

Featured in this issue

PROFILE on PubChem [Page 04](#)

IN THE SPOTLIGHT... Approved Drugs [Page 08](#)

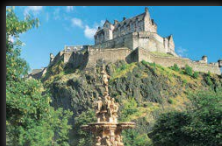
SPECIAL FEATURE on Proteases [Page 10](#)

...plus regular features including, database news ([Page 02](#)) and the "students' and post-docs' corner" ([Page 12](#))

NC-IUPHAR Meeting Report

Edinburgh, 11-13 April 2014

[See page 15 for more details](#)



A message from the Chairman

Pharmacology at the cross-roads: Cape Town and NC-IUPHAR

NC-IUPHAR and the Guide to PHARMACOLOGY will be very present at The World Congress of Pharmacology in Cape Town, and this gives us a great opportunity to meet **you** and also for **you** to give us feedback and to contribute to the activities of IUPHAR – it is free! See [pp13-14](#) for further details

We are engaged in a very ambitious project: producing a database on all the drug targets encoded by the human genome with the best ligands to investigate these targets. We have 80 expert subcommittees of pharmacologists (~630 scientists) who help us, so this is a world-wide project and you can all help. Our curators are present at the meeting (see the IUPHAR stand) and can show you the free web-site you can access. We also have several symposia including one specifically on NC-IUPHAR and the Guide to PHARMACOLOGY (Tuesday 1530H). The availability of a major grant from the Wellcome Trust, with support from IUPHAR, the British Pharmacological Society (BPS) and our sponsors (thanks!) has allowed us to have 5 curators working on the pharmacology of these targets, and this power, coupled to the multiple expert subcommittees, allows a new vision on target validation and we will extend the database to include translational pharmacology with our clinical colleagues. Chris Southan adds his strong bioinformatic and chemistry experience to our structure/activity curation; this is detailed in the newsletter ([pp 8-9](#)). Furthermore, with ASPET, we are setting up educational initiatives online.

Not all is good news, however. First, our good friend Prof. Tony Harmar, who led the database initiative in Edinburgh, died of cancer in April. Tony and his wife Jillian and their family were very noble during the 18 month battle: our brief tribute is inside ([p 18](#)) – a full obituary will be in the next newsletter. We are immensely grateful to Prof. Jamie Davies of Edinburgh for stepping in to ensure continuity. His work, intelligence and sheer unflappability are a great succour, in running this busy team.

Second, we cannot hide the fact that drug discovery, although a great hope for the future, has not led to all the benefit that we expected, as quickly as expected. Jeffrey Cummings has claimed that the failure rate in the development of drugs for Alzheimer's is 99.6%. This is unsustainable. One reason may be that other targets are more important than those addressed. Hence we have recommendations on alternative splicing, heterodimers, allosteric, epigenetic targets and work on immunopharmacology and non-coding RNAs, in alliance with HGNC. We also support the role of academic drug discovery in rare diseases (Thursday 1330H). IUPHAR is therefore well-placed to step up to this challenge.

Cape Town gives us the opportunity to meet pharmacologists from throughout the world and to extend our collaborations – please take this opportunity! We also hope to thank all our subcommittee members.

Let us all have a great conference!

Michael Spedding, Chairman of NC-IUPHAR

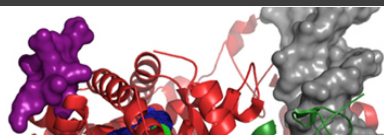


17th World Congress of Basic and Clinical Pharmacology

Cape Town,
South Africa,
13-18 July 2014

**Robert Lefkowitz,
Nobel Laureate for
Chemistry in 2012,
is to open WCP2014**

<http://www.wcp2014.org>
See pages 13 and 14 for
[more details](#)



IUPHAR/BPS
Guide to PHARMACOLOGY

About the IUPHAR/BPS Guide to PHARMACOLOGY

The IUPHAR/BPS Guide to PHARMACOLOGY portal (<http://www.guidetopharmacology.org>) is being developed to assist research in pharmacology, drug discovery and chemical biology in academia and industry, by providing: [1] an authoritative synopsis of the complete landscape of current and research drug targets; [2] an accurate source of information on the basic science underlying drug action; [3] guidance to researchers in selecting appropriate compounds for *in vitro* and *in vivo* experiments, including commercially available pharmacological tools for each target; and [4] an integrated educational resource for researchers, students and the interested public.

The IUPHAR/BPS Guide to PHARMACOLOGY portal has been online since December 2011. The current release of the database (June 2014) integrates data from two sources. The first of these is the IUPHAR Database (IUPHAR-DB), which provides in-depth, integrative views of the pharmacology, genetics, functions and pathophysiology of important target families, including G protein-coupled receptors (GPCRs), ion channels and nuclear hormone receptors (NHRs). The second is the BPS 'Guide to Receptors and Channels' (GRAC), a compendium, previously published in print, providing concise overviews of the key properties of a wider range of targets than those covered in IUPHAR-DB, together with the endogenous ligands, experimental drugs, radiolabeled ligands and probe compounds, with recommended reading lists for newcomers to each field.

Developed under the auspices of the IUPHAR Committee on Receptor Nomenclature and Drug Classification (NC-IUPHAR), the resource is an authoritative reference and educational resource for pharmacologists, clinicians and allied disciplines. All data in IUPHAR-DB can now be accessed through the IUPHAR/BPS Guide to PHARMACOLOGY.

An update from the Database Team

Some developments since the November 2013 newsletter:

- **Web-site:** The new IUPHAR/BPS Guide to PHARMACOLOGY web site now includes all content from IUPHAR-DB; new downloadable drug and target lists, a website demo video, and links out to our new blog and The Concise Guide to PHARMACOLOGY 2013/2014;
- **Database updates: GPCRs:** Dopamine D₁, Somatostatin sst₃ and sst₅, Angiotensin, Bile acid receptor, Lysophospholipid receptors, MAS1; **VGICs:** Ca_v1-4;
- **Approved drug and clinical target curation:** Annotation of approved drug ligand pages with clinical use and mechanism of action information and FDA approval dates. Annotation of interactions tables with approved drugs and primary target symbols;
- **Ligand page updates:** We have completed a quality control check of our ligand in consultation with PubChem and many of our ligand entries have been updated with CID cross-links and contextual comments;
- **Annotation of ligand lists:** Our complete ligand list now includes tabs for approved drugs and labelled ligands;
- **Epigenetic targets:** Ligand-target interaction data from recent reviews added for epigenetic targets.



Database statistics

Target class	Number of targets
7TM receptors	394
G protein-coupled receptors including orphans	388
Orphan G protein-coupled receptors	129
Other 7TM proteins	6
Nuclear hormone receptors	48
Catalytic receptors	240
Ligand-gated ion channels	84
Voltage-gated ion channels	141
Other ion channels	47
Enzymes	1134
Transporters	507
Other protein targets	68
Total number of targets	2663

Chemical class	Number of ligands
Synthetic organics	4097
Metabolites	576
Endogenous peptides	706
Other peptides including synthetic peptides	1149
Natural products	205
Antibodies	53
Inorganics	33
Others	8
Approved drugs	1071
Withdrawn drugs	43
Drugs with INNs	1532
Labelled ligands	561
Total number of ligands	6819

Number of binding constants	42086
Number of references	23436



OUT-AND-ABOUT WITH THE DATABASE TEAM

In April **one of our curators, Helen Benson**, represented the team at the [Seventh International Biocuration Conference](#) at the University of Toronto, and presented a [poster](#) outlining our approved drug and clinical target curation. This visit followed the previous year's meeting of the International Society for Biocuration in Cambridge, UK, attended by both Helen and database developer Joanna Sharman.



Over the four days of the conference, the programme of talks and workshops covered many themes relevant to our work, as well as discussing the challenges facing biocurators today. These challenges include how curatorial work will evolve in an age of big data, and the role of crowdsourcing and text mining in managing the volume of biological data to be included in online databases. Keynote speakers Suzanna Lewis and Lincoln Stein discussed these themes with their respective talks on optimisation of curation and whether Big Data will 'crush' curation. One of the main themes from the talks and the workshops was the role and implementation of clinical and anatomical ontologies to databases. Additionally, several talks discussed data standards and controlled vocabularies, with particular regard to pathway curation. This issue is particularly pertinent to us as we now include enzyme pathways in our database.

The database team has now expanded to five, and our pipeline for ligand and target curation is constantly evolving to achieve optimum methods. It was therefore invaluable for us to learn more about the projects of other research groups, and to hear about which areas have become key focus points for the field. As always, it was a pleasure to meet others working in the field and we look forward to attending this event in the future.

Our database developer, Joanna Sharman, attended [Edinburgh Neuroscience Day](#), an annual day of talks and poster presentations involving over 300 researchers with an interest in neuroscience.



