NC-IUPHAR

Annual Report

2012/13

IUPHAR

International Union of Basic and Clinical Pharmacology

Introduction

The 1st November 2012 was an exciting day for NC-IUPHAR, the IUPHAR database (IUPHAR-DB: http://www.iuphar-db.org) and British Pharmacological Society (BPS) *Guide to Receptors and Channel*s (GRAC) teams, since it marked the start of three years funding for our projects from the Wellcome Trust, 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 NC-IUPHAR/BPS Guide to PHARMACOLOGY web portal (http://www.guidetopharmacology.org).

The past year has seen the continuing evolution of NC-IUPHAR, along with major enhancements to IUPHAR-DB and the ongoing development of the Guide to PHARMACOLOGY.

The Guide to PHARMACOLOGY was officially launched in December 2011, and updated again in July 2012, and now includes pages on catalytic receptors, enzymes and transporters, adding to existing data on GPCRs, ion channels and nuclear hormone receptors. This marked the completion of constructing the database version of GRAC (GRAC-DB), the first milestone in the development of the Guide to PHARMACOLOGY.

We are now working towards integrating IUPHAR-DB and GRAC-DB into a single database to provide two levels of detail of the data and information on drug targets in the form of; (i) condensed overviews, and (ii) expanded coverage.

Future directions for NC-IUPHAR

NC-IUPHAR are developing a knowledge environment that will 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 scientific literature. It will be a valuable tool for basic and clinical scientists seeking new approaches for drug discovery research, and the diagnosis and treatment of disease, and a valuable teaching resource for students of pharmacology and translational medicine.

There continues to be major efforts to define the main variables in drug/receptor interactions including the parameters that can lead to variation in receptor function and pharmacology (i.e. biased signalling, splice variation, hetero-oligomerisation, allosteric modulation, post-translational modification, linkage to multiple signalling cascades). These areas are of great interest because they may considerably expand the repertoire of potential targets for drug development, and are under evaluation by working groups, which will lead to a number of reports about issues which are of crucial importance for pharmacology.

Several exciting projects which have been initiated in the past two years, and these are at various stages of advancement. These including the characterisation of the enzymes involved in epigenetics (*e.g.* histone-modifying enzymes), as well as transporters and non-coding RNAs (inititaive with HGNC and miRBase). Subcommittees formed to address these and 'statement-of-intent' articles have been commissioned for publication in *British Journal of Pharmacology*.

More recent considerations by NC-IUPHAR are the representation of antibodies (contacts with the Antibody Society), the full annotation of pattern recognition receptors, secreted phospholipase A2 enzymes, guanylyl cyclases and phosphodiesterases (all of which are already outlined in GRAC) in IUPHAR-DB, and discussions with the relevant experts are now at an advanced stage. We are exploring new ways of creating meetings with experts to define the key therapeutic targets.

An important new direction is accompanying the new IUPHAR Immunopharmacology Section and defining the immunological/inflammatory targets in disease states, with their main pharmacology.

A major new undertaking is to provide an integrated educational component within the Guide to PHARMACOLOGY with access to high quality training in the principles and techniques of basic and clinical pharmacology. Endorsable online e-learning courses relevant to pharmacologists will be identified, and linked-through to (*e.g.* Coursera, Udacity, edX, Saylor.org, and others). Interactions with BPS (Prescribe and pharma-CAL-ogy) and ASPET are also being explored. Using 'mashups' (a combination/remix of aspects two or more teaching sources that have been integrated into one source) packages of pharmacology-related e-learning will be defined (*e.g.* bioinformatics, data mining, statistics, neuropharmacology), and tailored for specific groups of users of the Guide to PHARMACOLOGY (*e.g.* chemists, physiologists).

Organisation

Core committee

The core committee of NC-IUPHAR has been revised (see Appendix I) with the inclusion of Doriano Fabbro, Switzerland as a core member. The biannual core NC-IUPHAR meetings are now themed and we have established an alliance with the Japanese Pharmacology Society who pay the travel for two members*, but who are invited according to the meeting themes.

