2011 NC-IUPHAR / IUPHAR-DB Report

Michael Spedding, Eliot Ohlstein, Rick Neubig, and Tony Harmar

This year has seen a continuing evolution of NC-IUPHAR with a record number of publications; major enhancements to the IUPHAR database (IUPHAR-DB: www.iuphar-db.org) and encouraging steps towards financial security despite a very difficult environment.

In a major new partnership, IUPHAR are joining forces with the British Pharmacological Society to support the development of a single world-class website providing access to dynamically updated, searchable versions of IUPHAR-DB and the BPS *Guide to Receptors and Channels* (GRAC). BPS and IUPHAR will underwrite equal shares of the costs of the project, which will involve close collaboration between the editors of GRAC, NC-IUPHAR and the IUPHAR-DB team at the University of Edinburgh (headed by Tony Harmar). As always, we depend on sponsorship to deliver IUPHAR's financial contribution to the project; recent donations from Servier, GlaxoSmithKline and from an anonymous benefactor are very gratefully acknowledged.

1. Organisation.

The committee of NC-IUPHAR has been revised (see appendix). The Editors of GRAC are already full members of NC-IUPHAR and play a full role in the work of that committee.

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. There will be a discussion on this at the next NC-IUPHAR meeting with the president of IUPHAR.

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 part of the database with email alerts.

Subcommittee chairs propose a list of experts, ratified by NC-IUPHAR, to ensure adequate representation of the field. The chairman 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 subcommittee meets to establish consensus on classification, and to ensure that the NC-IUPHAR guidelines are complied with. NC-IUPHAR benefits from a privileged relationship with ASPET and core publications appear in *Pharmacological Reviews*.

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2. Publications.

A record number of publications has appeared in *Pharmacological Reviews*, reflecting the activity, generally, of NC-IUPHAR and specifically, the dedication and efficiency of the editor, Eliot Ohlstein. The publications are listed in appendix 1.

3. Meetings and Symposia.

WorldPharma2010.

NC-IUPHAR organised a Workshop *"Translating the human genome: from orphan G-protein coupled receptors to novel therapeutic targets"*, chaired by Anthony Davenport and Michael Spedding. Topics included receptors for apelin, relaxin and trace amines, together with a talk on GPR3, an orphan GPCR modulating amyloid secretion in Alzheimer's disease. Focused conferences co-organised by NC-IUPHAR members included *"Nuclear receptor targets for treatment of diseases"* (Bart Staels and Vincent Laudet), *"Ion channelopathies: New windows on complex disease and therapy"* (Bill Catterall) and *"G protein-coupled 7TM receptors: From molecular to physiological function"* (Brian Kobilka and Jean-Philippe Pin). Roger Pertwee and Allyn Howlett (Chairs of the NC-IUPHAR Subcommittee on Cannabinoid Receptor Nomenclature) were co-organisers of the 20th Annual Symposium of the International Cannabinoid Research Society, held as a satellite meeting of WorldPharma2010 in Lund, Sweden from 24th – 27th July.

20th Neuropharmacology Conference.

This conference entitled "High Resolution Neuropharmacology: Structure Changes the Paradigm" was a joint venture between Neuropharmacology and NC-IUPHAR held in San Diego on 10th - 12th November 2010 as a satellite to the 2010 meeting of the Society for Neuroscience. The theme of the meeting was to highlight how emerging structural data are providing new insights into the molecular properties of receptors, ion channels and transporters, revolutionizing pharmacological concepts, and leading to new ideas of drug discovery and development. The proceedings of the conference were published as a special issue (21 articles) of *Neuropharmacology,* edited by the organising committee.

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4. The IUPHAR database: IUPHAR-DB (www.iuphar-db.org).

IUPHAR-DB now covers 616 human and rodent drug targets from four protein families: G protein-coupled receptors (GPCRs), voltage-and ligand-gated ion channels (VGICs and LGICs) and, in a recent addition, 49 nuclear hormone receptors (NHRs). IUPHAR-DB now receives over 125,000 visits from about 160 countries each year.