Joanna also 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 was also invited to attend a workshop 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.

Chemical curator Chris Southan started his 2014 representations with an invited visit to the April 29th – May 1st BioIT World, Boston, as co-organiser and presenter at a Workshop entitled [“A Bar Code for Chemical Structures: Using the InChI to Transform Connectivity between Chemistry, Biology, Biomedicine and Drug Discovery”](#). His individual workshop presentation was entitled [“Transformative Utility of InChIKey Searching in the Mother of all Databases”](#). A poster related to the database was also presented on [“Will the real drugs please stand up?”](#).

In May 6th Chris had the privilege of being one of the opponents in a (successful) PhD examination for The Faculty of Pharmaceutical Sciences, University of Copenhagen. The trip included a presentation to the department and the GPCRDB team entitled [“Will the real drugs and targets please stand up? Evolving consensus-based curatorial strategies”](#).

On June 1-5th Chris attended the [10th International Conference on Chemical Structures](#). His oral presentation was entitled [“Will the real drug targets please stand up?”](#).

As an alumnus from his [work on the ELIXIR project](#) in 2008/9 Chris attended the June 12th [EMBL-EBI 20th Anniversary celebrations](#). He also took the opportunity to visit the EBI and Cambridge on the next day for discussions with a range of collaborators including UniProt, MEROPS, ChEMBL, Reactome and NextMove Software.

Database Principal Investigator Jamie Davies attended the SULSA Synthetic Biology Meeting, in Edinburgh on 10th June and presented our poster [“Exploiting Edinburgh’s Guide to PHARMACOLOGY database as a source of protein design information for synthetic biology”](#).

ABOUT THE AUTHOR

Evan Bolton is Lead Scientist of the PubChem project at the U.S. National Center for Biotechnology Information, which is part of the U.S. National Library of Medicine at the U.S. National Institutes of Health. He received his Ph.D. in Physical Chemistry from the University of Georgia in 1995. Halfway through his Ph.D., Evan started research in the area of chemical information and informatics with the American Cyanamid company. This sparked his passion for chemical data informatics. Over the course of ten years at both large and small life sciences companies, Evan pioneered research-focused intranet applications by combining chemical informatics, scientific data systems, and commercial drug discovery software suites. These included, among others, chemical substance registration, biological data analysis, bioactivity visualization, and chemical library design systems. Evan joined the PubChem project early in 2004. In the subsequent ten years, Evan helped to lead the design and development of PubChem into the resource that it is today. Evan has authored thirty peer-reviewed papers and book chapters to date. A passionate enthusiast to improve a researcher's ability to access and share desired information, Evan works collaboratively with the global chemical biology community to help improve and expand the publically available information content.



Evan Bolton

PROFILE **PubChem**

The PubChem Project – a platform to collaborate and share information in the chemical biology community

Evan Bolton, Ph.D.

National Center for Biotechnology Information
Bldg. 38A, Room 8S810

National Library of Medicine

National Institutes of Health

8600 Rockville Pike, Bethesda, MD 20894

Since its founding in 1836, the U.S. National Library of Medicine (NLM - <http://www.nlm.nih.gov/>) has a long tradition of being at the heart of information innovation. Among many notable achievements (<http://apps.nlm.nih.gov/175/milestones.cfm>), NLM is the world's largest biomedical library. It produces electronic information resources for a wide array of topics that are searched billions of times a year by millions of people around the globe.

A division of NLM formed in 1988, the National Center for Biotechnology Information (NCBI - <http://www.ncbi.nlm.nih.gov/>) develops new information technologies to aid in the understanding of fundamental molecular and genetic processes that control human health and diseases. As a part of this, NCBI creates systems for storing and analyzing relevant domain knowledge, coordinating efforts to gather this information globally, and facilitating its use. One early prominent achievement of NCBI researchers is invention of the Basic Local Alignment Search Tool (BLAST) algorithm for locating regions of similarity between biological sequences. In addition, popular web-based resources such as PubMed, GenBank, and PubChem are provided by NCBI.

PubChem (<https://pubchem.ncbi.nlm.nih.gov/>) is an open archive for chemical substances and their biological activities. It first became available in September 2004 to house the output of the Molecular Libraries Program (MLP - <http://mli.nih.gov>). The primary goal of PubChem is to be an on-line resource providing comprehensive information on the biological activities of substances. A "substance" in this context means any biologically testable entity, such as a small molecular chemical structure, RNAi, carbohydrate, etc. Depending on your perspective, there are two sides to PubChem: an open archive and a public resource.

As an open archive, PubChem allows anyone to voluntarily contribute information on chemical substances and associated biological assay experiments. Examples of data collected per substance beyond the chemical structures and names include, among others: link-back URLs to the providing resource, cross references to other NCBI databases (such as PubMed IDs and protein GIs) and to other resources (for instance patent record identifiers), and textual comments. All substance and assay records are versioned when updated, allowing you to see a record as it existed at a particular moment in time.

As a public resource, PubChem allows anyone to freely access collected information. Tools are available to search, subset, select, analyze, and download PubChem contents. Contributed data is integrated in numerous ways, including with the biomedical literature, sequences, pathways, and key ontologies. Data provenance is maintained throughout the system, making it possible to know who gave what information. Furthermore, PubChem provides programmatic interfaces that can be embedded in external (non-PubChem) web pages. Bulk download of PubChem contents is available by means of the NCBI FTP site (<ftp://ftp.ncbi.nlm.nih.gov/pubchem/>).

Continued on page 05...

Continued from page 04...

In the past ten years as an open archive, PubChem has experienced phenomenal growth in contributed information. To date (as of June 2014), PubChem includes more than 260 substance and 60 assay data contributors who have provided in excess of 134 million substances, 50 million compounds, one million biological assay descriptions, and 226 million biological activity result outcomes (where an outcome is a set of reported values resulting from a substance being tested in an assay). The biological assays in PubChem cover over 6.1 thousand unique sequence protein targets, 2.9 million tested substances, and 1.9 million tested compounds. The contributors to PubChem are diverse and include chemical suppliers, journals, database collections (government, public, and private), and individual research labs. Key contributors of biological activity information include those from the MLP Molecular Screening Center Network, the European Bioinformatics Institute resource ChEMBL, the siRNA screening consortium, and the U.S. National Cancer Institute Developmental Therapeutics Program (NCI/DTP).

As the data content has grown, so too has the usage. PubChem routinely serves millions of web requests per day. Programmatic data access tends to generate more than half of this web traffic. As a function of time, the percentage of programmatic usage of PubChem is expected to grow.

PubChem encourages and facilitates external web-based resources to dynamically access data. The logic as to why is simple. Maintaining an effective mirror of PubChem data contents is difficult. The contents amount to 100s of Gigabytes and change daily (sometimes dramatically). By providing high-availability web-based data interfaces, on-line chemical biology resources have more options to bring relevant and current PubChem data contents directly to their users. Programmatic interfaces such as PUG REST (https://pubchem.ncbi.nlm.nih.gov/pug_rest/PUG_REST_Tutorial.html) and the JavaScript-based user-interface (UI) PubChem Widgets (<https://pubchem.ncbi.nlm.nih.gov/widget/docs/>) help to enable this. In addition, PubChem is actively expanding the scope of programmatic and UI interface offerings to meet the needs of the chemical biology community. This may soon include the means to not only 'pull' data content but to 'push' data content to the PubChem Upload system (<https://pubchem.ncbi.nlm.nih.gov/upload/>). Given the popularity of electronic laboratory notebooks (ELNs) and laboratory information management systems (LIMS), this may help make publishing data into PubChem as easy as a push of a button.

With the rise of cloud-based computing, programmatic access to PubChem content is not enough. When researchers need to perform large-scale analyses requiring many millions of queries in a relatively short period of time, data must be local to computing resources. To help these researchers, the PubChemRDF linked data project (<https://pubchem.ncbi.nlm.nih.gov/rdf/>) helps to pick up where PubChem programmatic services leave off. PubChemRDF annotates PubChem data using the resource description framework (RDF - <http://www.w3.org/TR/rdf-primer/>) approach. RDF is a component of semantic web technologies and breaks down information into machine readable discrete pieces, called "triples". Each "triple" is organized as a trio of "subject-predicate-object". For example, in the phrase "atorvastatin may treat hypercholesterolemia," the subject is "atorvastatin," the predicate is "may treat," and the object is "hypercholesterolemia." Using PubChemRDF, one can download the desired RDF formatted data files from the PubChem FTP site (<ftp://ftp.ncbi.nlm.nih.gov/pubchem/RDF/>), import them into a so-called triplestore (<http://en.wikipedia.org/wiki/Triplestore>) or RDF-aware graph database (http://en.wikipedia.org/wiki/Graph_database), and query using a SPARQL query interface (<http://www.w3.org/TR/rdf-sparql-query/>). Together these help enable the local data access required in a cloud-based computing environment to PubChem data with minimal effort by researchers.

