPdb, and to keep existing users updated.

- **Facebook:** These pages are updated with regular features, database news and links to papers on topics relevant to the database content. Facebook users are able to 'Like' the databases and the individual items posted by the curators. We currently have >2900 'likes'
- **Twitter:** Updates to our feeds include a 'at-a-glance' version of the regular features on our Facebook pages, 're-tweets' of items posted by our >580 followers and Twitter users we follow, and tweets about key papers 'Following' various other databases, publications, suppliers and individuals working in the fields of pharmacology and bioinformatics is a useful marketing tool for the databases (so please follow us).
- **LinkedIN:** The Curation Team and Committee Chairs have increased their reciprocal connectivity over 2014/15 and have thereby significantly extended the collective inter-network outreach for posting major updates
- **Blogging:** The 'guidetopharmacology blog' (http://blog.guidetopharmacology.org/) allows the database team to share feature developments, technical updates, articles or events at a greater level of detail and cross-linking than shorter postings typical of the other three networks (guest posts are welcome)
- **Slideshare:** The Slideshare account (http://www.slideshare.net/GuidetoPHARM) allows the database team to share slide sets and posters with the community. The site allows users to find related content by topic. Our slides are proving to be popular with over 600 views so far
- **Wikipedia:** The Wikipedia pages for GtoPdb are regularly updated, and we are in constant contact with Wikipedia to ensure that links from their ligand and targets pages point to GtoPdb

Recent GtoPdb web interface and database developments

Background

The IUPHAR/BPS Guide to PHARMACOLOGY (GtoPdb; http://www.guidetopharmacology.org) is an open access database providing pharmacological, chemical, genetic, functional and pathophysiological data on the targets of drugs. It includes literature-derived, quantitative data on the actions of approved and experimental compounds at their targets. GtoPdb aims to provide concise overviews of the key properties of a wide range of established and potential drug targets, with nomenclature information, selective ligands and background reading. Developed under the auspices of the International Union of Basic and Clinical Pharmacology (IUPHAR) and the British Pharmacological Society (BPS), the data are curated by an international network of >650 expert contributors coordinated by the IUPHAR Nomenclature Committee (NC-IUPHAR). GtoPdb includes data on >2700 targets and their interactions with ligands. Targets are divided into families and the information is summarised on a single page. More detailed information and drug lists are provided for a subset of important targets. The data are linked to other databases, including Entrez, UniProt, ChEMBL, DrugBank, PubChem and reference citations in PubMed. Each of the >7500 small molecule and peptide ligands is manually annotated with 2D chemical structures or amino acid sequences, nomenclature and clinical information for approved drugs. *The Concise Guide to PHARMACOLOGY* (http://www.guidetopharmacology.org/concise) is a biennial publication 'snapshot' of the database with the key properties of each target family, intended as a quick desktop reference guide. Current work includes completing the annotation of all the targets of currently approved drugs, as well as those in development and the likely future candidate targets. With future funding, the intention is to expand into the areas of immunopharmacology, stem cell pharmacology and environmental pharmacology. Educational resources to guide scientists and students in pharmacological principles and techniques are also being developed. GtoPdb is run by one full-time database developer, four full-time curators and one part-time project administrator, with joint funding from IUPHAR and BPS, and a three year grant from The Wellcome Trust (initiated in November 2012). The GtoPdb team are led by Professor Jamie Davies as the database Principal Investigator at the University of Edinburgh.