Recent enhancements

A summary of recent improvements to IUPHAR-DB has been published in Nucleic Acids Research (see Sharman *et al* reference in the Appendix). Significant progress has been made in the gene coverage, ligand presentation and database searchability. Receptors are now linked to 3D structural information on the Protein Data Bank. A few receptor pages are still awaiting completion; placeholders containing basic information are provided (please contact us if you can help with annotation). Ligand molecules now have dedicated data pages displaying structural information, electronic descriptors, physico-chemical properties, systematic names, biological activity, lists of similar compounds and links to other databases such as DrugBank, ChEMBL and PDB. 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*).*

A "traffic-light" system has been introduced to allow curators and contributors to easily keep track of the receptor annotation status and to encourage our audience to get involved in the curation process. Databases linked to from genes in IUPHAR-DB now include InterPro (protein sequence analysis and classification), TreeFam (a database of phylogenetic trees of animal genes) and data on mouse phenotypes, alleles and disease models from MGI (http://www.informatics.jax.org/).

GPCR pages recently updated include

- The Hydroxycarboxylic acid (HCA) family of receptors (formerly called the Nicotinic acid receptor family)
- The Lysophospholipid (LPA and S1P) receptors (awaiting final review)
- The Frizzled family receptors FZD3 and FZD4
- Pages for several orphan GPCRs, including GPR39, LPAR6, GPR35, GPR87 and P2RY10.
- Graphs of GPCR gene expression in mouse tissues adapted from Regard et al. (2008). Cell, 135(3): 561-71 have been added for all GPCRs.

Work on **Ligand-Gated ion Channels**, following the complete classification/ nomenclature system published by Collingridge *et al* (2009b) is underway. The classification system, introduced at a very well attended conference cohosted with *Neuropharmacology*, has now been cited >100 times in the two years since publication.

- Annotation of 5-HT_3 receptors, glycine receptors and ZAC is complete
- The Ionotropic glutamate ligand-gated ion channel subunits have been added to the database with nomenclature and database links; full annotation is provided for the GluA2 subunit
- Annotation of several ligand-gated ion channel subunits, including the δ, ε, θ and π GABAA subunits and the P2X7 subunit, is complete, with more to follow soon.

Future developments in IUPHAR-DB

A priority in 2011 will be to create the web portal giving access to both GRAC and IUPHAR-DB. 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 GRAC and IUPHAR-DB in a single coherent effort will enhance the value of both IUPHAR-DB and GRAC. For example, we hope to introduce an expert recommended “gold-standard” set of ligands for each drug target. This will consist of commercially available, well-validated compounds with suitable properties for in vivo/in vitro work. 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).

5. Future directions for NC-IUPHAR.

The next meeting (agenda attached) shows how scientifically dynamic NC-IUPHAR is. There are 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, 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.

NC-IUPHAR and HGNC collaborate on the nomenclature and are making databases of all the human genes encoding receptors and other drug targets. Furthermore we plan to assess all the “druggable genome” in an effort to provide real support to innovative drug discovery throughout the world.

Projects which are under consideration include characterisation of receptors linked to tyrosine kinase and cytokine receptors, but even though NC-IUPHAR is a very

flexible organisation, ambitious projects require funding and project completion is also dependent on this.

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)

6. 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 done uniquely for the good of science.

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Appendix 1.

NC-IUPHAR publications in *Pharmacological Reviews* (2009-2011)

Chun J, Hla T, Lynch KR, Spiegel S and Moolenaar WH (2010) International Union of Basic and Clinical Pharmacology. LXXVIII. Lysophospholipid receptor nomenclature. Pharmacol Rev 62:579-587.

Dubocovich ML, Delagrange P, Krause DN, Sugden D, Cardinali DP and Olcese J (2010) International Union of Basic and Clinical Pharmacology. LXXV. Nomenclature, classification, and pharmacology of G protein-coupled melatonin receptors. Pharmacol Rev 62:343-380.