Continued on page 06...

DID YOU KNOW?

The IUPHAR/BPS Guide to PHARMACOLOGY is a source of chemical data in PubChem

We have just completed a round of updates to the Guide to PHARMACOLOGY (GtoPdb) ligands deposited in PubChem. Each of our almost [7000 ligands is given a unique Substance ID \(SID\)](#) which links to the original entry in the submitter database. These SIDs map to over [5000 Compounds \(CIDs\)](#) – validated chemical structures describing PubChem Substances.

A number of the submitted structures are [unique to GtoPdb](#), with no other source providing the same chemical structure in PubChem. This demonstrates our unique position in curating the pharmacological literature.

GtoPdb ligand pages link to the corresponding PubChem Compounds. We always try to resolve our ligand structures to the consensus structure (i.e. the one with the most submitters) in PubChem, e.g. in cases of ambiguity of stereochemistry, we give alternative structures in the comments.

For more info see our blog: <http://blog.guidetopharmacology.org/category/chemical-curation/>



Dinner with Evan on his visit to Edinburgh

Having lots of data is useful but not enough. Data annotation can be very helpful to give a context to improve human understanding of data. For example, when looking at the biological activity of a chemical substance, it may be useful to know if the tested substance is an active ingredient of a drug or if the assay target is an established drug target. Extensive annotation can be found in PubChem for thousands of chemicals. These tend to be drugs, endogenous ligands, industrial chemicals, and environmental pollutants, where the biological effects and properties of the molecule are reasonably well studied and, to some extent, known. There are also many tens of thousands of lesser studied chemicals mentioned in the biomedical literature with some limited annotation information. Millions more chemicals have available biological tests or are found in the patent literature. However, PubChem contains tens of millions of unique chemicals; more than 85% of these have no known annotation. While PubChem incorporates available annotation information as is possible, the biological effects of many chemicals are simply unknown. To help users quickly find related records with annotation, PubChem uses chemical similarity. (See **Figure 1** showing the PubChem Related Chemicals carousel UI widget.) For those records in PubChem that do have annotation, a number of "classifications" may be available.

Figure 1. Related Compounds with Annotation widget for rofecoxib (CID 5090).

Classifications are a form of annotation. They may assert, for instance, the biological role of a chemical substance or the biological function of an assay target. They are used to organize PubChem records. The PubChem Classification Browser (<https://pubchem.ncbi.nlm.nih.gov/classification/>) allows one to navigate, search, and analyze PubChem content by means of classification annotation. For example, one can find all "cyclooxygenase inhibitors" in PubChem as annotated by NLM's Medical Subject Headings (MeSH). (See **Figure 2** showing the classification browser in action.) IUPHAR/BPS Guide to Pharmacology database receptor-based classification annotations can be used to annotate PubChem content in a similar fashion.

Figure 2. Find PubChem chemical records classified by MeSH as "Cyclooxygenase Inhibitors" using the PubChem Classification Browser.

<https://pubchem.ncbi.nlm.nih.gov/classification/#hid=1&search=Cyclooxygenase%20Inhibitors&view=list>

Continued on page 07...

Continued from page 06...

PubChem is in the midst of a technology refresh. Web technologies are evolving, with now widespread web-browser support for 'game-changing' HTML5 technologies (<http://en.wikipedia.org/wiki/HTML5>), including CSS3 and the '<canvas>' tag. PubChem usage and data contents are increasing, requiring continual improvements in both the scalability and speed of interfaces. The devices we use to access the web are evolving, with mobile devices now accounting for more than 20% of NCBI web traffic. Most PubChem web pages are optimized for a PC desktop screen size of 1024x768 pixels, high-bandwidth (+100KB/s) network, low latency (<50ms) data access, and a computer mouse to interact with a web page; however, smart phone and tablet devices tend to have smaller screens, use touch "gestures", and operate on 3-G networks (characterized by low-bandwidth and high-latency). For these reasons and more, PubChem has initiated a revamp of its user interfaces. One of the fruits of this labor is PubChem Search (<https://pubchem.ncbi.nlm.nih.gov/search/>) (See Figure 3 showing PubChem Search in action). An eventual replacement for PubChem Structure Search and the PubChem Bioactivity Datadicer, PubChem Search provides an interactive search system with faceting controls. It uses NoSQL technology (<http://en.wikipedia.org/wiki/NoSQL>) found in the Apache Lucene/SOLR project (<http://lucene.apache.org/solr/>).

Figure 3. PubChem Search provides a unified interface to query content.

The screenshot displays the PubChem Search interface. At the top, the PubChem logo is on the left, and 'SEARCH 1.0 BETA' and 'Current System' are on the right. Below the logo is a navigation bar with tabs for 'Compounds', 'Bioassays', 'Bioactivities', 'Targets', and 'Patents'. Underneath, there are search method tabs: 'Keyword', 'Structure', and 'Molecular Formula'. The 'Structure' tab is active, and sub-tabs for 'Similarity', 'Substructure', and 'Superstructure' are visible. A search input field contains the SMILES string 'c1ccccc1'. Below the search bar, there are 'Search Options' and 'Query Hints' buttons. A pagination bar shows '1 to 20 of 553' results, with '1' selected. Below this, there are filters for 'Relevance' (set to 'Relevance'), 'Concise' (selected), and 'Detailed'. The main results area shows two entries: 'benzene' (PubChem CID: 241; MF: C₆H₆; MW: 78.111 g/mol; IUPAC Name: benzene) and 'AC1NP5ZY' (PubChem CID: 5150536; MF: C₆H₅⁺; MW: 77.103 g/mol; IUPAC Name: cyclohexatriene). A faceted search panel on the right is titled 'Molecular Weight' and shows a histogram of counts versus Molecular Weight (Daltons). The histogram has a peak at 217, with a highlighted bar for the range '100 - 200: 217'. Below the histogram are input fields for 'Enter MIN', '≤ RANGE <', and 'Enter MAX'.

In conclusion, a primary aim of PubChem is to help enable researchers: by allowing scientific professionals and organizations to synergize efforts and collaboratively make discoveries faster, by giving a context to research data, and by empowering scientists to spend more time thinking about research problems. This is achieved by providing a platform to exchange chemical biology information, by integrating contributed information with other biomedical resources and annotation, and by removing barriers to find and access relevant research results. The more PubChem can help bring together high-quality information content and awareness of the chemical biology resources that produce them, the greater the impact to science. In addition, by harnessing improvements in technology, PubChem is working towards making more content dynamically accessible by other research-based web-sites. While the past ten years yielded fundamental changes in how we think about information, it may well be that the next ten years will yield even more dramatic and enabling improvements for researchers. PubChem intends to do its part to achieve this.



IN THE SPOTLIGHT...



Approved Drugs

Their curation in the database

As a major objective of our Wellcome Trust grant, populating the database with approved drugs presents key curatorial challenges. Notwithstanding, many had already been captured, in particular those directed against receptors and channels, before this phase of funding support. The team thus had prior engagement with drug curation while expanding the ligand collection. Approved drugs is a central topic in pharmacology (and other domains of biomedicine), so only those aspects pertinent to the task can be covered here. Those seeking more background can explore our recent blog post on “Will the real drugs please stand up?” that includes literature links as well as our own poster.

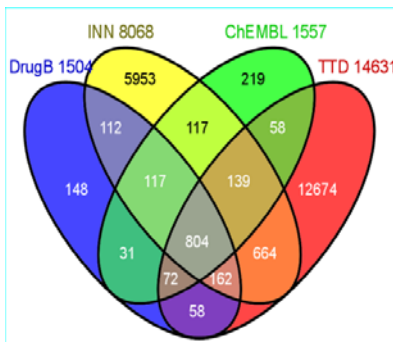
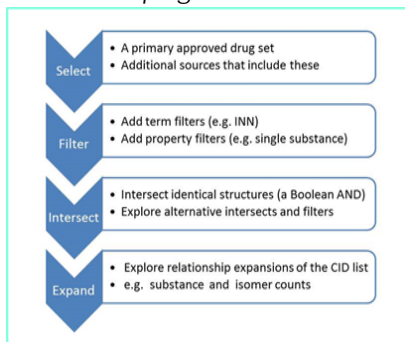
From the established precedents in NC-IUPHAR, our first approach to any new phase of curation is to seek to appoint a subcommittee to support the team in technical and strategic aspects. We have named this the “Drug Target and Chemistry Curation Subcommittee” (DRUTACCS) since their collective expertise covers both ligand and protein annotation. The current members are: Helen Benson (GToPdb, UK), Michael Gilson (BindingDB, USA), Arnaud Gohier (Servier, France), Edgar Jacoby (Janssen, Belgium), Chido Mpamhanga (MRC-T, UK), Plamen Petrov (AstraZeneca, Sweden), Roger Sayle (NextMove, UK), David Sharpe (RSC/ChemSpider, UK), Christopher Southan (Committee Chairman, GToPdb, Sweden), Michael Spedding (Spedding Research Solutions, France) and Paul Thiessen (NCBI/PubChem, USA). We are grateful to have such a wealth of experience to draw on for ligand and target curation.

