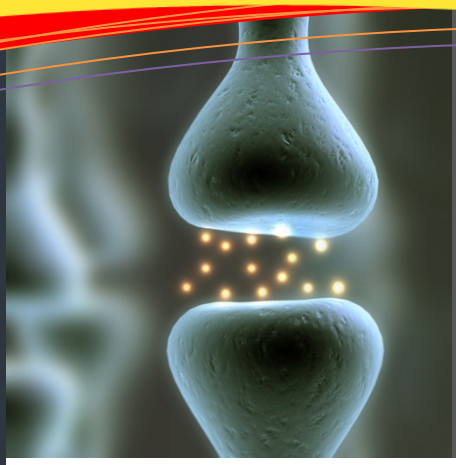
ISSUE 03 NOVEMBER 2012

The biannual newsletter from the IUPHAR Committee on Receptor Nomenclature and Drug Classification

NC-IUPHAR news



Featured in this issue

IUPHAR
International Union of Basic and Clinical Pharmacology

NC-IUPHAR Meeting Report

Paris, 26-28 October 2012

Details of the most recent NC-IUPHAR meeting are available on Page 9

CAPE TOWN, SOUTH AFRICA
WCP2014
17TH WORLD CONGRESS OF BASIC & CLINICAL PHARMACOLOGY

Call for Session Proposals

17th World Congress of Basic and Clinical Pharmacology

Cape Town, South Africa, 13-18 July 2014

Deadline for proposals 15 November 2012

http://www.wcp2014.org

A message from the Chairman

Nomenclature committees must be really boring! Old men debating how many angels can dance on a pin… who cares!

Well, you might, because NC-IUPHAR is trying (with its partners) to classify all the receptor systems and drug sites coded by the human genome, describing the appropriate experimental systems, best ligands, and potential experimental traps, using a unique management structure which already benefits from the freely given efforts of ~700 scientists. The goal is major - how to address the recent massive increase in knowledge, synthesise it into a usable format, and diffuse it to all scientists in the world. We are addressing new research fields (epigenetic targets, non coding RNAs, receptor polymorphisms) and are setting up a series of articles to classify them, and also point out the experimental pitfalls in these new areas. We are a unique mix of industrial and academic scientists, and we don't do "automated data trawling" but we are an expert-driven system, with ~70 subcommittees: but any motivated scientist is welcome to contribute - this means you!

The core committee of NC-IUPHAR (20 successful scientists from different fields) meets twice a year in Paris to coordinate activities, invite scientists in breakthrough areas to give their perspectives, and ratify the propositions of expert groups. The meetings must be effective as scientists continue to fly economy from far-flung destinations to work extensively over a weekend in Paris.

NC-IUPHAR has established IUPHAR-DB, a receptor database (http://www.iuphar-db.org/) run by Tony Harmar's group of curators in Edinburgh, with a list of many of the receptor classes, freely available on the world-wide web to all scientists - receiving queries from >140 countries. Thus we ask you to distribute to your research staff our web site as a source of information - try it now; it has links to all the main genome databases and to OMIM, the link with inherited diseases, *etc*.

A collaboration with the British Pharmacological society has put their Guide to Receptors and Channels (GRAC) into a related database with a common portal (http://www.guidetopharmacology.org/). We intend the Guide to PHARMACOLOGY to be a "one stop pharmacology shop" with a web site and links to articles on the major challenges to pharmacology. A particular goal will be to define how new targets can be useful drug discovery targets, with clear indications of the difficulties involved. As you can see from the list of goals on pages 3, 4 and 5 of this newsletter, these are the major pharmacological questions of our time. We need help from all interested scientists to achieve this goal - and in return you can get well cited publications!

The importance of this task has been recognised by the Wellcome Trust which has awarded us £540.000 over 3 years. In this time of limited budgets, this is a major recognition of the validity of our approach.

So join us!

Michael Spedding, Chairman of NC-IUPHAR

IUPHAR DATABASE

International Union of Basic and Clinical Pharmacology

About the IUPHAR Database

The IUPHAR Database (IUPHAR-DB) is an open access, online database providing detailed, expert-driven, manually curated annotation of the primary literature on the pharmacological, physiological and genetic properties of human and rodent receptors and other drug targets, together with the substances that act on them. The database currently includes information on the products of genes from four major protein classes (G protein-coupled receptors, nuclear hormone receptors, voltage- and ligand-gated ion channels) and over 3250 bioactive molecules (endogenous ligands, licensed drugs and key pharmacological tools) that interact with them. Developed under the auspices of the IUPHAR Committee on Receptor Nomenclature and Drug Classification (NC-IUPHAR), IUPHAR-DB is an authoritative reference and educational resource for pharmacologists, clinicians and allied disciplines. IUPHAR-DB can now be accessed through the new Guide to PHARMACOLOGY Portal.

www.iuphar-db.org

An update from the IUPHAR Database Team

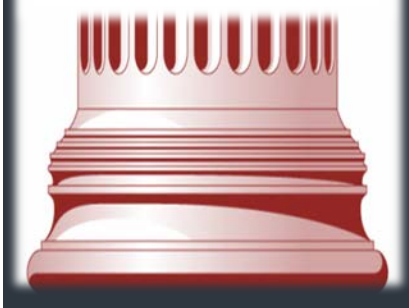
2012 has seen the completion of the Guide to PHARMACOLOGY portal and the introduction of new content and features to IUPHAR-DB:

