NC-IUPHAR REPORT – 2012

Introduction and Key Issues

The past year has seen the continuing evolution of NC-IUPHAR along with major enhancements to the IUPHAR database (IUPHAR-DB: http://www.iuphar-db.org). Significantly, our joint initiative with the British Pharmacological Society (BPS) has led to the recent launch of a new open access portal, http://www.guidetopharmacology.org, which integrates IUPHAR-DB and the BPS *Guide to Receptors and Channel*s (GRAC). This is a major achievement and will ultimately provide a unique, authoritative global resource open 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.

We have also announced an alliance with DiscoveRx for research and ligand assignation of orphan GPCRs.

Pharmacology also has to face the fact that drug discovery and development is facing a difficult time, but preclinical and clinical pharmacology is key to translation success of drug discovery. NC-IUPHAR must also be at the forefront of the new pharmacologies which are developing (epigenetics, miRs, *etc*).

1. Organisation

The committee of NC-IUPHAR has been revised (see Appendix 1). The Editors of GRAC are already full members of NC-IUPHAR and play a full role in the work of that committee. Geographical reach has been enlarged, but this brings the challenge of funding travel, and also the time for travel of the experts involved. The twice yearly core NC-IUPHAR meetings are now themed and we have made an alliance with the Japanese Pharmacology Society, who pay the travel for two new members*, but who are invited according to the meeting theme.

Corresponding Members

In order to broaden the expertise of the core committee, the number of corresponding members has been increased. Corresponding members attend selected meetings of NC-IUPHAR and include representatives of the major pharma companies. They now include a subgroup of clinical pharmacologists who will provide advice on translational aspects of receptor pharmacology.

Evolving Pharmacology

Anthony Davenport leads a group which monitors the “de-orphanisation” of GPCRs. Particularly important and timely breakthroughs are included in the Hot Topics section of the database along with email alerts.

Subcommittee chairpersons propose a list of experts, ratified by NC-IUPHAR, to ensure adequate representation of the field. The chairperson of each subcommittee plays a critical role co-ordinating the actions of the subcommittee, organising meetings and finalising documents and the website pages. However we encourage the presence of postdocs in the subcommittee as chairs simply do not have enough time to fill in the various template fields – postdocs can therefore get publication credits, and several NC-IUPHAR publications have become citation classics. The h-index of IUPHAR is >60. The subcommittees meet to establish consensus on classification, and to ensure that the NC-IUPHAR guidelines are complied with. We now have more than 60 subcommittees.

2. Publications and Symposia

NC-IUPHAR benefits from a privileged relationship with ASPET and BPS, with core nomenclature articles appearing in *Pharmacological Reviews,* while in a new series of general “state-of-the-field” review articles are published (alongside database updates) in the *British Journal of Pharmacology*.

Five NC-IUPHAR nomenclature articles have appeared in *Pharmacological Reviews* (Editor, Eliot Ohlstein) so far during the 2011-2012 period, reflecting the activity of NC-IUPHAR. The publications are listed in Appendix 2. In addition, the inaugural NC-IUPHAR commissioned review for the *British Journal of Pharmacology* (Editor-in-Chief, Ian McGrath) has recently been published by Harmar *et al*, entitled “IUPHAR Reviews 1: Pharmacology and functions of receptors for vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide”.

NC-IUPHAR and Neuropharmacology hosted a symposium on “High Resolution Neuropharmacology : structure change the paradigm” with world experts on crystal structure, and how structure-based pharmacology can be used to define orthosteric and allosteric drug interactions at all drug targets –

and also how the drug variables listed in Table 1 can be controlled. NC-IUPHAR edited the 20 articles (Neuropharmacology, 2011, 60 (1)).

3. The IUPHAR database (IUPHAR-DB)

IUPHAR-DB now covers 627 genes encoding G protein-coupled receptors (GPCRs), voltage- and ligand-gated ion channels (VGICs and LGICs), nuclear hormone receptors (NHRs), and in a recent addition the 10 enzymes of the lanosterol biosynthesis pathway. The database now receives over 125,000 visits from about 160 countries each year. Having one full-time database developer and two full-time curators, under the aegis of the database chair, Professor Tony Harmar at Edinburgh, has allowed real progress to be made.