Our extensive prior experience with curating and annotating both small molecules and peptides, indicated two things. Firstly, we had already been converging on the PubChem compound identifier (CID) as a reference choice for the molecular specification (*i.e.* we included links that pointed to that identical structure). Secondly, we found that different sources presented more equivocal cases for approved drugs than we expected (*e.g.* they often mapped to different CIDs), especially considering their approval by stringent national procedures. This inter-source discordance had already been highlighted in a comparison of approved drugs in 2009 that recorded only 807 structures in-common ([PMID:20298516](#)). Checking to see what was available in 2014, we found numbers spanning 1216 in the FDA Maximum Daily Dose Database (PubChem Assay ID 1195) up to 2750 for the NCGC Pharmaceutical Collection ([PMID:21525397](#)), a difference of 2-fold! We thus decided to adopt the concept from [PMID:20298516](#), namely that concordance between multiple sources indicated where a structure was probably correct. In addition, we noted an increasing number of drug-containing sources could be computationally compared by exploiting the internal PubChem chemistry rules (*e.g.* submitted substances identical at the stereo, E/Z and isotope levels are merged into CID records with the same InChI).

The work flow for doing this is shown below on the left. The results to the right are expressed as a Venn diagram of the CID intersect between four sources that include approved drugs. These are ChEMBL (phase 4), DrugBank (approved), Therapeutic Target Database (TTD) and all CIDs that included a WHO International Non-proprietary Name (INN). Note that there are different ways of selecting and filtering intersects that will produce different results, so the one below is shown as an illustrative example (general approaches to drug database content comparison are described in [PMID:24533037](#), and if you would like technical details on the intra-PubChem triage just contact us).

Continued on page 09...

Continued from page 08...



This intersecting has many advantages for us. Firstly, as a *de facto* core set, a consensus list is an efficient curatorial starting point (e.g. the 804 intersect in the Venn diagram above). Secondly, by inspecting differences in sets we gain insights into why sources show different capture (e.g. we now know TTD is behind on updating and there is also a time lag for new INNs to appear in PubChem sources). Thirdly, we can efficiently expand our coverage by “walking-out” from the 4-way intersect (e.g. the 117 and 139 sets where DrugBank and ChEMBL disagree with each other but agree on the INNs). Finally, we are making a major update of all our ligand entries in PubChem that includes iterative checking of structures. We will then be able to QC “inside vs. outside” by including our own entries in Venn comparisons of the type shown above. In addition, the team is compiling a dossier of drug structure and/or naming “quirks” we have either come across during checking or new error cases picked up from Twitter. We will then not only add a succinct curators note with relevant cross-pointers but also describe selected examples in a series of blog posts (along with our source comparison work, these could form the basis of a future publication).

Beyond refining the consensus approach, our efforts and consultations have led us to additional strategic choices. Firstly, attempts by other resources at total approved drug structure capture have revealed many associated problems (including defining completion in the context of different national pharmacopeia). We thus now declare our objective as stringently selecting structures (or pointers for biologicals) only for approved drugs with data-supported pharmacological relevance. Consequently, nutraceuticals, other metabolites, endogenous hormones and simple inorganic salts (with the exception of Lithium of course) have been masked from our molecular mechanism of action (mtoa) relationships. We thus control the “maximal mapping” problem that can degrade the data mining specificity of other resources (as discussed in [PMID:24533037](https://pubmed.ncbi.nlm.nih.gov/24533037/)). Another challenge is prodrug-to-drug relationships. In this case we have arrived at a useful solution exemplified in <http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=1613> where all approved ACE inhibitors are listed with the “prils” (prodrugs) and “lats” (drugs) having cross-pointers. Following this precedent, we intent to expand cross-pointing to include active drug metabolites and approved drug mixtures. Within a year of starting this new phase our approved drug count rose ~80% to 996 records this April (including small molecules, peptides and antibodies), and our current count will be updated when this round of PubChem processing is concluded.

The widespread representational differences, in both databases and documents, between what our experience clearly indicates are the same canonical drugs, is a crucial issue in cheminformatics, medicinal chemistry and pharmacology. The problem will persist until there is not only more inter-source collaboration for standardisation (including wider use of InChI) but also when regulatory bodies and pharmaceutical companies eventually commit to explicitly verifying (and thereby provenancing) public database structure records for clinically tested drugs. In the meantime, with the support of our esteemed DRUTACCS members, our approaches to compiling a core approved drug list (with declared caveats) and stringent activity mappings to primary protein targets, will enhance our reputation as a valuable and trusted resource.

Those seeking more background can explore our blog post “Will the real drugs please stand up?” <http://www.slideshare.net/GuidetoPHARM/southan-sharman-bioitposter-1>. In addition there is an excellent overview of PubChem in this newsletter (see [page 4](#))

Chris recently joined the GtoPdb curation team working from Sweden. Previously he established the TW2Informatics Drug Discovery Informatics Consultancy in Göteborg Sweden, working mainly on patent informatics. Prior to this he was a contractor for the AstraZeneca Knowledge Engineering Program (2009-2011). Earlier positions include the ELIXIR Database Provider Survey for the EBI (2008-9), Principle Scientist and Bioinformatics Team Leader at AstraZeneca, Mölndal (2004-7) and senior bioinformatics positions in Oxford Glycosciences (2002-3) Gemini Genomics (2001) and SmithKline Beecham (1987-2000). He has 58 PubMed entries, is an Honorary Professor of Proteomics at Nottingham University, PhD from the University of Munich, M.Sc. in Virology from Reading University and a B.Sc.Hons. Biochemistry from Dundee University. Further information is on his LinkedIn profile.

Twitter: <http://twitter.com/#!/cdsouthan>

Blog: <http://cdsouthan.blogspot.com/>

LinkedIn: <http://www.linkedin.com/in/cdsouthan>

TW2Informatics: http://www.cdsouthan.info/Consult/CDS_cons.htm

Publications: <http://www.ncbi.nlm.nih.gov/pubmed/?term=Southan%20CIAuthor%0A&cmd=DetailsSearch>

Presentations: <http://www.slideshare.net/cdsouthan>



Chris Southan

ABOUT THE AUTHOR

A.J. (Tony) Turner is Professor of Biochemistry in the Faculty of Biological Sciences at the University of Leeds, U.K. He received his B.A. in Natural Sciences and Ph.D. in biochemistry from the University of Cambridge and, after a period as Royal Society Research Fellow at the Mario Negri Institute of Pharmacology in Milan, he took up a lectureship in biochemistry at the University of Leeds, where he has since remained. He was Head of the School of Biochemistry and Molecular Biology in Leeds from 1996-2004 and Faculty Dean from 2004-2007. He has also served as Chief Editor of both the *Biochemical Journal* (1987-1994) and the *Journal of Neurochemistry* (1999-2010) and is currently Chair of Publications for the International Society of Neurochemistry and Council Member of the European Society for Neurochemistry of which he was President from 1992-1996. His research has focused around peptide and protein processing, especially in relation to cardiovascular and neurodegenerative diseases and he and his colleagues discovered and first characterized the key zinc metalloproteases, neprilysin and angiotensin converting enzyme-2 (ACE2). He has published over 250 peer-reviewed articles and was honoured by receiving the Biochemical Society Distinguished Service Award (2005) and being elected a Fellow of the Academy of Medical Sciences (2012).



Tony Turner

SPECIAL FEATURE

Pharmacology of human proteases: past, present and future

Tony Turner, MA, PhD, Cambridge
Professor of Biochemistry
School of Molecular and Cellular Biology
University of Leeds

NC-IUPHAR protease/hydrolase sub-committee chair – a.j.turner@leeds.ac.uk

Proteolytic enzymes (proteinases, proteases, peptidases, terms often used synonymously and interchangeably) are hydrolases cleaving peptide bonds. They play key roles from life to death: in fertilization, development, cell signalling and, of course, apoptosis and cell death. They comprise more than 2% of the human genome (almost 600 genes) divided into five major catalytic groups: metallo, serine, cysteine, threonine and aspartic, in descending order of abundance. They distribute roughly equally between intracellular and extracellular locations with just 16 “intra-membrane proteases” specialised to cleave within the lipid bilayer (e.g. the Alzheimer’s disease (AD) target, γ -secretase). Almost a hundred different human hereditary diseases are attributable to human protease gene mutations. As Chair of the recently established protease and hydrolase NC-IUPHAR sub-committee, I shall try and put this major target area into some perspective, highlighting challenges ahead.