- *Completion of Guide to PHARMACOLOGY:* updated in July 2012, Guide to PHARMACOLOGY now includes pages on catalytic receptors, enzymes and transporters, adding to existing data on GPCRs, ion channels and nuclear hormone receptors;
- *Data updates:* several GPCR and ion channel subunit pages updated, pilot project to include data on enzymes;
- *Full annotation for Class A orphan GPCRs:* two undergraduate students completed an 8-week summer project, interrogating the literature on Class A orphan receptors and uploading information to the database pages;
- *Enhancements to ligand pages:* addition of International Non-Proprietary Names and clinical information for approved drugs and creation of an abbreviated name field;
- *Changes to the ligand list:* introduction of an 'endogenous peptides' category, renaming of 'small organics' to 'metabolites',
- *Peptide sequences:* sequences and chemical/post-translational modifications curated for >1200 synthetic and endogenous peptides, introduction of 'similar ligands' feature enabling users to find peptides with similar sequences;
- *New links and collaborations:* new links to other databases and upload of IUPHAR-DB bioactivity data to PubChem as part of a continued collaboration;
- *Social media:* creation of Twitter and Facebook pages for IUPHAR-DB and the Guide to PHARMACOLOGY, including regular features, news and topical papers;
- *Public engagement:* Presentation of posters at BPS Neuropeptide and Physiological Society meetings.

The IUPHAR Database team, based in Edinburgh, Scotland (left to right).
Adam Pawson (Database curator), Joanna Sharman (Database developer), Tony Harmar (Database chairman) and Helen Benson (Database curator)

Latest Database Statistics

- The IUPHAR Database now covers 626 human protein coding genes including 358 GPCRs, 140 VGICs, 70 LGICs, 48 NHRs, 10 enzymes and their rodent orthologues
- >3250 distinct ligand molecules
- 372 endogenous peptide ligands of 39 GPCR families
- >480 approved drugs, and WHO designated INNs for drugs where the compound is an active ingredient
- >7350 interactions between protein targets and distinct ligand molecules
- >130,000 visits from >160 countries per year
- Guide to PHARMACOLOGY covers an extended list of targets including Catalytic receptors, Transporters and Enzymes
- GRAC database includes data for >1800 targets interacting with ~3000 unique ligands



IUPHAR
International Union of Basic and Clinical Pharmacology

IUPHAR DATABASE
International Union of Basic and Clinical Pharmacology

GRAC BJP
Guide to Receptors and Channels

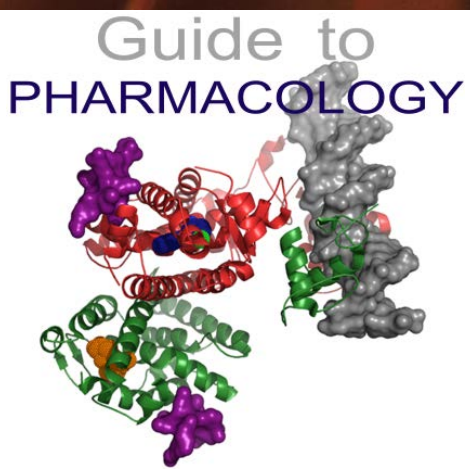
BPS BRITISH PHARMACOLOGICAL SOCIETY
Today's science, tomorrow's medicines

BPS Winter Meeting

London, 18-20 December 2012

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

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



In the spotlight...

www.guidetopharmacology.org

'An expert-driven guide to pharmacological targets and the substances that act on them'

Since 2004, the British Pharmacological Society (BPS) has published 'Guide to Receptors and Channels' (GRAC) as a supplement to the British Journal of Pharmacology, freely available in print and online, and updated every 1-2 years. GRAC is a compendium of pharmacological data, presently providing information on the properties of over 1800 established, or potential, drug targets, the key licensed medicines and experimental drugs that act on them and recommended reading lists for newcomers to each field.

In a collaboration between the BPS and IUPHAR, we have developed the 'Guide to PHARMACOLOGY' (http://www.guidetopharmacology.org), with the aim of providing an open access resource covering all aspects of pharmacology for student and professional pharmacologists, industry experts and the interested public. The first milestone of this initiative was the construction of an open access online database version of the 5th (2011) edition of GRAC, the GRAC Database, which can now be accessed from the Guide to PHARMACOLOGY Portal website alongside the IUPHAR Database.

The GRAC Database currently provides access to peer-reviewed information on the pharmacological, chemical, genetic, functional and pathophysiological characteristics of G protein-coupled receptors, ion channels, nuclear hormone receptors, catalytic receptors, transporters and enzymes. The GRAC database adds value to the information contained in the printed compendium, by providing hyperlinks from drug targets to corresponding entries in other relevant databases, and to citations in PubMed. Each of the ~3000 unique drugs, endogenous substances and radioligands described in GRAC is now fully annotated with manually curated 2D chemical structures, calculated physico-chemical properties, the IUPAC name, synonyms and hyperlinks to relevant external chemistry databases.