A summary of recent improvements to IUPHAR-DB has been published in Nucleic Acids Research (see Sharman *et al* reference in Appendix 1). A subsequent update on database enhancements has also been presented at the recent Neuroscience Day 2012, Royal College of Physicians, Edinburgh.

Recent enhancements and updates to IUPHAR-DB:

1. **The database now contains over 3800 distinct ligand molecules**, ranging from synthetic organic chemicals to natural products and peptides; an important recent addition is the curation of the sequences and post-translational modifications of ~500 endogenous peptide ligands. 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; unlike other databases IUPHAR-DB is an expert driven database so the compounds are “best in class”.
2. **Curation of the endogenous peptides of GPCRs:** The annotation of sequences, structural and protein precursor data, and database links for all the endogenous peptide ligands of ~39 GPCR families has been completed. Endogenous ligands for are listed in a separate table on their receptor database pages. For each endogenous peptide, the sequences of human, mouse and rat peptides were compared and species differences noted. Predicted and experimentally confirmed post-translational modifications, and information on precursor proteins and the encoding gene was collected. Database links to UniProt, HGNC, MGI, and RGD were added and the peptides linked to their receptors. Future plans include implementing tools for sequence-based searching and clustering of related peptides based on sequence similarity;
3. **The database search interface has also been enhanced**, allowing for navigation of the ligand chemical structure space covered by IUPHAR-DB and GRAC through text, identity, similarity, substructure and SMARTS-pattern queries. An example of a ligand page can be seen at http://www.iuphar-db.org/DATABASE/LigandDisplayForward?ligandId=5. Ligand searches can be conducted using names, chemical identifiers and chemical structures (see, http://www.iuphar-db.org/DATABASE/chemSearch.jsp);
4. **New enzyme database:** We have created database pages for the 10 enzymes of the lanosterol biosynthesis pathway, including HMG CoA reductase (HMGCR), the target of the statin drugs used in the treatment of hypercholesterolaemia. The database now provides comprehensive information on the endogenous substrates, reaction mechanisms and recommended inhibitors of each enzyme, with appropriate background reading, an introductory review on the pathway and links to sources of further information online;
5. **Enhanced information on diseases:** The diagnosis, prevention and treatment of orphan and neglected diseases present a huge unmet medical need, representing an important emerging focus of drug discovery efforts by commercial and academic groups worldwide. We now collaborate with Dr Ségolène Aymé and her team at http://www.orpha.net, the database of the European Union Committee of Experts on Rare Diseases, to share information on the genetic and molecular bases of rare diseases and the actions of orphan drugs. We are creating reciprocal links between drug target and disease information in orpha.net (*e.g.* http://bit.ly/wqSbpp);
6. **Recent database page updates (Feb/March 2012):**

   GPCR updates:

   - GPCR pages that have been recently updated include: β-Adrenoceptors and Adrenoceptor introduction, Calcitonin receptors, Cannabinoid receptor introduction and

Orexin receptors;

- The Lysophospholipid receptors have been split into two families: Lysophospholipid (LPA) receptors and Lysophospholipid (S1P) receptors.

New annotation for LGICs:

- The GABAA subunits α3, α4, α5, β2, β3, γ1, γ2 and γ3 now have full annotation.

7. **New external database links:**
    - Links from receptor/channel pages to DrugBank target pages, giving information on approved drugs which act on them;
    - Links from ligand pages to the Human Metabolome Database - a public database containing detailed information about small molecule metabolites found in the human body;
    - Where available, links have been provided from GPCR, ion channel and NHR pages to genes in Orphanet, the Portal for Rare Diseases and Orphan Drugs. Receptor and ion channel pathophysiologies have been linked up to expert-curated disease information available in Orphanet;
    - Links from ligand pages to BindingDB - a public database of measured binding affinities, focusing mainly on proteins considered to be drug-targets and small, drug-like molecules;
    - The enzyme pages link to BRENDA, the Comprehensive Enzyme Information System, KEGG, the Kyoto Encyclopedia of Genes and Genomes, which contains pathway, gene and chemical information, and the IUBMB Enzyme Nomenclature database.