There are numerous examples of pharmacological and pharmaceutical success in protease biology with perhaps the best examples being angiotensin converting enzyme (ACE) inhibitors and HIV protease inhibitors. ACE inhibitors, as anti-hypertensives, have been around now for more than 30 years and were an instant success when captopril was launched in 1981 but are not without side-effects partly as a result of the promiscuity of the enzyme. This is a relatively common problem in protease drug development, a current example being the failure in clinical trials of γ -secretase inhibitors such as semagacestat, in part due to cleavage of other proteins such as notch, leading to skin cancers. Hence, it is important to evaluate as fully as possible the physiological substrate profile of any target protease. The renin-angiotensin system (RAS), however, provides a diverse group of proteases in addition to ACE as potential targets including renin, ACE2 and aminopeptidase A. The renin inhibitor, aliskiren, received FDA approval in 2007 and has a number of theoretical advantages over ACE inhibition, not least because it catalyses the rate-limiting step of the pathway. And there is still much scope for refinement of ACE inhibitors since it has two complementary active sites (N- and C-domains). Since the C-domain is dominant in blood pressure regulation, selective inhibitors of this domain are being explored as new drug candidates. Other recent successes in protease drug development include inhibitors of dipeptidyl peptidase IV in diabetes and hepatitis C virus inhibitors.

The easy hits in the field have, however, long gone and other potential protease candidates have not (yet) succeeded in delivering effective drugs. A classic example is the large family of matrix metalloproteases (MMPs), and their close relatives the ADAMs, together comprising around one-third of all metalloproteases.

Continued on page 11...

Continued from page 10...

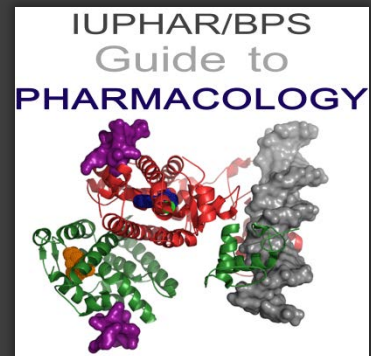
Huge investment went into the development of MMP inhibitors in cancer as potential anti-metastatic agents in the 80s and 90s. The outcomes of clinical trials, however, were generally unsuccessful often with decreased survival and side-effects. A variety of factors probably led to these failures but, in part, again relating to the broad specificity of these enzymes and a lack of detailed understanding of their precise roles in cancer progression. There is, however, renewed interest in the field in the light of a new generation of more selective inhibitors although precisely which MMPs to target is still somewhat unclear. The other major therapeutic area promising much but delivering nothing so far is that of AD where there are multiple protease targets in the pathway from amyloid precursor protein to amyloid β -peptide neurotoxic oligomers (α -, β - and γ -secretases, amyloid-degrading enzymes such as neprilysin). Again, factors mitigating against success have been enzyme promiscuity, late-stage diagnosis and treatment, and the heterogeneity of the disease itself. This sub-committee also deals with other hydrolases which include another AD target, acetylcholinesterase, where inhibitors are in routine clinical use, although only temporary palliatives.

In summary, the profusion, diversity and overarching biological functions of proteases provide excellent and numerous therapeutic targets. Often, as drug targets, they are readily accessible for example as plasma enzymes or ectoenzymes. There have been spectacular successes in rational drug development, all providing excellent pharmacological teaching tools, but some protease classes are intrinsically difficult. The problems to be addressed include substrate promiscuity and the occurrence of overlapping family members providing redundancy. New approaches provide new opportunities but require more subtle targeting, for example of exosites, different domains, or activity modulators. In some cases enzyme activation rather than inhibition is the desired approach (e.g. ACE2, α -secretase). There is also scope for other therapeutic avenues, including epigenetic approaches. Nowhere are new strategies more needed than in AD and other neurodegenerative diseases.

The protease/hydrolase sub-committee currently comprises myself as Chair, David Fairlie, Neil Rawlings, Chris Overall and Christopher Southan and will be expanded further to ensure we get comprehensive coverage of this major therapeutic area. The database is being developed and currently includes pages with genomic and structural information for 175 proteases and 14 hydrolases with activity records in ChEMBL. Detailed ligand activity (K_i or IC_{50}) mapping has been curated for 46 proteases and 14 hydrolases for either approved prodrugs, drugs, clinical candidates or selected research compounds. Clinical candidates and research compound mappings will be extended for these classes, depending on overall priorities for target expansion. We will aim to keep you updated on the protease/hydrolase database and welcome comments and suggestions. It is a very large and productive area of pharmacology to cover so we appreciate your support and input.

Tony Turner's research group at the University of Leeds (from left to right): Natalia Nalivaeva, Caroline Kerridge, Nikolai Belyaev, Natasha Makova, Nicola Clarke, Tony Turner, Alison Whyteside, Paul Kelly, Eva Babusikova, David Hicks, and Daria Bagrova.

<http://www.fbs.leeds.ac.uk/staff/profile.php?un=bmb6ajt>



Pharmacology 2014

(formerly the BPS Winter Meeting)

London, 16-18 December 2014

Queen Elizabeth II Conference Centre, Broad Sanctuary, Westminster, London, SW1P 3EE

<http://www.bps.ac.uk/meetings/Pharmacology2014>

Visit the BPS stand for promotional material about the Guide to PHARMACOLOGY Portal



STUDENT EXPERIENCES

Katerina Gospodinova, fourth year undergraduate student at the University of Edinburgh, BSc Biomedical Sciences (Pharmacology)

Being a Pharmacology undergraduate student at the University of Edinburgh, last summer I undertook a ten-week placement with the Guide to PHARMACOLOGY team. My task was to give a start to a new section in their database (which will be added to the website in the near future) dedicated to non-coding RNAs, especially microRNAs and long non-coding RNAs, by creating a template, summarizing their main features, and subsequently collecting information on some of the most important and studied representatives. Previously considered as non-functional 'junk' or transcriptional noise, I was astonished by the fact that the so called 'dark matter' of the genome is actually involved in many processes, both regulating gene expression and influencing the transcription and translation of other coding and non-coding sequences.

Despite being a computer rather than a lab-based placement, I found the project interesting and enjoyable. Not only has it revealed to me a whole new world, namely that of the non-coding RNAs, but it also helped me further develop skills crucial for my future as a scientist such as critical thinking, problem solving and handling databases, different in nature. Moreover, the summer project has turned out to be a stepping stone in pursuing research as a career. Exploring this rapidly expanding and highly innovative area of biology, I have decided that studying non-coding RNAs and their potential implication as a novel drug targets would become the focus of my future work. As a result, I am currently working on a project aiming to reveal a potential interaction between DISC1 and its antisense long non-coding RNA- DISC2, with both of them being directly disrupted by a balance translocation that co-segregates with schizophrenia, bipolar disorder and recurrent major depression in a large Scottish family.

Finally, I would like to thank Adam Pawson, Elena Faccenda, Joanna Sharman, Helen Benson and Veronika Divincova both for giving me the opportunity to contribute to the Guide to PHARMACOLOGY development and for making my work with their team a highly beneficial experience. I would also like to express my deepest respect towards Professor Tony Harmar who sadly left us earlier this year.

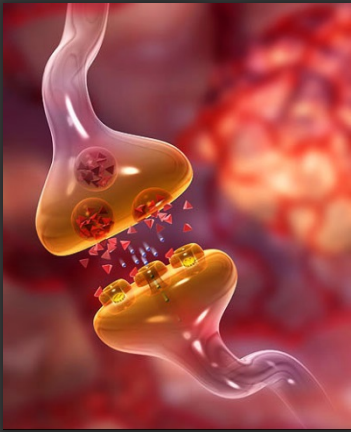
Share your experiences with us!

Tell us about your experiences while studying pharmacology, about your projects and future career ambitions, and we'll publish them in future newsletters.

enquiries@guidetopharmacology.org



Katerina



NOW AVAILABLE!!!