The long-term vision of the Guide to PHARMACOLOGY is to provide an unique, authoritative global resource intelligible to all members of the scientific community to maximise our expanding knowledge of how druggable genes affect health and disease and to discover new ways to diagnose, treat and prevent illness.

Focus on the Wellcome Trust grant: current work and future directions

Our long-term vision is to provide…

- A freely available, accurate, regularly updated source of information on the targets of all current licensed medicines and experimental drugs, to foster innovative drug discovery and provide an integrated educational tool for academia, industry and the interested public.
- An entry point into the pharmacological literature for basic and clinical scientists from other disciplines;
- Rich annotation of each drug target and ligand, together with expert summaries of the properties of each target and receptor family, presented in a concise, user-friendly format;
- A catalogue of the key pharmacological tools for the study of each drug target, with accurate quantitative and chemical information from the primary research literature, curated by experts;
- Human-centric data, placed in context with data from commonly used model species, supporting a translational approach to pharmacological research;
- Links to disease information, assisting the selection of targets and drugs for the development of new approaches for the treatment and diagnosis of disease;
- Extensive links from individual targets and drugs to other online resources providing information on genomics, genetics, medicinal chemistry, disease relevance and structural biology;
- Data that is linked to the primary research literature through PubMed.

If you have the expertise to contribute to our endeavour, please contact us: curators@iuphar-db.org

Exploring new targets

We are aiming to provide quantitative pharmacological information on all of the (human) targets of current prescription medicines and other likely targets of future small molecule drugs.

We currently provide detailed information on all ~220 G protein-coupled receptors (GPCRs) for which endogenous ligands have been identified, all voltage- and ligand-gated ion channels and all nuclear receptors encoded by the human, rat and mouse genomes, together with information on the key properties of "orphan" GPCRs, transporters, catalytic receptors and selected enzymes. We are expanding the resource to provide curated information on a further 863 targets so that the completed resource would contain detailed information on all the human targets of current prescription medicines, basing the scope on 435 human genes that are targets of current FDA-approved drugs. We will also provide basic information on the pharmacological properties of a further ~620 genes that are likely targets of future medicines, as defined by published screening literature.

IUPHAR International Union of Basic and Clinical Pharmacology

GRAC BJP Guide to Receptors and Channels

More about our mission, and who will benefit…

The revolution in genomics and molecular genetics has led to the identification of many novel approaches to the development of new medicines. However, there is an urgent need for an accessible and authoritative online synopsis of the complete landscape of existing and future drug targets, to foster innovative drug discovery and provide an integrated educational tool for academia, industry and the interested public.

We are creating a resource which will enable researchers and students to exploit the full potential of the considerable amount of information on drug action available in the published literature, by providing a definitive overview of the landscape of existing and future drug targets. It is intended that the novice researcher (or those conducting investigations into new areas) could identify pertinent literature, clarify nomenclature issues, categorise the available assays and identify the most useful experimental tools (including chemical tools, drugs and radio-ligands) and procedures.

Key data are presented in a standardised and structured format, which can be analysed to form new hypotheses, validate conclusions and guide future research.

DID YOU KNOW?

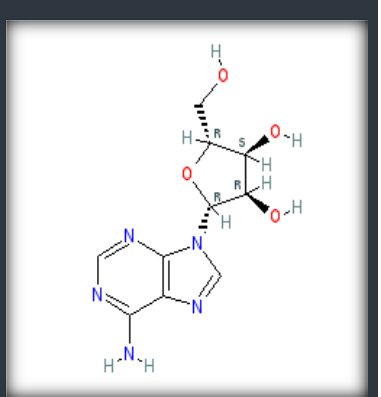
…we provide a wide range of information on ligand molecules in our databases

The IUPHAR Database and Guide to PHARMACOLOGY now contain over 5000 distinct ligand molecules, ranging from synthetic organic chemicals to natural products and peptides.

Information provided about ligands includes 2D structures, calculated physical-chemical properties, synonyms, selectivity data at targets and links to external chemical structure databases and to co-crystallised 3D structures in the Protein Data Bank.

An important recent addition is the curation of the sequences and post-translational modifications of >600 endogenous peptide ligands and well as structural information for >600 synthetic peptides, modified forms and toxins.

The database search interface allows for navigation of the ligand chemical structure space covered by the IUPHAR and GRAC databases through text, identity, similarity, substructure and SMARTS-pattern queries.



Focus on our chemical curation work

Working towards accurate online chemical information

We undertake rigorous curation of the structure and nomenclature of the chemical substances in the IUPHAR Database and Guide to PHARMACOLOGY, shared and refined in collaboration with other databases.

