

## CHALLENGES FOR PHARMACOLOGY

### NC-IUPHAR, 2007+

The International Union of Pharmacology Committee on Receptor Nomenclature and Drug Classification (NC-IUPHAR, composition in appendix) has the mission of:

- 1. issuing guidelines for receptor and ion channel classification, and addressing the main issues in pharmacology today,*
- 2. classifying the major receptor and ion channel systems,*
- 3. facilitating the interface between the discovery of new sequences from the Human Genome Project and the designation of the derived proteins as functional receptors and ion channels – also designating the receptor polymorphisms which are functionally important,*
- 4. setting up a website with access to data on all known receptor systems, freely available to all scientists, anywhere in the world.*

Pharmacology is at a crucial point because we have access to sequences for almost all of the receptors in the human genome. This is a unique opportunity to make a rare definitive scientific statement because the task of annotating sequence for function is the work of pharmacologists. Receptors are the site of action for many of the currently available drugs and the absolute definition of the majority of the receptors in genome is now possible. Furthermore, pharmacology, the study of the interaction of chemical substances with living organisms, is at a key point, with a constant search for new drugs – but also with increasing awareness of what harm some chemicals can do to our environment.

We list all the G protein-coupled receptors, voltage-gated ion channels, nuclear receptors, and, shortly, ligand-gated ion channels which are known to be in the human genome, with data on their rat and mouse homologues, where relevant. This database lists the main pharmacology associated with these proteins, as proposed by our subcommittees.

NC-IUPHAR has established close links with the Human Genome Organisation (HGNC), which attributes gene names; the International Union of Pure and Applied Chemistry (IUPAC), to standardise correct use of drug names; and the International Union of Biochemistry and Molecular Biology (IUBMB) to collaborate on receptor-related enzyme nomenclature.

However, we also need YOU (!) to give us feedback, interactions and potential new directions. NC-IUPHAR has limited funds, and is made up of busy scientists who give up their free time to perform their work in the committee or the expert receptor subcommittees. It is not an elite club, but a group of dedicated individuals who believe in pharmacology – we welcome all contributions (contact the chairman: [michael.spedding@fr.netgrs.com](mailto:michael.spedding@fr.netgrs.com) or the database chair: [Tony.Harmar@ed.ac.uk](mailto:Tony.Harmar@ed.ac.uk), or for the USA: [eliot@venuvics.com](mailto:eliot@venuvics.com)).

## **CURRENT STRATEGY**

NC-IUPHAR now comprises >60 subcommittees on receptor and ion channel nomenclature and each subcommittee comprises between 6–20 international experts. The plethora of new targets means that now we may invite single scientists to contribute to receptors for which there is sufficient evidence to indicate a genuine receptor, but where the classification of this receptor is not controversial. Important new initiatives are addressed by working groups, which explore and develop possible future directions for the committee, and for receptor pharmacology. For example, the possibility that different receptors may form heterodimers may markedly change the pharmacology of a given class of compounds – but how real are the changes? What criteria must be fulfilled to show that the changes exist? A group of experts (chair – J-P Pin) has reviewed the subject and issued guidelines (Jean-Philippe Pin, Richard Neubig, Michel Bouvier, Lakshmi Devi, Marta Filizola, Jonathan A. Javitch, Martin J. Lohse, Graeme Milligan, Krzysztof Palczewski, Marc Parmentier, Michael Spedding. (2007). International Union of Basic and Clinical Pharmacology. Recommendations for the recognition and nomenclature of G protein-coupled receptor heteromultimers. *Pharmacological Reviews*. 59 5-13).

A high priority for NC-IUPHAR has been the complex issue of nomenclature for the plethora of multi-subunit receptors and ion channels. An entire issue of *Pharmacological Reviews*, edited by Bill Catterall, George Chandy and George Gutman, addressed the challenges for the nomenclature of the **voltage-gated ion channels** and breaks new ground in resolving old difficulties. The NC-IUPHAR subcommittees have proposed nomenclature for the major ion channel families which is, for the most part, consistent with the recommendations for receptor nomenclature. **Ligand-gated ion channels** will be fully classified by the end of 2008.

The list of non-sensory 7-transmembrane receptors (7-TMRs) in the human genome, divided into their main structural classes designated by Steve Foord, is a major step forward, as we consider that there will be few other structurally-related receptors left to discover. Gordon Shepherd is maintaining a database of all the sensory 7-TMRs. An evolving pharmacology committee has been formed, chaired by Anthony Davenport, to ascribe changes in the status of 7-TM receptors (orphan receptors).

By the end of 2008 we also expect to complete the database on the 48 **nuclear hormone receptors**. Dr. Vincent Laudet has overseen the work on nuclear hormone receptors and edited a compendium on nuclear hormone receptors which was distributed to all participants at the 15th World Congress of Pharmacology (IUPHAR 2006) in Beijing. It was published in *Pharmacological Reviews* at the end of 2006 and will form the basis of the database. We need to adapt the database to this compendium and then revalidate the templates and articles with the authors.

Resources are limited and we have had to prioritise our activities. We have not yet achieved a classification of **receptors linked to tyrosine kinase** (TKRs), and this can only be started after 2007, although contributions are welcome.

## **ORIGINS OF NC-IUPHAR**

The mission for NC-IUPHAR was initiated in 1987 at the Xth International Congress of Pharmacology, with Sir Colin Dollery playing a role in the initiation. In 1989, the

Executive Committee of IUPHAR named Paul Vanhoutte (France) as chairman of a revised and enlarged committee. This committee energetically expanded its activities and the number of subcommittees (to 33), eventually producing the first official compendium on the occasion of the XIIIth International Congress of Pharmacology at Munich in 1998. Paul Vanhoutte was elected president of IUPHAR in 2002, and Robert Ruffolo (USA) was chairman of NC-IUPHAR from 1998-2002 with Michael Spedding as secretary, who became chairman from 2002. Anthony Harmar has driven the database, which is localised in Edinburgh.