Our long-term aims are to provide:

- an authoritative synopsis of the complete landscape of current and research drug targets, providing quantitative pharmacological information on all of the (human) targets of current prescription medicines and other likely targets of future small molecule drugs
- an accurate source of information on the basic science underlying drug action, and rigorous curation of the structures and nomenclature of the chemical substances in the resource, shared and refined in collaboration with other databases, including ChEMBL, ChemSpider, DrugBank and PubChem with whom we have strong ties
- guidance to researchers in selecting appropriate compounds for in vitro and in vivo experiments, including commercially available pharmacological tools for each target
- information on clinically used drugs in the resource (e.g. approval date, ADME, molecular mechanism of action, summary of clinical use)
- an integrated educational resource for researchers, students and the interested public (our sister site, the IUPHAR/ASPET Pharmacology Education Project developed with seed funding provided by ASPET)

Recent developments

1. **New features of the web interface and database:**
    - All pages previously on IUPHAR-DB.org now available on the GtoPdb site
    - Dynamic 'Events' banner has been introduced on the homepage advertising upcoming events
    - Overview pages for target classes and superfamilies: while browsing the target family lists you can now click on the 'Overview' icon to access overviews, subfamily lists and further reading for target super families
    - Target ID now clearly visible on target pages
    - The data-supported primary targets of drugs are indicated with a new symbol 
    - NC-IUPHAR subcommittee and family contributors box introduced at bottom of family pages

- New 'Specialist databases' section created to highlight database links that are of particular interest on specific target and ligand pages, for example the IMGT/mAb-DB resource for antibodies
- Links added to neXtProt, a knowledgebase of human proteins providing access to a range of high-quality datasets with tools to mine them
- New file formats added to the download page; we now also provide a MySQL version of the database, in addition to the original PostgreSQL version. If you use either of these versions, we'd ask that you please let us know and we'd be grateful for feedback.
- A substantive compilation of FAQs is now available
- Our 'Help' pages now include a 'walkthrough' demo of the website produced by Professor Tony Harmar prior to his retirement; this resource complements the tutorial already available *via* our 'Resources' menu and we especially hope our new users will find it valuable for getting to grips with the site
- Search term auto completion; as you type in search terms which match target or ligand names in the database these now come up as a list of suggestions; clicking on a result links straight to the database page for that entity; searches now work with Greek characters *e.g.* α,β
- Ligand search tools:
    - Our chemical structure search tool now uses the Marvin JS structure editor from ChemAxon, which replaces the older Java version; the new JavaScript version has the advantage of cross-platform compatibility
    - This version should also be compatible with tablets and mobile devices
    - Useful features include the ability to import molecules through various file formats, structural identifiers or by compound name
    - Compounds can also be exported in many different formats or as an image file

2. **General overview of the content of the database:**
    - Concise target family summary pages are available for GPCRs, voltage-, ligand-gated, and other ion channels, nuclear hormone receptors, catalytic receptors, transporters and enzymes, other protein targets' has now been added
    - More detailed views are available for all GPCRs, voltage- and ligand-gated ion channels, and nuclear hormone receptors
    - Expandable tree navigation scheme for all the targets in the resource
3. **Target updates:**
    - **GPCR updates:** Adenosine 2A, Angiotensin, Bombesin, Bile acid, Calcitonin, Class Frizzled GPCRs, Complement C5a1 and C5a2 receptors, Dopamine D1, D3 and D5 receptors, Formylpeptide, Lysophospholipid (LPA) and Lysophospholipid (S1P), Melanocortin, Melanin-concentrating hormone, Melatonin, Neuromedin U, Neuropeptide FF/neuropeptide AF, P2Y1 and P2Y12 receptors, Parathyroid hormone, Platelet-activating, Somatostatin sst3 and sst5 receptors, Trace amine TA1
    - Links to BitterDB added for Taste 2 Receptors
    - Cross-links added between GPCRDB and GtoPdb, and the UniProt and HGNC databases now link to GtoPdb
    - Data on experimentally generated mutations from GPCRDB
    - **Voltage-gates ion channel updates:** Inwardly rectifying potassium channels, K2P channels, Two-P potassium channels, Voltage-gated calcium channels, Voltage-gated potassium channels, Voltage-gated sodium channels
    - **Enzyme updates:** curation of phase III kinase inhibitors and ~20 protease clinical candidates or lead compounds, *e.g.* BACE1
    - **Protease updates:** This target class now includes a first (for the database) with a predrug > prodrug > drug triplet; these were curated from a paper describing how MMP12 produces its own inhibitor in a two-step activation procedure; we now have ligand entries for the peptide substrate of the protease, the prodrug and the drug; Increased ligand mappings to FII (thrombin) ACE, PSEN1, BACE1 and BACE2
    - **Kinase and epigenetic target updates:** affinity data for many kinase inhibitors including those in

clinical trials; several new epigenetics targets added into the Other Protein Targets section, including chromatin modifying enzymes, bromodomain-containing proteins, ribosomal factors and kelch-like proteins