The Concise Guide to PHARMACOLOGY 2013/14

- Concise overviews of the key properties of over 2,000 targets with pharmacology
- Links to open access knowledgebase of drug targets and their ligands (www.guidetopharmacology.org)
- Official IUPHAR classification and nomenclature for human drug targets
- Easy to use tables comparing related targets
- Produced in conjunction with NC-IUPHAR
- Direct links via www.guidetopharmacology.org to detailed views of target and ligand properties from the IUPHAR/BPS Guide to PHARMACOLOGY
- Direct links from gene symbols and UniProt IDs to corresponding entries in HGNC and UniProt
- Recommended further reading with direct links to citations in PubMed
- Permanent, point-in-time record that will survive database updates
- **Now available at:**
<http://www.guidetopharmacology.org/concise>

IUPHAR/BPS
Guide to
PHARMACOLOGY



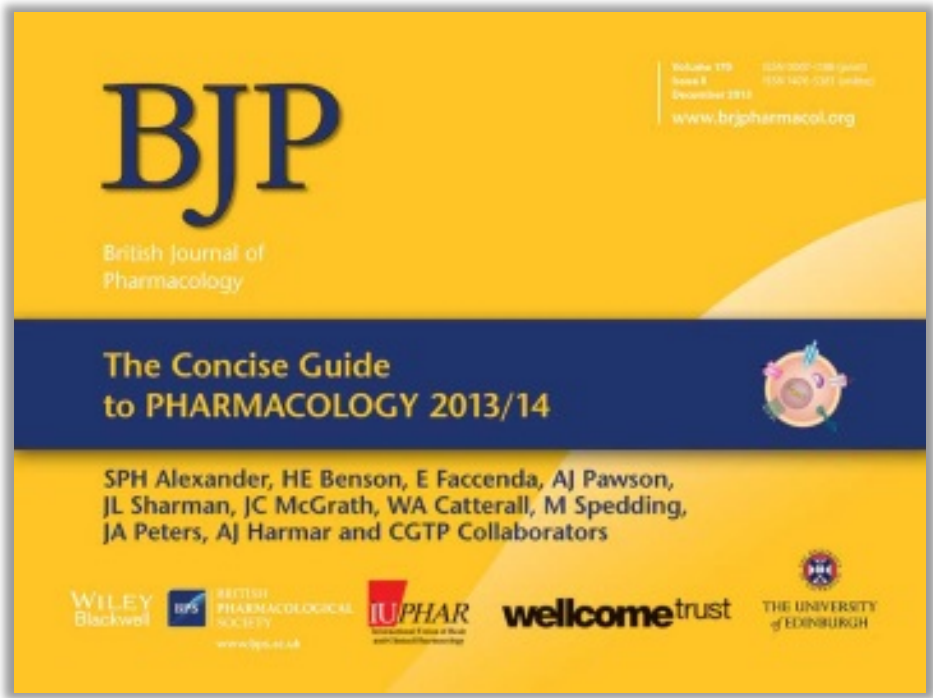
**9th
ADRENOCEPTOR
SATELLITE MEETING**
Receptor structure
changes the
pharmacology
paradigm

James Black Conference of the
British Pharmacological Society.

Major Sponsor: National
Research Foundation of South
Africa

Kruger National Park, South
Africa, 19-23 July 2014

Plenary speakers
include Brian Kobilka
(Nobel Laureate for
Chemistry in 2012) and
Arthur Christopoulos



About NC-IUPHAR

The IUPHAR Committee on Receptor Nomenclature and Drug Classification (NC-IUPHAR), founded in 1987, is chaired by Michael Spedding (France). NC-IUPHAR has the objective of issuing guidelines for the nomenclature and classification of all the (human) biological targets, including all the targets of current and future prescription medicines; 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; designating polymorphisms and variants which are functionally important; developing an authoritative and freely available, global online resource, the IUPHAR database, which is now accessible via the Guide to PHARMACOLOGY portal (<http://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.

NC-IUPHAR at WCP2014

The [17th World Congress of Basic and Clinical Pharmacology](#) takes place in Cape Town, South Africa, 13-18 July 2014.

[There is a very exciting program and a number of NC-IUPHAR committee and subcommittee members, and affiliates are giving plenary lectures and symposia.](#)

Plenary lectures by NC-IUPHAR affiliates:

IUPHAR's Analytical Pharmacology Lecture, **Arthur Christopoulos** - Adventures in allostery: From function to structure

Yoshikatsu Kanai - Amino acid transporters in oncology

Simon Maxwell - Challenges in training tomorrow's prescribers

Kozo Kaibuchi - Protein Phosphorylation in Signal transduction

Richard Neubig - Signal transduction in therapeutics

Doriano Fabbro - Tyrosine kinase inhibitors

Martin Michel - Autonomic pharmacology of the urogenital tract

Symposia including NC-IUPHAR affiliates:

Orphan G protein-coupled receptors- What are the new ligand and new drug targets? (Adam Pawson, Anthony Davenport, Janet Maguire, Stephen Alexander)

Structural Basis for Ion Channel Pharmacology (including Bill Catterall)

NC-IUPHAR and guide to pharmacology (Sir Colin Dollery, Michael Spedding, Adam Pawson, Christopher Southan, Simon Maxwell)

Update in geriatric pharmacology Optimal Prescribing in Older Patients: The challenge of Multiple Comorbid Conditions and Polypharmacy (including Darrell Abernethy)

Evolution, sport and modern diseases (including Michael Spedding)

Emerging Drug Targets (including Richard Neubig)

Glucocorticoids: new insights into mechanisms of action (including John Cidlowski)

Epigenetic mechanisms in cell- and drug-based heart failure therapies (including Lutz Hein)

Membership

Chair

Michael Spedding, France

Vice Chairs

Anthony Davenport, UK - Chairman Evolving Pharmacology Group
 Rick Neubig, USA - GPCRs
 Eliot Ohlstein, USA - Editor

Members

Stephen Alexander, UK
 Thomas Bonner, USA
 William Catterall, USA
 Arthur Christopoulos, Australia
 Sir Colin Dollery, UK
 John Cidlowski, USA
 Doriano Fabbro, Switzerland
 Kozo Kaibuchi, Japan
 Yoshikatsu Kanai, Japan
 Vincent Laudet, France
 John Peters, UK
 Jean-Philippe Pin, France

Corresponding members

Susan Amara, USA
 Michel Bouvier, Canada
 Thomas Burris, USA
 Stephen Charlton, UK
 Moses Chao, USA
 Steven Colletti, USA
 Graham Collingridge, UK
 Sue Duckles, USA
 Richard Eglen, USA
 Steven Foord, UK
 Gillian Gray, UK
 Debbie Hay, New Zealand
 Yu Huang, Hong Kong
 Allyn Howlett, USA
 Franz Hofmann, Germany
 Ad Ijzerman, The Netherlands
 Michael Jarvis, USA
 Terry Kenakin, USA
 Janos Kiss, Hungary
 Chris Langmead, Australia
 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
 Bart Staels, France
 Georg Terstappen, Germany
 Mary Vore, USA

Ex Officio

Patrick du Souich, Canada (Clinical) - IUPHAR President
 Sam Enna, USA - IUPHAR Secretary-General
 Urs Ruegg, Switzerland - 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
 Matt Wright, UK - representing HGNC

Past Chairs (ex officio)

Paul Vanhoutte, China
 Robert Ruffolo, 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



Participants of the April 2013 NC-IUPHAR meeting in Edinburgh, Scotland

NC-IUPHAR Meeting Report April 2014

The Spring NC-IUPHAR meeting was held in Edinburgh from 11-13th April 2014. In addition to many of the core members of the committee being in attendance, we were delighted to be joined by our invited guests, Stephen Anderton, Steve Charlton, Chris Connolly, Gillian Gray, Graeme Henderson, Mo Shahid, Tony Turner and David Wyllie.

The meeting began with a tribute to Tony Harmar who sadly passed away the evening before. A full tribute to Tony can be found on [page 18](#) of this newsletter.

Two pre-meetings were held to discuss the clinical wishes of IUPHAR and efforts to obtain funding of the database into the future. These were followed by general discussions on interactions between IUPHAR, BPS and ASPET.

The database meeting took place on Friday afternoon and this provided the database team with an opportunity to update the committee on recent developments and enhancements to the database, updates on the status of targets and ligands, social media, interactions and collaborations with external resources.

The Saturday meeting began with a formal welcome by the Chairman, highlighting important issues that we need to address, and an overview of what we were aiming to achieve at the meeting. Key issues and action points from the database meeting on Friday were then summarised.

The committee were then treated to an excellent presentation from John Cidlowski entitled "The pharmacology of multiple glucocorticoid receptors - interactions with inflammation: How widespread is this phenomenon? This was followed by a discussion on the status of the epigenetics subcommittee and related targets in the database. A presentation and discussion was then led by John Peters on the past, present and future of ligand-gated ion channels at key issues that we need to resolve for the database.

The chairman provided a brief update on new areas of exploration for NC-IUPHAR, including non-coding RNAs and antibodies. After lunch, our special invited guest and chair of the proteases and hydrolases subcommittee, Tony Turner, gave a very thought provoking presentation on the past, present and future of drugs for human proteases, followed by a discussion on drugs in Alzheimer's disease led by our cheminformatician, Chris Southan. An update on the work of the Evolving Pharmacology Group was then provided by Anthony Davenport.