We aim to ensure that the structures and nomenclature of the chemical substances in the IUPHAR Database and Guide to PHARMACOLOGY are correct, **working in collaboration and sharing our data** with the teams responsible for ChemSpider, PubChem, DrugBank and the Human Metabolome Database. Databases of chemical information extracted from the literature frequently contain errors and ambiguities, owing to mistakes in curation, which tend to proliferate between databases when the content is downloaded and reused. A carefully curated core set of pharmacological tools with **unambiguous structural information** would be valuable to researchers selecting reagents for use in their research, avoiding the use, for example, of the wrong stereoisomer of a drug in an experiment. In addition, the provision of computational molecular descriptors (SMILES and InChI) allow searching of the IUPHAR Database and Guide to PHARMACOLOGY, and other chemoinformatics resources for substances that are structurally related to query compounds.

Establishing a "gold standard" set of recommended pharmacological tools

A major goal for the future is to help researchers to choose appropriate reagents for *in vitro* and *in vivo* experiments from the plethora of substances used in the literature. We are working towards providing a **"gold standard" set of readily available, recommended pharmacological tools** for each target (licensed drugs, commercially available experimental compounds, radioligands and imaging reagents). Desirable properties include high potency/affinity in commonly used experimental species, selectivity for the appropriate target type, appropriate pharmacokinetic properties (*e.g.* good bioavailability, suitable for oral dosing, appropriate half-life, first-order elimination kinetics, no autoinduction of enzymatic biotransformation and lack of pharmacokinetic interactions with other drugs).

Providing information on clinically used drugs

A resource linking information on the clinical uses of drugs to preclinical data and rigorously defined chemical structures would be valuable to basic and clinical scientists worldwide. For each clinically used drug listed in the IUPHAR Database and Guide to PHARMACOLOGY Portal, we are working to provide a **brief summary of therapeutic uses** of the drug (*e.g.* for atorvastatin "a competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase used in the treatment of hypercholesterolemia"), guided by a panel of eminent clinical pharmacologists from NC-IUPHAR (the Clinical and Translational Pharmacology Group). Consistent with the international focus of the IUPHAR Database and Guide to PHARMACOLOGY Portal, we are using the WHO database of International Nonproprietary Names (INN: http://www.who.int/medicines/services/inn/en/) and the WHO Anatomical Therapeutic Chemical (ATC) classification (http://www.whocc.no/atc) as the basis for the classification of clinically used drugs. Further information on clinical pharmacology is provided through links to DrugBank, which contains extensive information on therapeutic indications, absorption, metabolism, excretion and toxicity.

FROM THE CHAIRMAN

Talking Point in Pharmacology: Mechanisms of action

As an industrial and academic scientist, I have probably spent more time on the "mechanism of action" of drugs, receptors etc. than almost anything else. Yet, I remain cynical about the immense faith frequently put into the power of this term. As a Popperian scientist, I consider that a mechanism of action is a statement of a hypothesis which is falsifiable. Furthermore, experience shows that, 30 years on, we didn't really understand many of the basic issues in our mechanistic research. This then brings about a big issue: if we accept this, then the mechanism of action is not a property inherent in the molecule being described, but rather on the observer's knowledge. I often joke that the mechanism of action only defines the level of ignorance accepted by the people at a meeting - for example a meeting of GPs may accept "vasodilator" as a mechanism, or a meeting of molecular modellers may accept "interactions with Arg273 and Arg275", but neither really helps the other. Furthermore, even simple statements such as "drug Y is an X receptor antagonist" should take into account all the variables in a drug-receptor interaction (see Table 1 below) - and the fact that the drug will only have been tested on a few potential targets. This means that ratifying useful mechanisms, which are not easily falsifiable, requires groups of people that are knowledgeable and experienced - NC-IUPHAR!

Michael

Agonism, partial agonism, antagonism, inverse agonism
Onset and offset kinetics
Concentration of agonist
Site of action within the receptor (orthosteric, allosteric)
G protein coupling
Phosphorylation, acylation etc.
Transactivation (e.g. GPCRs modulated by tyrosine kinases)
Presynaptic/postsynaptic control
Receptor heterodimers
Receptor accessory proteins (*e.g.* coupling to PDZ domains) and associated coupling complexes
Chronobiological modulation of accessory proteins, receptor expression, *etc.*
Functional selectivity – ligand-induced differential signalling
Biologically important receptor polymorphisms (SNPs, pseudogenes, alternative splicing, mRNA editing)

Table 1. Some variables in Drug/Receptor interactions which would lead to different functional outputs from drugs

If you have the expertise to contribute to our endeavour, please contact us: curators@iuphar-db.org

PROFILE OF HGNC

The HUGO Gene Nomenclature Committee

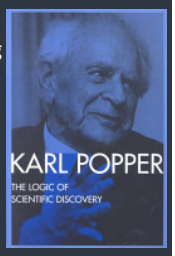
The HGNC (www.genenames.org) is the only worldwide authority assigning standardised human gene symbols and names, and has three key goals: providing unique standardised nomenclature for every human gene; ensuring this information is freely available, widely disseminated and universally used; and most recently, ensuring this nomenclature is expanded and utilised across vertebrate genomes. The online HGNC database contains 33,500 approved gene entries that include links to sequence accessions, genome browsers and databases, relevant publications, and other useful resources. Our aim is to provide nomenclature that is informative and acceptable to researchers in the field. To accomplish this we liaise with researchers working on specific genes, work closely with other nomenclature groups, consult experts for gene families, and collaborate with specialist databases, such as NC-IUPHAR. Our symbols are used extensively within the genetics and genomics communities and throughout the databases that concentrate on human genes and proteins, such as Entrez Gene, Ensembl, Vega, ENA/GenBank/DDBJ, GeneCards, UCSC genome browser and UniProt, as well as disease related databases such as Decipher, OMIM, and COSMIC. Please contact us at hgnc@genenames.org if you have any gene nomenclature queries.