Future developments: IUPHAR-DB and Guide to PHARMACOLOGY

A priority in 2012 will be to complete the curation of guidetopharmacology.org giving access to both IUPHAR-DB and GRAC. *When the curation of data from the 5th Edition of GRAC is complete in July 2012, guidetopharmacology.org will contain quantitative pharmacological information on over half of the targets of current licensed drugs. Key articles on new areas (epigenetics, transporters, microRNAs, etc) will define the nomenclature, link to existing databases and also point out the practical difficulties of working in these fields.*

We believe that the creation of two complementary resources, consistent in content but different in focus, each carrying the authoritative backing of both IUPHAR and BPS, will be immensely valuable as tools to assist research in pharmacology and drug discovery, to educate the next generation of biomedical and clinical scientists and to provide the general public with accurate information on how drugs work.

In the future, we hope that combining the expertise of the separate – but overlapping - panels of experts who contribute to IUPHAR-DB and GRAC in a single coherent effort will enhance the value of both IUPHAR-DB and GRAC. If funding is forthcoming, our future aims are to:

- To provide quantitative pharmacological information on *all* of the (human) targets of current prescription medicines and other likely targets of future small molecule drugs;
- To establish, for each drug target, a “gold standard” set of recommended pharmacological tools. This will consist of commercially available, well-validated compounds with suitable properties for *in vivo/in vitro* work;
- To provide rigorous curation of the structure and nomenclature of the chemical substances in the resource, shared and refined in collaboration with other databases, as outlined above;
- To provide information on clinically used drugs in the resource.

We are also planning to set up an online NC-IUPHAR expert directory which will include profile pages for database contributors and facilities for community networking and discussion around items such as Hot Topics (issues of current interest in the general field).

4. Future directions for NC-IUPHAR

There are now major efforts ongoing to define the main variables in drug receptor interactions (Table 1). Thus recommendations on critical issues for pharmacology - biased signalling, receptor

heterodimers, epigenetic drug targets, miRs and transporter classifications, will be all addressed.

The multiple variables in drug-receptor interactions, shown in Table 1, are under evaluation by working groups and this will lead to a number of reports in the near future - about issues which are of crucial importance for pharmacology.

The clinical translational pharmacology group will discuss how to respond best to the wishes of our clinical colleagues and to translate activity at receptor sites to clinical activity.

Several exciting projects which have recently been initiated include the characterisation of the enzymes involved in epigenetics, transporters and receptor tyrosine kinases. Chairpersons have been appointed to form subcommittees to address these. A more recent consideration by NC-IUPHAR is the representation of antibodies (contacts with the antibody society) and miRNAs on IUPHAR-DB and Guide to PHARMACOLOGY, and discussions with the relevant experts are at an advanced stage. We have continuing contact with our traditional partners of the Human Genome Nomenclature Committee (HGNC), IUPAC and IUBMB: the initiative on miRs is joint between HGNC and NC-IUPHAR.

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

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 (eg 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)

5. Acknowledgements

We are very grateful to our sponsors. We are also immensely grateful for the work done by our colleagues on NC-IUPHAR and all the contributing chairs and subcommittees. It is a privilege to be associated with so much work freely given for the good of science.

We repeat that NC-IUPHAR is a global resource and all scientists are welcome to contribute (contact: curators@iuphar-db.org).