An important potential new direction for NC-IUPHAR was introduced by way of a presentation by Chris Connolly on environmental pharmacology and the effect of pesticides on the insect population.

An update on the status and future of GPCRs in the database was provided by Rick Neubig and Adam Pawson, followed by a discussion on what industry needs from IUPHAR, with input from our industry experts Alex Phipps, Steve Charlton and Michael Spedding. The committee were updated on the status of NC-IUPHAR publications and the development of the new IUPHAR/ASPET Pharmacology Education Project.

The Saturday meeting concluded with an update from John Cidlowski and Tom Burris on the past, present and future of nuclear hormone receptors in the database, followed by a status report on voltage-gated ion channels by Bill Catterall.

The formal meeting dinner took place on Saturday night at the Scottish Malt Whiskey Society to celebrate the contributions of Sir Colin Dollery and Tom Bonner to the activities of NC-IUPHAR over decades since its inception. They were both presented with specially engraved glass plaques to mark their important and very much appreciated efforts.

The meeting concluded on the Sunday following a full morning session devoted to the NC-IUPHAR financial report by Urs Ruegg, discussions on the past, present and future of transporters in the database led by Steve Alexander. NC-IUPHAR links with pharmacology societies around the world and the new IUPHAR Immunopharmacology Section were highlighted, as were our preparations for the upcoming 17th World Congress of Basic and Clinical Pharmacology in Cape Town, South Africa in 2014.

Michael Spedding ended the meeting with a summary of the main points achieved at the meeting and action points. Finally, participants were reminded about the next meeting to take place in Paris in October 2014 and the Edinburgh meeting in April 2015.



Tom Bonner, Michael Spedding and Sir Colin Dollery



APRIL 2014 ATTENDEES

Steve Alexander
Stephen Anderton
Helen Benson
Tom Bonner
Jonathan Br un
Tom Burris
Bill Catterall
Steve Charlton
John Cidlowski
Chris Connolly
Anthony Davenport
Jamie Davies
Sir Colin Dollery
Sam Enna
Doriano Fabbro
Elena Faccenda
Gillian Gray
Simon Maxwell
Ian McGrath
Rick Neubig
Graeme Henderson
Adam Pawson
John Peters
Alex Phipps
Urs Ruegg
Mo Shahid
Joanna Sharman
Chris Southan
Michael Spedding
Anthony Turner
David Wyllie



We need your help! If you have some time and expertise to contribute to our endeavour, please contact us:

enquiries@guidetopharmacology.org

EXPERT DRIVEN ANNOTATION

The Guide to PHARMACOLOGY portal (which includes the IUPHAR Database) is maintained by a team of curators, with guidance from NC-IUPHAR and an international network of ~700 expert contributors, providing expert-driven annotation of the pharmacology of drug target systems from peer-reviewed primary literature sources.

A global knowledge environment for pharmacology students, academic and industrial scientists, and the interested public.

Subcommittees of NC-IUPHAR are responsible for developing the nomenclature for each drug target family and compiling data to be included in the database.

Where no relevant subcommittee exists, data are captured by the curators or individual experts and peer reviewed by at least two external referees.

Data are sourced from and referenced to the primary literature (peer-reviewed research publications rather than review articles), with links to citations in PubMed. Wherever possible, data are supported by more than one literature source. After review by the curators to ensure accuracy and consistency with the rest of the information in the database, the data are added to the development server.

After approval by NC-IUPHAR, the data are transferred to the public database. Data are reviewed at regular intervals (at least yearly) by subcommittees and other contributors and updated as necessary.

Our global network of expert contributors

NC-IUPHAR Subcommittee Chairs

G protein-coupled receptors Subcommittees

5-Hydroxytryptamine: Nick Barnes, John Neumaier
 alpha₁-adrenoceptors: Dianne Perez
 Apelin: Anthony Davenport
 Bombesin: Robert Jensen
 Calcium-sensing: Ed Brown, Hans Bräuner-Osborne
 Cholecystokinin: Laurence Miller
 Dopamine: Raul Gainetdinov
 Formylpeptide family: Richard Ye
 GABA_A: Bernhard Bettler
 Glucagon receptor family: Laurence Miller
 Histamine: Paul Chazot
 Leukotriene: Magnus Bäck
 Melanin-concentrating hormone: Jean-Louis Nahon
 Metabotropic glutamate: Jean-Philippe Pin
 Neuropeptide FF/neuropeptide AF: Jean-Marie Zajac
 Neuropeptide Y: Dan Larhammar
 Orexin: Christopher Winrow
 Peptide P₅₁₈: Jerome Leprince
 Proactin-releasing peptide: Helgi Schiöth
 Relaxin family peptide: Roger Summers
 Tachykinin: Susan Leeman, Steven Douglas
 Urotensin: Hubert Vaudry

Ligand-gated ion channels Subcommittees

John Peters (Liaison for all LGIC subcommittees)
 5-HT₃: John Peters
 GABA_A: Richard Olsen
 Glycine: Joseph Lynch
 Ionotropic glutamate: Graham Collingridge
 Nicotinic acetylcholine: Neil Millar
 P2X: Charles Kennedy
 ZAC: Timothy Hales

Antibodies Subcommittee

Alex Phipps

Drug Target and Chemistry Curation Subcommittee

Christopher Southan

Epigenetics Subcommittee

Rabinder Prinjha

Acetylcholine (muscarinic): Arthur Christopoulos
 alpha₁-adrenoceptors: Lutz Hein
 beta₂-adrenoceptors: Terry Hébert
 Bradykinin: VACANT
 Cannabinoid: Roger Partwee, Allyn Howlett
 Complement peptide: Peter Monk
 Endothelin: Anthony Davenport
 Free fatty acid: VACANT
 Galanin: Andrew Gundlach
 Glycoprotein hormone: VACANT
 Hydroxycarboxylic acid: Stefan Offermanns
 Lysophospholipid (LPA): Jerold Chung
 Melanocortin: Tung Fong, Helgi Schiöth
 Motilin: Anthony Davenport
 Neuropeptide S: Girolamo Calo
 Neurotensin: Jean Mazella
 P2Y: Geoffrey Burnstock
 Platelet-activating factor: VACANT
 Prostanoid: Robert Jones
 Relaxin-like: Nick Barker
 Trace amine: Janet Maguire
 Vasopressin and oxytocin: Bernard Mouillac

Voltage-gated ion channels Subcommittees

William Catterall (Liaison for all VGIC subcommittees)
 Calcium-activated potassium: George Gutman
 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

Non-coding RNAs Subcommittee

Matt Wright

Kinases Subcommittee

Doriano Fabbro

Adenosine: Adriaan Izerman
 Angiotensin: Sadashiva Karnik
 Bile acid: Anthony Davenport
 Calcitonin: Debbie Hay, David Poyner
 Chemokine: Philip Murphy
 Corticotropin-releasing factor: Richard Hauger, Frank Dautzenberg
 Estrogen (G protein coupled): Richard Neubig
 Frizzled: Gunnar Schulte
 Ghrelin: Birgitte Holst
 Gonadotrophin-releasing hormone: Adriaan Izerman
 Kisspeptin: Anthony Davenport
 Lysophospholipid (S1P): Sarah Spiegel
 Melatonin: Ralf Jockers
 Neuremedin U: Gary Willars
 Neuropeptide W/neuropeptide B: Anthony Davenport
 Opioid: Larry Toll
 Parathyroid hormone: Ted Usdin
 Prokineticin: Philippe Rondard
 Protease-activated: VACANT
 Somatostatin: Stephan Schulz
 Thyrotropin-releasing hormone: Marvin Gershengorn
 VIP and PACAP: VACANT

Nuclear hormone receptors Subcommittees

John Cidlowski and Thomas Burris (Liaisons for all NHR subcommittees)
 NHR subcommittees are being reformed

Pattern Recognition Receptors Subcommittee

Clare Bryant

Proteases Subcommittee

Anthony Turner

Transporters Subcommittee

Stephen Alexander

'Concise Guide to PHARMACOLOGY' Editors

Stephen Alexander, Anthony Harmar, John Peters

ANNOUNCEMENT

3rd Annual Meeting of the GDR 3545



LE CORUM, Montpellier, France, October 20-22 2014

For registration information and details of the preliminary programme, please visit: <http://www.gdr3545.com/index.php/news/events/97-3rd-annual-meeting-of-the-gdr-3545>



Recent publications

The collaboration between NC-IUPHAR, the American Society for Pharmacology and Experimental Therapeutics (ASPET) and the British Pharmacological Society (BPS) allows NC-IUPHAR subcommittees to publish nomenclature reports in *Pharmacological Reviews* and 'state-of-the-field' reviews in *British Journal of Pharmacology*. A selection of the most recent NC-IUPHAR related articles are listed below.