- **Disease information updates:** target pathophysiology updated with standardised disease nomenclature; disease synonyms; added Disease Ontology nomenclature and links to the Ontobee disease ontology browser; more links added to the OMIM and Orphanet disease databases

4. **Ligand updates:**
    - High specificity call-outs from ligand pages to PubMed clinical trial reports; N.B. the use of call outs for users offers an instant update from PubMed as opposed to a static link
    - Structural and clinical information for >500 approved drugs, taking our total drug count up to 1,201
    - Each of the tabs on our ligand list is now annotated with our 'approved drug' symbol, indicating approved drug ligands within each class
    - Annotation of, and cross-linking between prodrugs and their active forms
    - Created new category of 'labelled ligands' to include unstable isotopes, fluorescent tags or small chemical entities
    - Completed a quality control check in consultation with PubChem and many entries now updated with CIDs and contextual comments (details will be added to our blog)
    - Added activity data for approved, clinical candidate and research drugs for targets in Alzheimer's disease
    - NCATS and AstraZeneca repurposing compounds added
    - New monoclonal antibodies and small molecules included in pharma pipelines (including any novel drug targets)
    - Sourced available binding affinity data for all monoclonal antibodies in the database using a combination of BLAST sequence analysis, patent and literature searches, tagging primary targets as appropriate
    - Added all the unblinded compounds from SGC's epigenetics compound repository
    - Ligands modulating epigenetic targets (chromatin modifying enzymes and bromodomain-containing proteins) from several recent reviews
    - Many new kinase inhibitors
5. **Links and interactions with other resources:**
    - BindingDB - Subsequent to a visit from Michael Gilson in June (PI for BindingDB) we have extended our interactions via TCs. It transpires this database has both unique features and target > ligand content that we can utilize. The unique content arises from their particular scope of literature and patent extraction that extends to publications neither covered by ourselves nor ChEMBL.
    - EBI Database Teams - Through visits and teleconferences we have extended our valuable contacts with groups on the Hinxton Campus including UniProt (Benoit Bely), Reactome (Steve Jupe) and MEROPS (Neil Rawlings). Technical discussions have centred on enhancing reciprocal cross-linking
    - ECNP - We are working with ECNP in order to provide the molecular basis for their classification of psychiatry drugs. We have now curated all the drugs in the full ECNP list along with activity data. A new version of the ECNP app will include links from drug names to the database
    - GPCRDB - We now have reciprocal links between the two databases and are working to extend the interoperability between our two resources as well as applying for joint funding for these projects. In April, Joanna Sharman attended and presented a poster at the Barcelona GPCR Spring Conference organised by the GLISTEN network. This included presenting and discussing proposals for collaborations at the GPCRDB Satellite Meeting. Joanna recently attended a five-day workshop on web services at Radboud University in Nijmegen, organised by Prof Gerrit Vriend. A small group of developers of GPCR resources (including GPCRDB) attended the workshop to learn how to use the GPCRDB web services and to explore the technicalities of sharing data between our resources. Further discussions on our collaboration took place when Adam Pawson attended the GPCRDB satellite workshop at the GLISTEN Budapest 2014 Conference, 2-4th October.
    - Orphanet - We have had recent discussions with the Orphanet team to provide additional reciprocal links between our resources and to increase the visibility of GtoPdb on the Orphanet site. In

addition, we have had recent discussions with Ana Rath on interactions between our resources for future funding applications.