NC-IUPHAR REPORT – 2012

Appendix 1: NC-IUPHAR members

Chair
Michael Spedding, France

Vice Chairs

Anthony Davenport, UK	Chairman evolving pharmacology
Anthony Harmar, UK	Database Chairman
Richard Neubig, USA	GPCRs
Eliot Ohlstein, USA	Editor

Members
Steve Alexander, UK
Thomas Bonner, USA
Arthur Christopoulos, Australia
William Catterall, USA
Sir Colin Dollery, UK
Kozo Kaibuchi, Japan*
Yoshikatsu Kanai, Japan*
Vincent Laudet, France
John Peters, UK
Jean-Philippe Pin, France

Ex Officio

Patrick de Souich, Canada	IUPHAR President
Sam J. Enna, USA	IUPHAR Secretary General
Urs Ruegg, Switzerland	IUPHAR Treasurer
Matt Wright, UK	HGNC
Joanna Sharman, UK	database
Adam Pawson, UK	database
Helen Benson, UK	database

Past chairs (ex officio)
Paul Vanhoutte, Hong Kong
Bob Ruffolo, USA

Corresponding members
Michel Bouvier, Canada
Stephen Charlton, UK
Moses Chao, USA
Steven L. Colletti, USA
Graham Collingridge, UK
Sue Duckles, USA
Richard Eglen, UK
Steven Foord, UK
Allyn Howlett, USA
Franz Hofmann, Germany
Ad P. Ijzerman, The Netherlands
Michael F. Jarvis, USA
Terry Kenakin, USA
Janos Kiss, Hungary
Chris Langmead, UK
Ian McGrath, UK
Graeme Milligan, UK
Stefan Offermanns, Germany
Richard Olsen, USA
Graeme Semple, USA
David Searls, USA
Bart Staels, France

NC-IUPHAR REPORT – 2012

Huang Yu, Hong Kong

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

NC-IUPHAR REPORT – 2012

Appendix 2: Publications

NC-IUPHAR publications in *Pharmacological Reviews* (2011-2012)

Fredholm BB, Ijzerman AP, Jacobson KA, Linden J and Muller CE (2011) International Union of Basic and Clinical Pharmacology. LXXXI. Nomenclature and classification of adenosine receptors--an update. Pharmacol Rev 63:1-34.

Offermanns S, Colletti SL, Lovenberg TW, Semple G, Wise A and Ijzerman AP (2011) International Union of Basic and Clinical Pharmacology. LXXXII: Nomenclature and Classification of Hydroxy-carboxylic Acid Receptors (GPR81, GPR109A, and GPR109B). Pharmacol Rev. 2011 Jun;63(2):269-90.

Woodward DF, Jones RL, Narumiya S (2011) International Union of Basic and Clinical Pharmacology. LXXXIII: classification of prostanoid receptors, updating 15 years of progress. Pharmacol Rev. 2011 Sep;63(3):471-538.

Bäck M, Dahlén SE, Drazen JM, Evans JF, Serhan CN, Shimizu T, Yokomizo T, Rovati GE (2011) International Union of Basic and Clinical Pharmacology. LXXXIV: leukotriene receptor nomenclature, distribution, and pathophysiological functions. Pharmacol Rev. 2011 Sep;63(3):539-84.

Huang F, Wong X, Jan LY (2012) International Union of Basic and Clinical Pharmacology. LXXXV: calcium-activated chloride channels. Pharmacol Rev. 2012 Jan;64(1):1-15.

NC-IUPHAR reviews in the *British Journal of Pharmacology*

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. 2012 Jan 31. doi: 10.1111/j.1476-5381.2012.01871.x. [Epub ahead of print].

NC-IUPHAR publications in other journals

Collingridge GL, Pin JP, Hubbard RE, Kiss JP and Spedding M (2011) Introduction to the special issue on High Resolution Neuropharmacology. Neuropharmacology 60:1-2. (plus special issue, 20 articles)

Sharman JL, Mpamhanga CP, Spedding M, Germain P, Staels B, Dacquet C, Laudet V and Harmar AJ (2011) IUPHAR-DB: new receptors and tools for easy searching and visualization of pharmacological data. Nucleic Acids Res 39:D534-538.

Spedding M (2011) Resolution of controversies in drug/receptor interactions by protein structure. Limitations and pharmacological solutions. Neuropharmacology 60:3-6.

M Spedding, 21/3/2011.