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.

Kirby HR, Maguire JJ, Colledge WH and Davenport AP (2010) International Union of Basic and Clinical Pharmacology. LXXVII. Kisspeptin receptor nomenclature, distribution, and function. Pharmacol Rev 62:565-578.

Maguire JJ, Parker WA, Foord SM, Bonner TI, Neubig RR and Davenport AP (2009) International Union of Pharmacology. LXXII. Recommendations for trace amine receptor nomenclature. Pharmacol Rev 61:1-8.

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 [Epub ahead of print Mar 31 2011]

Pertwee RG, Howlett AC, Abood ME, Alexander SP, Di Marzo V, Elphick MR, Greasley PJ, Hansen HS, Kunos G, Mackie K, Mechoulam R and Ross RA (2010) International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB and CB. Pharmacol Rev 62:588-631.

Pitkin SL, Maguire JJ, Bonner TI and Davenport AP (2010) International Union of Basic and Clinical Pharmacology. LXXIV. Apelin receptor nomenclature, distribution, pharmacology, and function. Pharmacol Rev 62:331-342.

Schulte G (2010) International Union of Basic and Clinical Pharmacology. LXXX. The class Frizzled receptors. Pharmacol Rev 62:632-667.

Wu LJ, Sweet TB and Clapham DE (2010) International Union of Basic and Clinical Pharmacology. LXXVI. Current progress in the mammalian TRP ion channel family. Pharmacol Rev 62:381-404.

Ye RD, Boulay F, Wang JM, Dahlgren C, Gerard C, Parmentier M, Serhan CN and Murphy PM (2009) International Union of Basic and Clinical Pharmacology. LXXIII. Nomenclature for the formyl peptide receptor (FPR) family. Pharmacol Rev 61:119-161.

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NC-IUPHAR publications in other journals

Collingridge GL, Olsen R, Peters JA and Spedding M (2009a) Ligand gated ion channels. Neuropharmacology 56:1.

Collingridge GL, Olsen RW, Peters J and Spedding M (2009b) A nomenclature for ligand-gated ion channels. Neuropharmacology 56:2-5.

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.

Harmar AJ, Hills RA, Rosser EM, Jones M, Buneman OP, Dunbar DR, Greenhill SD, Hale VA, Sharman JL, Bonner TI, Catterall WA, Davenport AP, Delagrange P, Dollery CT, Foord SM, Gutman GA, Laudet V, Neubig RR, Ohlstein EH, Olsen RW, Peters J, Pin JP, Ruffolo RR, Searls DB, Wright MW and Spedding M (2009) IUPHAR-DB: the IUPHAR database of G protein-coupled receptors and ion channels. Nucleic Acids Res 37:D680-685.

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.

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Appendix 2. NC-IUPHAR members.

Chair:

Michael Spedding, France

Vice Chairs:

Anthony Harmar, UK	Chairman database, IUPHAR-DB
Eliot Ohlstein, USA	Editor
Anthony Davenport, UK	Chairman evolving pharmacology
Richard Neubig, USA	GPCRs

Members

Steve Alexander, UK	Thomas Bonner, USA
William Catterall, USA	Sir Colin Dollery, UK
Pierre Germain, France	Vincent Laudet, France
Alistair Mathie, UK	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
Chido Mpamhanga, UK	database
Joanna Sharman, UK	database

Past chairs (ex officio)

Paul Vanhoutte, Hong Kong
Bob Ruffolo, USA

Corresponding members

Michel Bouvier, Canada	Stephen Charlton, UK
Moses Chao, USA	Arthur Christopoulos, Australia
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
Ian McGrath, UK	Janos Kiss, Hungary
Chris Langmead, UK	Graeme Milligan, UK
Stefan Offermanns, Germany	Richard Olsen, USA
Graeme Semple, USA	David Searls, USA
Michael A. Trevethick, UK	Alan Wise, UK
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