Corresponding Members

In order to broaden the expertise of the core committee, the number of corresponding members (see Appendix I) has been further increased, to include Susan Amara (Director, NIMH), Debbie Hay (University of Auckland), Helgi Schiöth (Uppsala University) and Mary Vore (University of Kentucky). Corresponding members attend selected meetings of NC-IUPHAR and include representatives of the major pharma companies.

Evolving Pharmacology Group

Anthony Davenport leads a group (see Appendix I) 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.

Clinical Translational Pharmacology Group

In order to provide advice on the translational aspects of receptor pharmacology, a subgroup (see Appendix I) of clinical pharmacologists (core member, Sir Colin Dollery) discuss how best to respond to the wishes of our clinical colleagues and to translate activity at drug target sites to clinical activity.

Subcommittees

Chairpersons (see Appendix II) 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.

Publications and Outreach

Recent publications

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*.

Four NC-IUPHAR nomenclature articles (see Appendix III) have appeared in *Pharmacological Reviews* (Editor, Eliot Ohlstein) so far during the 2012/13 period, reflecting the activity of NC-IUPHAR. In addition, the second NC-IUPHAR commissioned review for the *British Journal of Pharmacology* (Editor-in-Chief, Ian McGrath) has recently been published by Terry Kenakin, entitled "New concepts in pharmacological efficacy at 7TM receptors: IUPHAR Review 2".

Newsletter

The biannual NC-IUPHAR newsletter had a major makeover and was distributed in the first week of November 2012, through a mailing list (using MailChimp - Email Marketing and Email List Manager software) comprising all IUPHAR member societies, NC-IUPHAR subcommittees and collaborators, pharmacology departments worldwide, and database users who have signed-up to receive news alerts; and was made available for download from the IUPHAR Database and Guide to PHARMACOLOGY homepages. The newsletter was also advertised on social media and the RSS feed.

Representation of NC-IUPHAR at conferences and meetings

The activities of NC-IUPHAR have been promoted by NC-IUPHAR representatives at the following conferences and meetings during the past year:

- Edinburgh Neuroscience, Edinburgh, March 2012;
- BPS Focused Meeting on Neuropeptides, London, June 2012;
- Physiology 2012 (The Physiological Society), Edinburgh, July 2012;
- Neuroscience 2012 (Society for Neuroscience), New Orleans, October 2012;
- BPS Winter meeting, London, December 2012.

Upcoming:

- Joint FEBS/Biochemical Society Focused Meeting; Exploring kinomes: pseudokinases and beyond, Cambridge, March 2013;
- The 6th International Biocuration Conference (International Society for Biocuration), Cambridge, April 2013.

Wikipedia pages

The Wikipedia pages for IUPHAR-DB and the Guide to PHARMACOLOGY have been created and updated.

Social media

Twitter and Facebook pages for IUPHAR-DB and the Guide to PHARMACOLOGY have been created, and include regular features, news and topical papers.

The IUPHAR Database (IUPHAR-DB) and the Guide to PHARMACOLOGY web portal

The IUPHAR 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 their rodent orthologues, and over 3250 bioactive molecules (endogenous ligands, licensed drugs and key pharmacological tools) that interact with them. The enzyme section of the database is being developed and currently includes the 10 enzymes of the lanosterol biosynthesis pathway (a pilot curation exercise), and more recently the full complement of protein kinases (see below). The database now receives over 135,000 visits from about 160 countries each year. The database is run by one full-time database developer, three full-time curators and one part-time project administrator, supervised by the database chair Professor Tony Harmar, all based in Edinburgh

A summary of recent improvements to IUPHAR-DB has been published in Nucleic Acids Research (see Sharman *et al.* 2013 reference in Appendix III).

