NC-IUPHAR

Annual Report

2016/17

IUPHAR
International Union of Basic and Clinical Pharmacology

Statement from the Chair

NC-IUPHAR is perhaps the most public success of IUPHAR, and is engaged in a major task; to define all the main drug targets encoded by the human genome, and annotate them in a database freely accessible world-wide...and, importantly, link them to therapeutics and pharmacological target validation. In this endeavour, we have received funding and support from the British Pharmacological Society, the University of Edinburgh and the Wellcome Trust. This enables us to make use of the tremendous efforts and insight of our expert subcommittees built up over many years, who provide the core information for the IUPHAR/BPS Guide to PHARMACOLOGY database. They also provide regular updates for the data to ensure the information is accurate and contemporary – we are all aware of the rapid pace of change in science in general, and in pharmacology/drug discovery, in particular.

Having said that, there seems to be a slowing of the pace in one area, which is the deorphanisation of GPCR lacking evidence for endogenous ligands. For other families of receptors, there are different stories. For the ligand-gated ion channels, we believe that we have the full complement of subunits and ligands in appropriate pairings. This is largely based on comparing sequences for the known LGIC subunits with predictions from the human genome. On the other hand, the nuclear hormone receptors, approximately half of the recognised NHR have limited or lack evidence for an endogenous ligand. It has been argued that these NHR function as transcription factors in their own right without the need for endogenous activation, but with the possibility of regulation through other mechanisms (phosphorylation, ubiquitinylation, SUMOylation, etc). Is it possible that orphan GPCR are regulated in a similar fashion but not through canonical transmitter/hormone activation?

One can speculate further as to the reasons for a slower process of GPCR deorphanisation, which are probably manifold. It may be that the endogenous ligands are particularly labile or low abundance, such that there is a technical hurdle to overcome in their identification. A second reason is that we have a shrinking pool of orphan GPCR on which to focus. This is an inevitable consequence of having a finite number of targets, defined using good structural comparisons. A third potential explanation is that there is limited desire on the part of funding agencies and the pharmaceutical industry to explore these unknowns. It has been argued that science is becoming risk-averse, with funding agencies generally less likely to take a chance on such explorations. I think we can all readily identify discoveries of fundamental importance which were not at all obvious when the research program was initiated.

We are also faced with repeated reports of the lack of reproducibility of data in pre-clinical pharmacology/drug discovery, which detracts from confidence in our roles. One way to reduce the risk in grant applications and to increase the confidence in our experimental outcomes is to improve experimental design and analysis. A better-validated dataset will inevitably provide a more predictable outcome when designing further experiments. So, one of the core aims of the database is to provide validated, evidence-rich datasets. An ongoing goal of NC-IUPHAR is to provide further guidance on best practice in the design and analysis of experiment, which we would hope to provide in the next couple of years.

For next year, another focus is WorldPharma in Japan. This provides an opportunity for pharmacologists from around the world to come together in Kyoto in July. NC-IUPHAR have invited Bryan Roth to deliver the Analytical Pharmacology Lecture, which he has titled "Towards a Molecular Understanding of Drug Action at GPCRs". We look forward to that greatly. NC-IUPHAR Deputy Chair, Arthur Christopoulos will deliver a Cutting Edge Lecture titled "GPCR Allostery and Bias in Modern Pharmacology: Structural, Pharmacological and Clinical Implications". We also have a number of symposia organized (and delivered) by members of NC-IUPHAR, including: "Computational Pharmacology, Databases and Drug Discovery" (David Gloriam, Christopher Southan and Adam Pawson), which will explore the benefits of *in silico* approaches for pharmacology; "Biased Agonism at G Protein-coupled Receptors: The Promise and the Challenges" (Anthony P. Davenport); and "New Controllers of Inflammation: What Are the Hottest Targets?" (Francesca Levi-Schaffer).

I would like to formally welcome new colleagues to the membership of NC-IUPHAR (see below) and to the IUPHAR/BPS Guide to PHARMACOLOGY database team in Edinburgh, and to thank a number of colleagues for their contributions to NC-IUPHAR in the last year, some of whom have decided to step down from the committee. Their altruism and dedication to NC-IUPHAR and pharmacology in general has made a significant contribution to help maintain the profile of the discipline at a time when there is fragmentation in both the industry and academia. I see part of the future role of NC-IUPHAR being to continue the trend of championing good science and, principally, good pharmacology. This particular role is definitely a challenge for NC-IUPHAR, but is achievable through working together with other IUPHAR committees and the huge numbers of scientists worldwide which are represented through IUPHAR.