- PubChem - We continue to increase the visibility and utility of our cross-links and data entries in PubChem. This includes collaborative engagement with their team concerning QC of our structures and a range of enhancements (see June newsletter for details). Consequent to our release 2014.2 we now have 7652 substance identifiers (SIDs) and 5713 compound identifiers (CIDs) (these numbers will change after our next release). Note that every SID links back to us via the "GTPLXXXX" link and these are included in the source mappings for each of the CIDs. The excess of SIDs over CIDs reflects our entries that do not have chemical structure representations (i.e. they cannot be merged into CIDs). The majority of these are peptides but it includes our antibody entries. Via a process of internal cross-checking we have also been able to revise selected entries and add new ones, between our major refresh submissions. With the PubChem BioAssay team we are looking at our interaction data with a view to updating and scaling-up our activity result depositions. This will offer powerful new query options not just for our customers but the entire PubChem user base.
- University of Edinburgh School of Informatics - The database team has a long-time collaboration with Peter Buneman's Database Group and are collaborators on his US-funded Data Citation grant. Peter organised a workshop attended by Joanna on Computational Challenges in Data Citation at the University of Pennsylvania, Philadelphia, which brought together three groups of people (Computer Scientists, Information Scientists and Data Scientists) to explore the technical challenges and research opportunities posed by the increasing demand to generate citations for large, complex datasets. One of the aims of the data citation grant is to develop computational solutions to the problem of archiving and citing complex and changing data. Thus Joanna is working with Peter and colleagues at UPenn on developing a mechanism to archive the GtoPdb in XML, which would not only allow versions of it to be cited but could also be converted into a document format, which could then form the basis of the next 'Concise Guide'

Production of *The Concise Guide to PHARMACOLOGY 2014/15*

A major effort for the database team in the coming months is the production of *The Concise Guide to PHARMACOLOGY 2014/15* (the next biennial update to the 2013/14 edition), which will be a snapshot of the concise target family summaries in the database, published as a series of PDFs, and intended to be a quick desktop reference guide. Details of the publication process:

- The Editors of the 'Concise Guide' are Steve Alexander and John Peters, with Eamonn Kelly and Neil Marrion joining as Editors in 2015
- The 2014/15 edition of the 'Concise Guide' will be published in autumn 2015
- Over 170 expert collaborators contributed to updating the concise target family summaries in the database in preparation for publication
- We are developing a method of producing the content from an XML version of the database, in collaboration with colleagues in the School of Informatics
- The PDF files will be in landscape format, and include embedded hyperlinks from gene names and UniProt IDs direct to HGNC and UniProt entries respectively, from target and ligand names direct to the IUPHAR/BPS Guide to PHARMACOLOGY, and from PubMed IDs direct to PubMed citations

Acknowledgements

We are very grateful to our sponsors. We are also immensely grateful for the work done by our colleagues in NC-IUPHAR and all the contributing chairs and subcommittee members. It is a privilege to be associated with so much work freely given for the good of science. We repeat that NC-IUPHAR is a global resource and all scientists are welcome to contribute (contact: curators@guidetopharmacology.org; enquiries@guidetopharmacology.org).

Appendix I: Membership of NC-IUPHAR

Chair (outgoing)
Michael Spedding, France

Vice Chairs
Anthony Davenport, UK - Chairman Evolving Pharmacology
Anthony Harmar, UK - Database Chairman
Rick Neubig, USA - GPCRs
Eliot Ohlstein, USA - Editor

Members
Stephen Alexander, UK
Thomas Bonner, USA
William Catterall, USA
Arthur Christopoulos, Australia
John Cidlowski, USA
Sir Colin T. Dollery, UK
Doriano Fabbro, Switzerland
Kozo Kaibuchi, Japan*
Yoshikatsu Kanai, Japan*
John Peters, UK
Alex Phipps, UK
Jean-Philippe Pin, France