Recent enhancements and updates

1. **Development of the kinase section of the database:** We recently expanded the information available on enzyme drug targets, including the addition of >500 protein kinases and quantitative data on their interactions with 72 approved drugs and experimental inhibitors. Quantitative data was provided by DiscoveRx and was derived using their KINOME*scan*® platform.
2. **Curation of the Class A Orphan GPCRs:** Full annotation for Class A orphan GPCRs by two undergraduate students was completed during an 8-week summer project, interrogating the literature on Class A orphan receptors and uploading information to the database pages; the Evolving Pharmacology Group has prepared an IUPHAR update article on the status of the Orphan GPCRs and recommendations for new pairings with cognate ligands, which has been accepted for publication in *Pharmacological Reviews* (see Appendix III);
3. **Curation of the Adhesion GPCRs (Class B Orphans):** Representatives of the Adhesion GPCR consortium, coordinated by Helgi Schiöth, have undertaken the full annotation of all the Adhesion GPCRs in IUPHAR-DB;
4. **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;
5. **Enhancements to ligand pages:** addition of International Non-Proprietary Names and clinical information for approved drugs and creation of an abbreviated name field;
6. **Ligand lists updates:**
   - The Ligand Lists now includes separate lists of 'Endogenous Peptides' (known to be encoded by genes in human, mouse and rat) and a list of 'Other Peptides' (encoded by genes in other species or synthetically derived);
   - The category 'Small organics' has been renamed 'Metabolites' to better reflect its content. This category includes organic molecules produced by the life processes of animals, such as (non-peptide) hormones and neurotransmitters, and their close analogues;
   - The 'abbreviated name' field from the ligand pages also appears as a field in the ligand list, therefore providing an 'at-a-glance' view for users who are experts in particular field when viewing the list.
7. **PubChem interaction:** make IUPHAR-DB and GRAC data available through PubChem and exploring methods for enhanced display, including a hierarchical classification of targets

with NC-IUPHAR nomenclature, which would make the data easier to navigate and give them a greater presence on PubChem pages;

8. **Database page updates (2012/13):** β-Adrenoceptors, Calcitonin receptors, Cannabinoid receptors, Orexin receptors, $GABA_B$, GnRH, Neuropeptide FF/AF, Neurotensin, Parathyroid hormone; Platelet-activating, Vasopressin and Oxytocin; Complement peptide, somatostatin receptor 2, Tachykinin, Neuromedin U, Adenosine, Hydroxycarboxylic, Thyropin-releasing hormone, Parathyroid hormone, Prostanoid, Neuropeptide S, formyl peptide receptor 1, trace amine receptor 1;
9. **New external database links and collaborations:**
    - DrugBank - Links from receptor/channel pages to DrugBank target pages, giving information on approved drugs which act on them;
    - HMDB - Links from ligand pages to the Human Metabolome Database - a public database containing detailed information about small molecule metabolites found in the human body;
    - Orphanet - 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;
    - BindingDB - 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;
    - Updated links from NCBI databases PubMed, Entrez Gene, Protein and Nucleotide to IUPHAR-DB and new links added from NCBI to Guide to PHARMACOLOGY/GRAC;
    - PubChem - In the second phase of our collaboration with PubChem we have uploaded bioactivity data for all 5-HT GPCRs to PubChem. We are working with the PubChem team to add information on NC-IUPHAR classifications, which will allow the searching of data by target and action, and the NC-IUPHAR classification will also be prominently displayed on PubChem compound pages;
    - HPRD - The Human Protein Reference Database (HPRD) depicts information on human protein functions including protein–protein interactions, post-translational modifications, enzyme-substrate relationships and disease associations;
    - PhosphoSitePlus - PhosphoSitePlus is a database of observed post-translational modifications in human and mouse proteins;
    - GUDMAP - The GenitoUrinary Development Molecular Anatomy Project (GUDMAP) is an international consortium working to generate gene expression data and transgenic mice. GUDMAP includes data from large-scale in situ hybridisation screens (wholemount and section) and microarray gene expression data of microdissected, laser-captured and FACS-sorted components of the developing mouse genitourinary system.