HGNC
HUGO Gene Nomenclature Committee

Matt Wright,
Gene Nomenclature Advisor, HGNC

FROM THE CHAIRMAN

Why all young scientists should read Karl Popper



When I was a young scientist just starting out, without Albert Einstein's brain, I felt uncomfortable with the idea that I could bring about major advances in knowledge. How could I be so pompous to imagine that I could be a good scientist?

By good fortune I read a book about Karl Popper and this changed my career, my way of doing science and especially – my experimental design! You probably haven't heard about him, but he is probably the greatest philosopher of science and his ideas are incredibly liberating. One of my difficulties was "how can I possibly discover the secrets of science?" – well he says you can't: but you *can* disprove hypotheses with good experiments. And I could live with the idea of being less wrong than others, whereas the thought of being right about such big issues was just too much. Indeed his definition of science comes down to what can be experimentally tested and falsified.

Just log on and carefully read the Wikipedia description of his work (which is quite accurate): an Austrian who saw violence, fled Hitler, and, as his contribution to the second world war, wrote an incredibly powerful intellectual refutation of Marx and totalitarianism. If you want to read how to support democracy (but not weakly), deal with tyranny, - and run good experiments: look him up.

We don't like to admit it, but the future can look depressing. It also looked like that before the second world war; so here is what Popper says: *"it is our duty to remain optimists. The future is open. It is not predetermined and thus cannot be predicted except by accident. The possibilities that lie in the future are infinite. The future depends upon ourselves. It is we who bear all the responsibility".*

He was a real scientific hero.

Michael

students and post-docs corner

STUDENT EXPERIENCES

"In summer 2012, I undertook an 8 week internship for the IUPHAR Database at the University of Edinburgh/British Heart Foundation Centre for Cardiovascular Science in the Queen's Medical Research Institute, supervised by Professor Tony Harmar. The project involved the curation of data for Class A orphan G protein-coupled receptors (GPCRs). It was rather daunting at the start of the internship, as I was completely new to data curation and clueless about the curation process. However, through many helpful discussions with Adam, Joanna and Helen (the curators for the IUPHAR Database), I began to get a better picture of what I needed to achieve and how I should proceed.

For each receptor, I needed to search various genomic and chemical databases including HGNC, RGD, MGI, and ChEMBL, as well as PubMed references to look for relevant data on agonists and antagonists, transduction mechanism of the receptor, physiological consequences of altering gene expression *etc*. The data was first entered into a template document, and then checked and proofread by Helen. Finally, I uploaded the data from each template into the production Database using a custom-built submission tool.

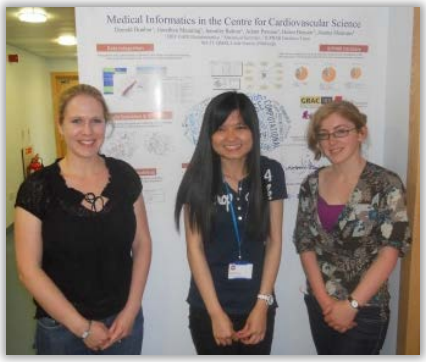
The difficult time during the internship was working on those receptors with a lot of references in PubMed. It took me quite some time to read and curate the data. However, the best time came when I had finished curating the data. I felt extremely contented when I saw a long list of information that I had curated displaying on the database webpages, and I knew I had done well. The experience I gained during my internship was invaluable.

I have now started my final year at the University of Edinburgh, and I know I will have a busy and exciting year ahead. I feel really honoured and happy to get the chance to work with the IUPHAR Database team, and contributing my little effort in building the content of the Database. An IUPHAR review article on orphan GPCRs for publication in *Pharmacological Reviews* has now been written, and I have been included as a co-author…my first scientific publication!"

(*This experience was contributed by Wen Chiy Liew, undergraduate student at the University of Edinburgh, from Malaysia*).

Share your experiences with us!

Email curators@iuphar-db.org or enquiries@guidetopharmacology.org and tell us about your experiences while studying pharmacology, about your projects and future career ambitions, and we'll publish them in future newsletters.



Jo, Wen Chiy and Helen

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 mission of issuing guidelines for classifying pharmacological targets, and addressing the main issues in pharmacology today; Facilitating the interface between the discovery of new sequences from the Human Genome Project and the designation of the derived proteins as functional pharmacological targets – also designating the natural variants which are functionally important; Developing the IUPHAR database (http://www.iuphar-db.org) and Guide to PHARMACOLOGY portal (http://guidetopharmacology.org) with access to data on all known receptor systems and other important targets, freely available to all scientists, anywhere in the world. NC-IUPHAR publishes articles on receptor nomenclature and guidelines for terminology in Pharmacological Reviews, in collaboration with ASPET, and also publish reviews on other topics in the British Journal of Pharmacology.