Ex Officio
Sam Enna, USA - IUPHAR President
Michael Spedding, France - IUPHAR Secretary-General
Petra Thürmann, Germany - IUPHAR Treasurer
Simon Maxwell, UK - Educational Site Project Leader
Jamie Davies, UK - Database Principal Investigator
Joanna Sharman, UK - Database Developer
Adam Pawson, UK - Senior Database Curator
Helen Benson, UK - Database Curator
Elena Faccenda, UK - Database Curator
Christopher Southan, Sweden - Chemical Curator
Veronika Divincova, UK - Project Administrator
Elspeth Bruford, UK - representing HGNC

Past Chairs (Ex Officio)
Paul Vanhoutte, Hong Kong
Bob Ruffolo, USA

Corresponding Members
Susan Amara, USA
Michel Bouvier, Canada
Thomas Burris, USA
Stephen Charlton, UK
Moses Chao, USA
Steven L. Colletti, USA
Graham Collingridge, UK
Sue Duckles, USA
Richard Eglen, UK
Steven Foord, UK
David Gloriam, Denmark
Gillian Gray, UK
Debbie Hay, New Zealand
Allyn Howlett, USA
Franz Hofmann, Germany
Yu Huang, Hong Kong
Ad P. Ijzerman, The Netherlands
Michael F. Jarvis, USA
Bong-Kiun Kaang, Korea
Terry Kenakin, USA
Janos Kiss, Hungary
Stefan Knapp, UK
Chris Langmead, Australia
Vincent Laudet, France
Margaret (Mandy) MacLean, UK
Fiona Marshall, UK
Alistair Mathie, UK
Ian McGrath, UK
Graeme Milligan, UK
Stefan Offermanns, Germany
Richard Olsen, USA
Helgi Schiöth, Sweden
Graeme Semple, USA
David Searls, USA
Roland Staal, USA
Bart Staels, France
Georg Terstappen, Germany
Mary Vore, USA

Clinical Translational Pharmacology Group (core member Sir Colin Dollery)
Ed Bullmore, UK
Robert Dow, UK
Garrett Fitzgerald, USA
Alex Phipps, UK
Patrick du Souich, Canada
David Webb, UK
Don Birkett, Australia

Appendix II: NC-IUPHAR Subcommittees (listing of chairs)

G protein-coupled receptors Subcommittees

5-Hydroxytryptamine: Nick Barnes, John Neumaier
Acetylcholine (muscarinic): Arthur Christopoulos
Adenosine: Adriaan Izjerman
alpha$_1$-adrenoceptors: Dianne Perez
alpha$_2$-adrenoceptors: Mika Scheinin
Angiotensin: Sadashiva Karnik
Apelin: Anthony Davenport
beta-adrenoceptors: Terry Hébert
Bile acid: Anthony Davenport
Bombesin: Robert Jensen
Bradykinin: VACANT
Calcitonin: Debbie Hay, David Poyner
Calcium-sensing: Ed Brown, Hans Bräuner-Osborne
Cannabinoid: Roger Pertwee, Allyn Howlett
Chemokine: Philip Murphy
Cholecystokinin: Laurence Miller
Complement peptide: Peter Monk
Corticotropin-releasing factor: Richard Hauger, Frank Dautzenberg
Dopamine: Raul Gainetdinov
Endothelin: Anthony Davenport
Estrogen (G protein coupled): VACANT
Formylpeptide family: Richard Ye
Free fatty acid: VACANT
Frizzled: Gunnar Schulte
GABA$_B$: Bernhard Bettler
Galanin: Andrew Gundlach
Ghrelin: Birgitte Holst
Glucagon receptor family: Laurence Miller
Glycoprotein hormone: Deborah Segaloff
Gonadotrophin-releasing hormone: Adriaan Ijzerman
Histamine: Paul Chazot
Hydroxycarboxylic acid: Stefan Offermanns
Kisspeptin: Anthony Davenport
Leukotriene: Magnus Bäck
Lysophospholipid (LPA): Jerold Chung
Lysophospholipid (S1P): Sarah Spiegel
Melanin-concentrating hormone: Jean-Louis Nahon
Melanocortin: Tung Fong, Helgi Schiöth
Melatonin: Ralf Jockers
Metabotropic glutamate: Jean-Philippe Pin
Motilin: Anthony Davenport
Neuromedin U: Gary Willars
Neuropeptide FF/neuropeptide AF: Jean-Marie Zajac
Neuropeptide S: Girolamo Calo′
Neuropeptide W/neuropeptide B: Anthony Davenport
Neuropeptide Y: Dan Larhammar
Neurotensin: Jean Mazella
Opioid: Larry Toll
Orexin: Christopher Winrow
P2Y: Geoffrey Burnstock
Parathyroid hormone: Jean-Pierre Vilardaga
Peptide P518: Jerome Leprince
Platelet-activating factor: VACANT
Prokineticin: Philippe Rondard
Prolactin-releasing peptide: Helgi Schiöth
Prostanoid: Xavier Norel
Protease-activated: Nigel Bunnett
Relaxin family peptide: Roger Summers
Relaxin-like: Nick Barker
Somatostatin: Stephan Schulz
Tachykinin: Susan Leeman, Steven Douglas
Trace amine: Janet Maguire
Thyrotropin-releasing hormone: Marvin Gershengorn
Urotensin: Hubert Vaudry
Vasopressin and oxytocin: Bernard Mouillac
VIP and PACAP: Joseph Pisegna