IUPHAR review article published on the Chemokine receptors.

Bachelier 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 Pharmacology. LXXXIX. Update on the extended family of chemokine receptors and introducing a new nomenclature for atypical chemokine receptors. *Pharmacol Rev.* 66: 1-79.

IUPHAR review update article published on orphan G protein-coupled receptors.

Davenport AP, Alexander SP, Sharman JL, Pawson AJ, Benson HE, Monaghan AE, Liew WC, Mpamhanga CP, Bonner TI, Neubig RR, Pin JP, Spedding M, Harmar AJ. (2013) International Union of Basic and Clinical Pharmacology. LXXXVIII. G Protein-Coupled Receptor List: Recommendations for New Pairings with Cognate Ligands. *Pharmacol Rev.* 65: 967-86.

NC-IUPHAR review articles published the British Journal of Pharmacology.

Fujita W, Gomes I, Devi LA. (2014) Revolution in GPCR Signaling: Opioid receptor heteromers as novel therapeutic targets. *Br J Pharmacol.* 2014 Jun 10. doi: 10.1111/bph.12798 [Epub ahead of print]

Kihara Y, Maceyka M, Spiegel S, Chun J. (2014) Lysophospholipid receptor nomenclature review: IUPHAR Review 8. *Br J Pharmacol.* 2014 Mar 7. doi: 10.1111/bph.12678 [Epub ahead of print]

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.* 2014 Mar 3. doi: 10.1111/bph.12665 [Epub ahead of print]

Dollery CT. (2014) Lost in Translation (LiT): IUPHAR Review 6. *Br J Pharmacol.* 171: 2269-90.

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.

Bonner TI. (2014) Should pharmacologists care about alternative splicing? IUPHAR Review 4. *Br J Pharmacol.* 171: 1231-40.

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.

Guide to PHARMACOLOGY article published in the Nucleic Acids Research Database Issue.

Pawson AJ, Sharman JL, Benson HE, Faccenda E, Alexander SP, Buneman OP, Davenport AP, McGrath JC, Peters JA, Southan C, Spedding M, Yu W, Harmar AJ and NC-IUPHAR. (2014) *Nucleic Acids Research* 2014 Jan;42(Database issue):D1098-106..

The Concise Guide to PHARMACOLOGY 2013/14.

Alexander SPH, Benson HE, Faccenda E, Pawson AJ, Sharman JL, McGrath JC, Catterall WA, Spedding M, Peters JA and Harmar AJ, CGTP Collaborators. (2013) The Concise Guide to PHARMACOLOGY 2013/14. *Br J Pharmacol.* 170: 1449-1867.

Articles published by members of the database team.

Southan C, Sitzmann M and Muresan S. (2013) Comparing the Chemical Structure and Protein Content of ChEMBL, DrugBank, Human Metabolome Database and the Therapeutic Target Database. *Mol Inform.* 32: 881-897.

Southan C, Hancock JM. (2013) A tale of two drug targets: the evolutionary history of BACE1 and BACE2. *Front. Genet.* 4: 293.

IN MEMORY OF...

Anthony (Tony) John Harmar FRSE, 28th November 1951 – 10th April 2014

Our good friend Prof Tony Harmar, who led the database initiative in Edinburgh, died of cancer in April.

Tony had a first degree in Biochemistry and a PhD in Pharmacology at the University of Cambridge followed by postdoctoral research at the Friedrich Miescher-Institut (Basle, Switzerland) and the Department of Pharmacology, University of Bristol. He was in the MRC Brain Metabolism Unit in Edinburgh from 1981 prior to joining the staff of the University of Edinburgh in 2001 with a Chair in Molecular Pharmacology.

Tony had an h-index of 40 from almost 200 papers in neuroscience with major contributions in the control of circadian rhythms. His expert knowledge and breakthroughs in class II GPCRs (he first joined NC-IUPHAR as an expert in this subject) led to research showing that rhythmic activity of the "master clock" driving circadian rhythms, located in the suprachiasmatic nuclei (SCN) of the hypothalamus, is dependent upon signalling between SCN neurons, mediated by the neuropeptide, vasoactive intestinal peptide (VIP). Mice lacking a receptor for VIP (the VPAC2 receptor, first identified by Tony in 1993) lack robust circadian rhythms of behaviour, electrical activity and gene expression in the SCN (Cell, 2002). His research showed that food intake is an effective zeitgeber capable of coordinating circadian rhythms of behaviour, peripheral clock gene expression, and hormone secretion, even in the absence of a functional SCN clock. This is crucial research in a very important area.

Tony made important advances in the field of the serotonin transporter (SERT), using transgenic mice overexpressing the human SERT gene, for example, the SERT transgenic mouse was shown to be an important model of pulmonary arterial hypertension, a devastating disease.

Tony's contributions to NC-IUPHAR were not restricted to class II GPCRs because he established the IUPHAR-Database. In 2012 IUPHAR-DB was viewed 131,000 times by 67,000 individuals from 166 different countries, or over 350 visits each hour. Tony grew the team into a team of 6 at the University of Edinburgh, tightly linked with the subcommittees in conjunction with the chair. He played a key role in establishing the collaboration between IUPHAR and BPS to jointly publish the BPS Guide to Receptors and Channels (GRAC) and the IUPHAR database. This undertaking resulted in the creation and successful launch of the Guide to Pharmacology (www.guidetopharmacology.org), which houses the combined data on therapeutic targets, drugs, and other ligands. This is and will be a key educational resource for all pharmacologists and pharmacology worldwide.

Tony was the main investigator in the Wellcome Trust grant and an active member of the team that put together the Guide to Pharmacology and the recent Concise Guide to Pharmacology, published with the BPS.

Tony had great force of character with a very special sense of humour, which could be wicked! He was a very talented musician and chorister. During all the time of his illness he was always positive, and creative in inventing ways to surmount it. Our thoughts are with his wife Jillian and their family.



Michael Spedding, Tony Harmar and Ian McGrath trying out new, very Scottish, hair styles.

Follow us on Facebook, Twitter, and *via* our RSS feed and blog



Search Guide to PHARMACOLOGY on Facebook to get all the latest news from the curators



Follow our Twitter feeds on @GuidetoPHARM



Subscribe to our RSS feed at <http://feeds.feedburner.com/GuideToPharmacology>



Keep up-to-date with our blog at <http://blog.guidetopharmacology.org/>



Ongoing and future NC-IUPHAR activities

- Wellcome grant projects
- Evolving Pharmacology – deorphanisation of GPCRs plus hot topics (web site); full list of GPCR orphans with
- Allosterism (and functional coupling) – applied to GPCRs, ion channels, nuclear hormone receptors and kinases
- Biased agonism and functional selectivity
- GPCR heterodimers – standards and lists
- Alternative splicing recommendations
- Biomarkers
- Target validation
- Gene and protein lists for receptors and all drug sites coordinated between HGNC and NC-IUPHAR – with epigenetic consideration
- Antibodies – collaboration with Marie-Paule Lefranc at IMGT
- Interaction with the IUPHAR immunopharmacology section
- Cyclases and Phosphodiesterases
- Epigenetics, list of targets and pharmacological difficulties
- Non-coding RNAs – with HGNC – list with pharmacological difficulties
- Proteases and Hydrolases
- Pattern recognition receptors
- Transporters
- Producing the *Concise Guide to PHARMACOLOGY* which replaces GRAC
- Pharmacology Education Project

How can you contribute to NC-IUPHAR projects?

If you have some time and expertise – contact the curators at enquiries@guidetopharmacology.org

Developed with support from

wellcometrust

IUPHAR
International Union of Basic and Clinical Pharmacology

BPS BRITISH PHARMACOLOGICAL SOCIETY
Today's science, tomorrow's medicines

Our sponsors



The database team



Jamie Davies,
database principal investigator;
Edinburgh, Scotland



From left to right: Veronika Divincova (project administrator), Elena Faccenda (curator), Joanna Sharman (database developer), Adam Pawson (senior curator) and Helen Benson (curator); Edinburgh, Scotland



Chris Southan,
cheminformatician/
curator; Göteborg, Sweden

...a parting thought

We welcome contributors!

Although we already cover about half of the targets of prescription medicines in the Guide to PHARMACOLOGY portal, there are many important areas that we do not yet cover. Moving forward, our goal is to add about 900 new targets (including all the targets of approved drugs). We have already made major advances on this, but we will need guidance from experts to help us curate and display the kind of data and information that our users would expect. If you would like to contribute your expertise to our effort, please contact us at enquiries@guidetopharmacology.org