Current and future work

With the Wellcome funding, our aims over the next three years 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 currently working on a new navigation scheme for all the new targets that will be included in the resource, and have established the priority list of targets to curate (*i.e.* the targets of prescription medicines).

Beginning with the ~20 registered protein kinase inhibitors, we will also be including clinical data for these drugs in the resource.

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; enquiries@guidetopharmacology.org).

Appendix I: 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
William Catterall, USA
Arthur Christopoulos, Australia
Sir Colin Dollery, UK
Doriano Fabbro, Switzerland
Kozo Kaibuchi, Japan*
Yoshikatsu Kanai, Japan*
Vincent Laudet, France
John Peters, UK
Jean-Philippe Pin, France

Ex Officio
Patrick du Souich, Canada (Clinical) (IUPHAR President)
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, Hong Kong
Bob Ruffolo, USA

Corresponding Members
Susan Amara, USA
Michel Bouvier, Canada
Stephen Charlton, UK
Moses Chao, USA
Steven Colletti, USA
Graham Collingridge, UK
Sue Duckles, USA
Richard Eglen, UK
Steven Foord, UK
Debbie Hay, New Zealand
Yu Huang, Hong Kong
Allyn Howlett, USA
Franz Hofmann, Germany
Ad Ijzerman, The Netherlands
Michael Jarvis, USA
Terry Kenakin, USA
Janos Kiss, Hungary
Chris Langmead, Australia
Alistair Mathie, UK
Ian McGrath, UK
Graeme Milligan, UK
Stefan Offermanns, Germany
Richard Olsen, USA
Helgi Schiöth, Sweden
Graeme Semple, USA
David Searls, USA
Bart Staels, France
Mary Vore, 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

Appendix II: Subcommittee chairs

G protein-coupled receptors

5-Hydroxytryptamine: Nick Barnes, John Neumaier
$alpha_1$-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-Louis Nahon
Metabotropic glutamate: Jean-Philippe Pin
Neuropeptide FF/neuropeptide AF: Jean-Marie Zajac
Neuropeptide Y: Dan Larhammar
Orexin: Christopher Winrow
Peptide P518: Jerome Leprince
Prolactin-releasing peptide: Helgi Schiöth
Relaxin family peptide: Roger Summers
Tachykinin: Susan Leeman, Steven Douglas
Urotensin: Hubert Vaudry

Acetylcholine (muscarinic): Arthur Christopoulos
$alpha_2$-adrenoceptors: Lutz Hein
beta-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: Girolamo Calo
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

GRAC Editors

Stephen Alexander, Anthony Harmar, John Peters

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
In revision

Epigenetics
Rabinder Prinjha

Tyrosine Kinase Receptors
Doriano Fabbro

MicroRNAs
Matt Wright

Transporters
Stephen Alexander

Appendix III: Publications

NC-IUPHAR publications in *Pharmacological Reviews* (2012/13)

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

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.

Klos A, Wende E, Wareham KJ, Monk PN. (2013) International Union of Pharmacology. LXXXVII. Complement Peptide C5a, C4a, and C3a Receptors. Pharmacol Rev. 65: 500-543.

Davenport AP, Alexander SPH, Sharman JL, Pawson AJ, Benson HE, Monaghan AE, Liew WC, Mpamhanga CP, Bonner TI, Neubig RR, Pin JP, Spedding M, and Harmar AJ. (2013) International Union of Basic and Clinical Pharmacology. XXX. G-protein coupled receptor list: recommendations for new pairings with cognate ligands. Pharmacol Rev, *In press.*

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

Kenakin T. (2013) New concepts in pharmacological efficacy at 7TM receptors: IUPHAR Review 2. Br J Pharmacol. 168: 554-75.

NC-IUPHAR publications in other journals

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).

Sharman JL, Benson HE, Pawson AJ, Lukito V, Mpamhanga CP, Bombail V, Davenport AP, Peters JA, Spedding M, Harmar AJ, and NC-IUPHAR. (2013) IUPHAR-DB: updated database content and new features. Nucl. Acids Res. 41 (Database Issue): D1083-8.