Ligand-gated ion channels Subcommittees
John Peters (Liaison for all LGIC subcommittees)

5-HT$_3$: John Peters
GABA$_A$: Richard Olsen
Glycine: Joseph Lynch
Ionotropic glutamate: Graham Collingridge
Nicotinic acetylcholine: Neil Millar
P2X: Charles Kennedy
ZAC: Timothy Hales

Voltage-gated ion channels Subcommittees
William Catterall (Liaison for all VGIC subcommittees)

Calcium-activated potassium: Len Kaczmarek
CatSper and Two-Pore: David Chapman
Cyclic nucleotide-regulated: Martin Biel
Inwardly rectifying potassium: Yoshihiro Kubo
Transient Receptor Potential: David Clapham
Two-P potassium: Steven Goldstein
Voltage-gated calcium: William Catterall
Voltage-gated potassium: George Gutman
Voltage-gated sodium: William Catterall

Nuclear hormone receptors Subcommittees
John Cidlowski and Thomas Burris (Liaisons for all NHR subcommittees

Androgen receptors: Nancy Weigel
Progesterone Receptors: Dean Edwards
Estrogen receptors: Kenneth Korach
Thyroid hormone receptors: Douglas Forrest
Vitamin D receptors: J. Wesley Pike
Mineralocorticoid receptors: Peter Fuller
LXR receptors: Donald McDonnell
Glucocorticoid receptors: Robert Oakley, Derek Cain
ROR receptors: Anton Jetten

Adenylyl cyclases Subcommittee
Carmen Dessauer

Gasotransmitters Subcommittee
Andreas Papapetropoulos, Csaba Szabo

Pattern Recognition Receptors Subcommittee
Clare Bryant

Antibodies Subcommittee
Alex Phipps

Guanylyl cyclases Subcommittee
Adrian Hobbs, Scott Waldman

Proteases Subcommittee
Anthony Turner

Drug Target and Chemistry Curation Subcommittee
Christopher Southan

Kinases Subcommittee
Doriano Fabbro

Transporters Subcommittee
Stephen Alexander

Non-coding RNAs Subcommittee
Andrew Baker

Epigenetics Subcommittee
Rabinder Prinjha

Concise Guide to PHARMACOLOGY Editors
Stephen Alexander, John Peters, Eamonn Kelly, Neil Marrion

Appendix III: NC-IUPHAR badged publications

NC-IUPHAR publications in *Pharmacological Reviews* (2014/15)

Bryant CE, Orr S, Ferguson B, Symmons MF, Boyle JP, and Monie TP. (2015) International Union of Basic and Clinical Pharmacology. XCVI. Pattern Recognition Receptors in Health and Disease. Pharmacol Rev April 2015 67:462-504

