A message from the Chairman

Pharmacology at the crossroads: 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 Hammar, 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
**About the IUPHAR/BPS Guide to PHARMACOLOGY**

The IUPHAR/BPS Guide to Pharmacology portal ([http://www.guidetopharmacology.org](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 D₃, Somatostatin sst₁ and sst₅, Angiotensin, Bile acid receptor, Lysophospholipid receptors, MAS1; VGICs: Caᵥ₁,1-4;
- **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**

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<tr>
<td>G protein-coupled receptors including orphans</td>
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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 Shaman.

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 Shaman, attended Edinburgh Neuroscience Day, an annual day of talks and poster presentations involving over 300 researchers with an interest in neuroscience.

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 J une 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”.

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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/).

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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 PubChem RDF linked data project (https://pubchem.ncbi.nlm.nih.gov/rdf/) helps to pick up where PubChem programmatic services leave off. PubChem RDF 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 PubChem RDF, 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.

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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.


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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.

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.
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), Amaud 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 workflow 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 (TID) 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).

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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 (mmao) relationships. We thus control the “maximal mapping” problem that can degrade the data mining specificity of other resources (as discussed in PMID:24533037). Another challenge is prodrug-to-drug relationships. In this case we have arrived at a useful solution exemplified in 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. 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. the 804 intersect in the Venn diagram above).
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.
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 exostes, 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 (Ki or IC50) 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 Keridge, 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
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 Shaman, 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

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 translation 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.

Membership

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Michael Spedding, France

Vice Chairs
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Heleen Benson, UK - Database Curator
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Veronika Divincova, UK - Project Administrator
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(core member Sir Colin Dollery)
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David Webb, UK
Don Birkett, Australia

About NC-IUPHAR at WC P2014

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 alloster: From function to structure
Yoshikatsu Kanai - Amino acid transporters in oncology
Simon Maxwell - Challenges in training tomorrow’s prescribers
Koiz Kabuchi - 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 Southam, Simon Maxwell)

Update in geriatric pharmacology Optimal prescribing in Older Patients: The challenge of Multiple Comorbid Conditions and Polypharmacy (including Darrell Abemethy)
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)
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 Tumer 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 issuesthat 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 Tumer, 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.
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.
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.**

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

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

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

**The Concise Guide to PHARMACOLOGY 2013/14.**

**Articles published by members of the database team.**
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.
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

Ongoing and future NC-IUPHAR activities

- Wellcome grant projects
- Evolving Pharmacology – deorphanisation of GPCRs plus hot topics (website); 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

The database team

- Jamie Davies, database principal investigator; Edinburgh, Scotland
- From left to right; Veronika Divincova (project administrator), Elena Faccenda (curator), Joanna Shamon (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