## **MEMBERSHIP**

The current membership of NC-IUPHAR is listed in Table 1. The Committee comprises researchers who have established reputations in the field of research on receptors and ion channels, in a range of disciplines from molecular biology, signal transduction, electrophysiology, structure–activity relationships, to drug discovery and development. Each member is a liaison officer with a group of activities. NC-IUPHAR meets every six months. At each meeting there is a particular theme (ion channel classification, receptor databases etc.) and a review of the progress of the various subcommittees. Individual members of NC-IUPHAR liaise with the subcommittees, communicating general recommendations from the committee and reporting back on proposed changes in nomenclature, or on the discovery of new receptors.

## **SUBCOMMITTEES**

Subcommittees are established to provide receptor classification for a particular family of receptor and attempt to bring consensus amongst the experts in the field. Subcommittee chairs are asked to propose a list of experts, embracing a wide range of different disciplines. The composition of the subcommittee, both initially and for any changes in membership, must be ratified by NC-IUPHAR to ensure adequate representation of the field. The chairman of each subcommittee plays a critical role coordinating the actions of the subcommittee, organising meetings and finalising documents. The subcommittee meets to establish consensus on classification, and to

ensure that the NC-IUPHAR guidelines are complied with. We are very grateful for their activities!

## **PUBLICATIONS**

The recommendations of the various subcommittees are published as definitive articles in *Pharmacological Reviews*, after ratification by NCIUPHAR, and revisions appear in the compendia. Occasionally, editorials in other specialist journals are published to ensure widespread dissemination of the propositions. Eliot Ohlstein has been appointed editor for NC-IUPHAR.

In the past, NC-IUPHAR has also convened the editors of the major pharmacology journals in order to communicate its recommendations and assess the feedback from the various NC-IUPHAR user-groups.

## **THE IUPHAR RECEPTOR DATABASE**

The IUPHAR Receptor Database has been developed initially from funds from an educational grant from Incyte Genomics, and subsequently from ICSU. The database was housed at the European Bioinformatics Institute, where it was developed through an academic collaboration with SWISS-PROT. The database is now independently maintained at the University of Edinburgh (Pr. A. Harmar; curators V. Hale and J. Sharman), using servers in the Centre for Bioinformatics (Director: Prof. Igor Goryanin). The database is now maintained by a joint initiative with the British Pharmacological Society.

## **Partnership between NC-IUPHAR and the BPS**

The British Pharmacological Society (BPS) has generously agreed to support the IUPHAR receptor database, and data will also be available for the BPS Guide to Receptors and Channels (GRAC), which are very different but very complementary products. Respectively, they represent a detailed online resource and a compact

desktop reference of key information on drug targets. However, similar working methods are used to obtain information from a network of international experts, which will be combined. The Edinburgh Office has experience in researching the literature, liaising with contributors and distilling information from the database into succinct summaries as used in GRAC and in our compendia published in Pharmacological Reviews (for an example page, see appendix). Thus there will be significant advantages to the BPS and NC-IUPHAR if the team in Edinburgh works on behalf of both organisations, with joint goals. In this respect, John Peters is both an editor of GRAC and a member of NC-IUPHAR. Support of £40,000 pa will pay for more than half of the Edinburgh costs.

### **Partnership between NC-IUPHAR and ASPET**

ASPET has been a continual supporter and has made major contributions to IUPHAR's activities over many years. ASPET (Pharmacological Reviews) has published IUPHAR's articles and the last two compendia on voltage-gated ion channels and nuclear receptors. The chairman wishes to acknowledge the dedication of the Pharmacological Reviews staff during these processes, where many articles were finalised in a very short time.

It is exciting that, following the publication of the first draft of the sequence of the human genome, pharmacology should be in such a pivotal position in designating function to so many genomic sequences. Furthermore, the multitude of factors between a published genomic sequence and an assigned receptor function in a given tissue (epigenomics, alternative splicing, messenger RNA editing, polymorphisms, the combinatorial nature of subunit association) ensures that it is unlikely that the work of NC-IUPHAR will diminish. NC-IUPHAR needs input with motivated scientists interested in receptors, so if you are interested please contact us!

Michael Spedding, chair  
Anthony Harmar  
Eliot Ohlstein  
Anthony Davenport

## NC-IUPHAR – MEMBERS

### ***Chair:***

Michael Spedding

### ***Vice chairs:***

Anthony Harmar – database chairman

Eliot Ohlstein

Anthony Davenport

### ***Members:***

Tom Bonner

William Catterall

Philippe Delagrance

Sir Colin Dollery

Steve Foord

Pierre Germain

Vincent Laudet

Rick Neubig

Eliot Ohlstein

Graeme Milligan

John Peters

Jean-Philippe Pin

David Searls

Valerie Hale and Joanna Sharman - receptor curators

Matthew Wright – representative from HGNC

### ***Ex officio members:***

Sue Duckles, IUPHAR president

Sam Enna, IUPHAR Secretary General

Urs Rugg, IUPHAR treasurer

### ***Past chairs:***

Paul Vanhoutte

Bob Ruffolo

### ***Corresponding members:***

Richard Olsen

Michel Bouvier

Arthur Christopoulos

Moses Chao

Franz Hofmann