Halls ML, Bathgate RA, Sutton SW, Dschietzig TB, Summers RJ. (2015) International Union of Basic and Clinical Pharmacology. XCV. Recent advances in the understanding of the pharmacology and biological roles of relaxin family peptide receptors 1-4, the receptors for relaxin family peptides. Pharmacol Rev. 67:389-440. [PMID:25761609]

Hamann J, Aust G, Araç D, Engel FB, Formstone C, Fredriksson R, Hall RA, Harty BL, Kirchhoff C, Knapp B, Krishnan A, Liebscher I, Lin HH, Martinelli DC, Monk KR, Peeters MC, Piao X, Prömel S, Schöneberg T, Schwartz TW, Singer K, Stacey M, Ushkaryov YA, Vallon M, Wolfrum U, Wright MW, Xu L, Langenhan T, Schiöth HB. (2015) International Union of Basic and Clinical Pharmacology. XCIV. Adhesion G Protein-Coupled Receptors. Pharmacol Rev. 67: 338-67. [PMID:25713288]

Gardella TJ, Vilardaga JP. (2015) International Union of Basic and Clinical Pharmacology. XCIII. The Parathyroid Hormone Receptors-Family B G Protein-Coupled Receptors. Pharmacol Rev. 67: 310-37. [PMID:25713287]

Vaudry H, Leprince J, Chatenet D, Fournier A, Lambert DG, Le Mével JC, Ohlstein EH, Schwertani A, Tostivint H, Vaudry D. (2015) International Union of Basic and Clinical Pharmacology. XCII. Urotensin II, urotensin II-related peptide, and their receptor: from structure to function. Pharmacol Rev. 67: 214-58. [PMID:25535277]

Kellenberger S, Schild L. (2015) International Union of Basic and Clinical Pharmacology. XCI. Structure, Function, and Pharmacology of Acid-Sensing Ion Channels and the Epithelial Na+ Channel. Pharmacol Rev. 67: 1-35. [PMID:25287517]

Christopoulos A, Changeux J-P, Catterall WA, Fabbro D, Burris TP, Cidlowski JA, Olsen RW, Peters JA, Neubig RR, Pin J-P, Sexton PM, Kenakin TP, Ehlert FJ, Spedding M, Langmead CJ. (2014) International Union of Basic and Clinical Pharmacology. XC. Multisite Pharmacology: Recommendations for the Nomenclature of Receptor Allosterism and Allosteric Ligands. Pharmacol Rev. 66: 918-947. [PMID:25026896]

Bachelerie F, Ben-Baruch A, Burkhardt AM, Combadiere C, Farber JM, Graham GJ, Horuk R, Sparre-Ulrich AH, Locati M, Luster AD, Mantovani A, Matsushima K, Murphy PM, Nibbs R, Nomiyama H, Power CA, Proudfoot AE, Rosenkilde MM, Rot A, Sozzani S, Thelen M, Yoshie O, Zlotnik A. (2014) International Union of Basic and Clinical Pharmacology. LXXXIX. Update on the Extended Family of Chemokine Receptors and Introducing a New Nomenclature for Atypical Chemokine Receptors. Pharmacol Rev. 66: 1-79. [PMID:24218476]

NC-IUPHAR reviews in the *British Journal of Pharmacology* (2014/15)

Fabbro D, Cowan-Jacob SW, Moebitz H. (2015) "10 things you should know about protein kinases" – IUPHAR Review 14 Br J Pharmacol. 2015 Jan 29. DOI: 10.1111/bph.13096 [Epub ahead of print] [PMID:25630872]

Beaulieu J-M, Espinoza S, Gainetdinov RR. (2014) Dopamine receptors: an update – IUPHAR Review 13 Br J Pharmacol. 172: 1-23. [PMID:25671228]

Maguire JJ, Davenport AP. (2014) Endothelin@25 – new agonists, antagonists, inhibitors and emerging research frontiers: IUPHAR Review 12 Br J Pharmacol. 171: 5555–72. [PMID:25131455]