Membership

Chair
Michael Spedding, France

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

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

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Michel Bouvier, Canada
Stephen Charlton, UK
Moses Chao, USA
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Sam Enna, USA - IUPHAR Secretary-General
Urs Ruegg, Switzerland - IUPHAR Treasurer
Joanna Sharman, UK - Database Developer
Adam Pawson, UK - Senior Database Curator
Helen Benson, UK - Database Curator
Elena Faccenda, UK - Database 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

Ongoing and future NC-IUPHAR activities

- The Guide to PHARMACOLOGY portal with BPS/GRAC – Wellcome grant
- Evolving Pharmacology – deorphanisation of GPCRs plus hot topics (web site)
- Full list of GPCR orphans with pharmacology
- New annotated list of GPCRs with recommendations for orphans
- Allosterism (and functional coupling) – applied to GPCRs, channels, and receptor tyrosine kinases
- Biased agonism and functional selectivity
- GPCR heterodimers – standards and lists
- Alternative splicing recommendations
- Gene and protein lists for receptors and all drug sites coordinated between HGNC (*Profile on Page* 6) and NC-IUPHAR – with epigenetic consideration
- Non-coding mRNAs – with HGNC – list with pharmacological difficulties
- Transporters – initiative with Susan Amara – scientific director of NIMH
- Epigenetics, list of targets and pharmacological difficulties – Rab Prinjha
- Tyrosine kinase receptors – including allosteric modulations – Doriano Fabbro

IUPHAR
International Union of Basic and Clinical Pharmacology

NC-IUPHAR Meeting Report

The autumn NC-IUPHAR meeting was held in Paris from the 26th to 28th October 2012. In addition to many of the core members of the committee being in attendance, we were delighted to be joined by our invited guests, **Philip Murphy** (National Institute of Allergy and Infectious Diseases, NIH, and NC-IUPHAR Chairperson for the Chemokine receptors), **Helgi Schiöth** (Uppsala University, and Chairperson for the Melanocortin and Prolactin-releasing peptide receptors), **Doriano Fabbro** (Novartis, and Chairperson for protein kinases), **Kozo Kaibuchi** (Nagoya University, and on behalf of the Japanese Pharmacological Society), **Jonathan Brüün** (Chief Executive of the British Pharmacological Society) and **Kevin Kearns** (Deputy Chief Executive of the British Pharmacological Society).

The meeting began on the Friday with general discussions on the interactions between IUPHAR and the British Pharmacological Society. This was followed by the database meeting, during which the curators gave a presentation on the current status and recent developments of the IUPHAR database and Guide to PHARMACOLOGY portal. Following the presentation, a number of issues were discussed, including developing the Guide to PHARMACOLOGY portal as a knowledge base for academics and students, enhancing the usability of the resources and the future curation of new drug targets for inclusion in the databases. The database chairman **Tony Harmar** then gave a presentation on the database team's requirements and plans for the next 3 years from the start of the **Wellcome Trust** funding period on the 1st November 2012. A number of action points were put in place.

On the Saturday, NC-IUPHAR Chairman **Michael Spedding** welcomed the participants, gave an overview on the activities and structure of NC-IUPHAR, and presented the main objectives of the meeting. The morning began by revisiting important issues raised during the database meeting on the Friday afternoon, followed by a number of discussions relating to important issues in pharmacology today. The main topics that were discussed included: the application of allostery to GPCRs, ion channels, nuclear hormone receptors and tyrosine kinases receptors **(Chris Langmead);** biased signalling **(Rick Neubig);** the status of the voltage- and ligand-gated ion channels subcommittees presented by **Bill Catterall** and **John Peters** respectively; a report on the activity of the Emerging Pharmacology Committee dealing with the status of orphan GPCRs **(Anthony Davenport);** and Editor's reports by **Eliot Ohlstein** and **Ian McGrath** on the status of manuscripts in the pipeline for *Pharmacological Reviews* and *British Journal of Pharmacology*. During the day we heard presentations from **Helgi Schiöth** on 'Drug discovery and the human genome' and on 'Adhesion GPCRs'; **Phillip Murphy** on the status of the chemokine receptor family and decoy receptors, and the activity of the chemokine receptor subcommittee; and with respect to a new activity by NC-IUPHAR, **Doriano Fabbro** gave a presentation on the complete pharmacological classification of tyrosine kinase receptors and future plans to include these as targets in the IUPHAR database.

The meeting concluded on the Sunday following a full morning session devoted to the NC-IUPHAR financial report by **Urs Ruegg**, discussions on nuclear hormone receptors, drug targets in epigenetics and transporters, links with pharmacology societies around the world, and the programme for the **17th World Congress of Basic and Clinical Pharmacology in Cape Town, South Africa in 2014**.

Michael Spedding ended the meeting with an insightful presentation on 'How exercise and the bacteriome affects the human brain and metabolism' with implications for lipid metabolism and lipid effects on GPCRs. Finally, participants were reminded about the next meeting to take place in Edinburgh, Scotland in April 2013 and the Paris meeting in October 2013.

ATTENDEES

Steve ALEXANDER, UK
Helen BENSON, UK
Tom BONNER, USA
Jonathan BRÜÜN, UK
William CATTERALL, USA
Anthony DAVENPORT, UK
Sir Colin DOLLERY, UK
Sam ENNA, USA
Doriano FABBRO, Switzerland
Anthony HARMAR, UK
Kozo KAIBUCHI, Japan
Kevin KEARNS, UK
Janos KISS, Hungary
Chris LANGMEAD, Australia
Ian McGRATH, UK
Philip MURPHY, USA
Rick NEUBIG, USA
Eliot OHLSTEIN, USA
Adam PAWSON, UK
John PETERS , UK
Jean-Philippe PIN, France
Urs RUEGG, Switzerland
Joanna SHARMAN, UK
Helgi SCHIÖTH, Sweden
Michael SPEDDING, France

Annual meeting of the GDR-3545, Paris 29th-31st October 2012

The GDR3545 on "G Protein-coupled Receptors : from physiology to drugs (RCPG-Physio-Med)" was created in 2012 by the CNRS, currently directed by Ralf Jockers (University Paris Descartes, Paris), and is composed of approximately 600 members working in 57 research teams from different research organizations in France (CNRS, Inserm, CEA, INRA, etc.). This exciting meeting, which took place directly after the NC-IUPHAR meeting, and included a session on IUPHAR activities presented by Michael Spedding (Chair of NC-IUPHAR), as well as lectures by Philip Murphy and Chris Langmead.

We need your help! If you have some time and expertise to contribute to our endeavour, please contact us: curators@iuphar-db.org

Our global network of expert contributors

NC-IUPHAR Subcommittee Chairs

Note: Full lists of subcommittee members, current and past contributors can be found on the IUPHAR-DB website

G protein-coupled receptors

5-Hydroxytryptamine: Nick Barnes, John Neumaier
α_1-adrenoceptors: Dianne Perez
Apelin: Anthony Davenport
Bombesin: Robert Jensen
Calcium-sensing: Ed Brown, Hans Bräuner-Osborne
Cholecystokinin: Laurence Miller
Dopamine: Kim Neve
Formylpeptide family: Richard Ye
$GABA_B$: Bernhard Bettler
Glucagon receptor family: Laurence Miller
Histamine: Paul Chazot, Rob Leurs
Leukotriene: Magnus Bäck
Melanin-concentrating hormone: Jean Boutin
Metabotropic glutamate: Jean-Philippe Pin
Neuropeptide FF/neuropeptide AF: Jean-Marie Zajac
Neuropeptide Y: Dan Larhammar
Orexin: Christopher Winrow
Peptide P518: Anthony Davenport
Prolactin-releasing peptide: Helgi Schiöth
Relaxin family peptide: Roger Summers
Tachykinin: Susan Leeman, Steven Douglas
Urotensin: Hubert Vaudry

Acetylcholine (muscarinic): Arthur Christopoulos
α_2-adrenoceptors: Lutz Hein
β-adrenoceptors: Terry Hébert
Bradykinin: Fredrik Leeb-Lundberg
Cannabinoid: Roger Pertwee, Allyn Howlett
Complement peptide: Peter Monk
Endothelin: Anthony Davenport
Free fatty acid: Graeme Milligan
Galanin: Andrew Gundlach
Glycoprotein hormone: Vacant
Hydroxycarboxylic acid: Stefan Offermanns
Lysophospholipid (LPA): Jerold Chung
Melanocortin: Tung Fong, Helgi Schiöth
Motilin: Anthony Davenport
Neuropeptide S: Rainer Reinscheid
Neurotensin: Jean Mazella
P2Y: Geoffrey Burnstock
Platelet-activating factor: Ewa Ninio
Prostanoid: Robert Jones
Relaxin-like: Nick Barker
Trace amine: Janet Maguire
Vasopressin and oxytocin: Bernard Mouillac

Adenosine: Adriaan Izjerman
Angiotensin: Walter Thomas
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 Ijzerman
Kisspeptin: Anthony Davenport
Lysophospholipid (S1P): Sarah Spiegel
Melatonin: Margarita Dubocovich
Neuromedin U: Gary Willars
Neuropeptide W/neuropeptide B: Anthony Davenport
Opioid: Brian Cox
Parathyroid hormone: Ted Usdin
Prokineticin: Philippe Rondard
Protease-activated: JoAnn Trejo
Somatostatin: Stephan Schulz
Thyrotropin-releasing hormone: Marvin Gershengorn
VIP and PACAP: Anthony Harmar

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

$5\text{-}HT_3$: John Peters
$GABA_A$: Richard Olsen
Glycine: Joseph Lynch
Ionotropic glutamate: Graham Collingridge
Nicotinic acetylcholine: Neil Millar
P2X: Charles Kennedy
ZAC: Timothy Hales

Voltage-gated ion channels
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

Nuclear hormone receptors
Vincent Laudet (Liaison for all NHR subcommittees)

Epigenetics
Rabinder Prinjha

Tyrosine Kinase Receptors
Doriano Fabbro

MicroRNAs
Matt Wright

Transporters
Stephen Alexander

GRAC Editors
Stephen Alexander, Anthony Harmar, John Peters

NEWS BITE

NC-IUPHAR to expand links with DiscoveRx

Since 2011, IUPHAR-DB has provided direct product links from its orphan GPCR pages to corresponding DiscoveRx PathHunter® β-Arrestin GPCR Assay resources. In a new collaboration involving the curation of data for all human protein kinases, IUPHAR-DB will include DiscoveRx kinase inhibitor data generated on the KINOME*scan*℠ platform for over 70 compounds across 400 kinases.