Tough DF, Lewis HD, Rioja I, Lindon MJ, Prinjha RK. (2014) Epigenetic pathway targets for the treatment of disease: accelerating progress in the development of pharmacological tools: IUPHAR Review 11. Br J Pharmacol. 171: 4981–5010. [PMID:25060293]

Fujita W, Gomes I, Devi LA. (2014) Revolution in GPCR Signaling: Opioid receptor heteromers as novel therapeutic targets: IUPHAR Review 10. Br J Pharmacol. 171: 4155–76. [PMID:24916280]

Cox BM, Christie MJ, Devi L, Toll L, Traynor JR. (2014) Challenges for opioid receptor nomenclature: IUPHAR Review 9. Br J Pharmacol. 172: 317–23 [PMID:24528283]

Kihara Y, Maceyka M, Spiegel S, Chun J. (2014) Lysophospholipid receptor nomenclature review: IUPHAR Review 8. Br J Pharmacol. 171: 3575–94. [PMID:24602016]

Bäck M, Powell WS, Dahlén SE, Drazen JM, Evans JF, Serhan CN, Shimizu T, Yokomizo T, Rovati GE. (2014) International Union of Basic and Clinical Pharmacology. Update on Leukotriene, Lipoxin and Oxoeicosanoid Receptors: IUPHAR Review 7. Br J Pharmacol. 171: 3551–74. [PMID:24588652]

Dollery CT. (2014) Lost in Translation (LiT): IUPHAR Review 6. Br J Pharmacol. 171: 2269–90. [PMID:24428732]

Schulz S, Lehmann A, Kliewer A, Nagel F. (2014) Fine-tuning somatostatin receptor signalling by agonist-selective phosphorylation and dephosphorylation: IUPHAR Review 5. Br J Pharmacol. 171: 1591-9. [PMID:24328848]

Bonner TI. (2014) Should pharmacologists care about alternative splicing? IUPHAR Review 4. Br J Pharmacol. 171: 1231–40. [PMID:24670145]

Dijksterhuis JP, Petersen J, Schulte G. (2014) WNT/Frizzled signalling: receptor–ligand selectivity with focus on FZD-G protein signalling and its physiological relevance: IUPHAR Review 3. Br J Pharmacol. 171: 1195–1209. [PMID:24032637]

Additional GtoPdb Curation Team publications that include the Wellcome Trust grant acknowledgment

Southan C. (2015) Expanding opportunities for mining bioactive chemistry from patents. Drug Discovery Today: Technologies. 2015 Feb 10. doi:10.1016/j.ddtec.2014.12.001 [Epub ahead of print]

Lipinski CA, Litterman NK, Southan C, Williams AJ, Clark AM, Ekins S. (2014) Parallel Worlds of Public and Commercial Bioactive Chemistry Data. J Med Chem. 2014 Dec 4. [Epub ahead of print] [PMID:25415348]

Appendix IV: Database Statistics

Target class	Number of targets
7TM receptors	395
G protein-coupled receptors including orphans	389
Orphan G protein-coupled receptors	129
Other 7TM proteins	6
Nuclear hormone receptors	48
Catalytic receptors	239
Ligand-gated ion channels	84
Voltage-gated ion channels	141
Other ion channels	47
Enzymes	1148
Transporters	508
Other protein targets	116
Total number of targets	2726

Chemical class	Number of ligands
Synthetic organics	4734
Metabolites	582
Endogenous peptides	732
Other peptides including synthetic peptides	1181
Natural products	220
Antibodies	103
Inorganics	34
Approved drugs	1201
Withdrawn drugs	63
Drugs with INNs	1768
Labelled ligands	580
Total number of ligands	7586

Number of curated binding constants	12829
Number of binding constants from large scale screens	31207
Number of references	26001

Appendix V: Funds available as of 31st March 2015**

IUPHAR and BPS contributions:	£58,025.33 (for salaries only)
Wellcome Trust grant:	£134,703.00 (for salaries, meetings, travel, *etc.*)
Total funds available:	**£192,728.33**

**** These figures do not include contributions from other NC-IUPHAR income sources**