DiscoveRx

EXPERT DRIVEN ANNOTATION

The IUPHAR Database and Guide to PHARMACOLOGY Portal are 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.

IUPHAR
International Union of Basic and Clinical Pharmacology

GRAC BJP
Guide to Receptors and Channels

FROM THE DATABASE CHAIRMAN

Wellcome Trust Grant Success

1st November 2012 will be an exciting day for the IUPHAR-DB and GRAC teams, since it marks the start of three years funding for the project from the Wellcome Trust and with continued support from IUPHAR and BPS. Our goal is to add about 900 new targets (including all the targets of prescription medicines) to the content of IUPHAR-DB and GRAC, delivered through the new Guide to PHARMACOLOGY portal.

A project administrator and third curator have been recruited, but we are still looking for a curator with expertise in chemoinformatics.

More than half of the new targets are enzymes – familiar territory for the GRAC editors but not previously covered in IUPHAR-DB.

We'd be pleased to hear from any volunteers who might be able to help with specific target families (*e.g.* proteases). As always, we are looking for the invaluable support of our network of volunteer experts to make this project a success.

Tony

Tony Harmar, Database Chairman

Recent NC-IUPHAR related 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 Calcium-Activated Chloride Channels.

Huang F, Wong X, Jan LY. (2012) International Union of Basic and Clinical Pharmacology. LXXXV: Calcium-Activated Chloride Channels. Pharmacol Rev. 64: 1-15.

IUPHAR review article published on the nomenclature, function and pharmacology of Orexin receptors.

Gotter AL, Webber AL, Coleman PJ, Renger JJ, Winrow CJ. (2012) International Union of Basic and Clinical Pharmacology. LXXXVI. Orexin Receptor Function, Nomenclature and Pharmacology. Pharmacol Rev. 64: 389-420.

IUPHAR review article published on the pharmacology and functions of VIP and PACAP receptors.

Harmar AJ, Fahrenkrug J, Gozes I, Laburthe M, May V, Pisegna JR, Vaudry D, Vaudry H, Waschek JA, Said SI. (2012) IUPHAR Reviews 1: Pharmacology and functions of receptors for vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide. Br J Pharmacol. 166: 4-17.

How to use the IUPHAR Database: step-by-step protocol and examples.

The IUPHAR Database team has produced a comprehensive protocol describing how to use the IUPHAR Database for Receptor Binding Techniques published by Springer Protocols, with step-by-step instructions, screenshots, examples and tips to help users make the most of the database.

Mpamhanga CP, Sharman JL, Harmar AJ, and NC-IUPHAR. (2012) How to Use the IUPHAR Receptor Database to Navigate Pharmacological Data. Methods Mol Biol. 897: 15-29. In Receptor Binding Techniques edited by Anthony P. Davenport (Springer Protocols). [PMID: 22674159].

IUPHAR Database update article accepted for the 2013 Nucleic Acids Research Database Issue.

Sharman JL, Benson HE, Pawson AJ, Lukito V, Mpamhanga CP, Bombail V, Davenport AP, Peters JA, Spedding M, Harmar AJ, and NC-IUPHAR. IUPHAR-DB: updated database content and new features. Nucleic Acids Research. *In press*

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How can you contribute to NC-IUPHAR projects?

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

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MERCK MILLIPORE

…a parting thought

We welcome contributors!

Although we already cover about half of the targets of prescription medicines in IUPHAR-DB and GRAC, delivered through 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 prescription medicines). To do this, 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 curators@iuphar-db.org or enquiries@guidetopharmacology.org

FROM THE CHAIRMAN

Pharmacology, a Nobel profession

My first oral presentation was at a BPS meeting, where I was grilled hard by two eminent pharmacologists sitting on the front row - Jim Black and John Vane, both of whom subsequently won Nobel prizes. I can still remember every second of the exchanges! I was 22 at the time… then I was able to interact with Bob Furchgott, who won the Nobel prize for showing that endothelial-derived relaxing factor (EDRF) was NO (with Ferid Murad and Louis Ignarro).

The BPS and NC-IUPHAR have just run a symposium at the American neuroscience meeting on how structural aspects of GPCRs are critical for modern pharmacology, and we celebrated the work of Bob Lefkowitz and Brian Kobilka, our newest Nobels.

Pharmacology is a major science and these Nobel prize winners shows this clearly. Not only that, but all these outstanding scientists were and are remarkable people, open and encouraging to young scientists.

NC-IUPHAR salutes Bob Lefkowitz and Brian Kobilka.

Michael

IUPHAR International Union of Basic and Clinical Pharmacology