Steve Alexander

Chairman of NC-IUPHAR

Current activities and future directions for NC-IUPHAR

Major efforts are continuing 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, receptor polymorphisms, hetero-oligomerisation, allosteric modulation, post-translational modification, epigenetic targets, non-coding RNAs, and 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. All these areas have been or will be developed for relevance for pharmacology, and additionally may be useful funding application areas to ensure the future sustainability of NC-IUPHAR activities, and the IUPHAR/BPS Guide to PHARMACOLOGY database (GtoPdb; http://www.guidetopharmacology.org/) project.

In addition to GtoPdb, publications are a key feature of NC-IUPHAR thanks to our long-term relationships with *Pharmacological Reviews* and the *British Journal of Pharmacology* for publishing reviews. These reviews are vital elements of our profile since they provide a feedback mechanism whereby we have an objective measure of our usefulness for the pharmacological community. As has been noted on many occasions, an H-index close to 80 is a testament to the work of NC-IUPHAR over the last two decades. All our publications can be viewed here (http://www.guidetopharmacology.org/nciupharPublications.jsp#2017). Our current aim is to broaden the scope of these reviews, beyond GPCRs, ion channels and NHRs, into the enzymes and transporters.

A milestone of the 2015/16 period was the publication of the *Concise Guide to PHARMACOLOGY 2015/16*. The next issue in this series will be published in the summer of 2017, and this endeavour has been a major undertaking to the GtoPdb team and *Concise Guide* editors.

The immense recent growth of knowledge about drug targets, with increasing detail becoming available from structural approaches, has had a dramatic impact on drug discovery and pharmacology, and importantly, NC-IUPHAR classifications have been widely adopted. In the past year, we have made great strides to proactively include new drug targets in the GtoPdb, and recruit experts to advise on them; to date we have 2826 annotated protein targets in the GtoPdb, with 8993 ligands, including all approved drugs (1334). For full details of GtoPdb content at the most recent database release, see (http://www.guidetopharmacology.org/about.jsp#content).

There is growing research interest, academically, clinically and industrially, in the pharmacology of immunity, inflammation and infection in defining the immunological/inflammatory targets in disease

states, with their main pharmacology. Within the research community, there is an urgent need for a pre-competitive, unbiased resource that will integrate high-level expertise in immunity, inflammation and infection, pharmacology and medicinal chemistry. At present, immunological and pharmacological knowledge are held by separate communities and the best resources fall short of what is needed. GtoPdb is the best molecular pharmacology database, but is currently limited in the immunity, inflammation and infection area. We successfully secured funding from the Wellcome Trust to extend GtoPdb into this arena, and to produce a 'Guide to IMMUNOPHARMACOLOGY (GtoImmuPdb; http://www.guidetoimmunopharmacology.org/immuno/index.jsp): Integration of targets, diseases and therapies into an expert-driven database'. We are now 17 months into the project, and May 2017 saw the launch of beta-release v1.0 (http://bit.ly/2vWHEp5), followed by beta-release v2.0 in August 2017 (http://bit.ly/2eH2GAE).

We have also created a new sister database to GtoPdb – SynPHARM, a database of drug-responsive protein sequences available at http://synpharm.guidetopharmacology.org/about/data/. You can read more about SynPHARM here (http://bit.ly/2vhn693).

One of the milestones of 2015/16 period was the successful application to the Wellcome Trust to fund the 'The Guide to Immunopharmacology' project (see above), led by Jamie Davies in Edinburgh and bringing together collaborators from six countries as co-investigators on the application. We have plans to further extend our resources into areas including natural product research and anti-infectives (an antimicrobial extension of GtoPdb), and efforts are well underway to identify support from organizations (BBSRC, Wellcome Trust, MRC) for these endeavours. More details to follow!

The GtoPdb team and collaborators have recently published an article assessing the potential impact of systems pharmacology on therapy development. To realize the full potential of databases of pharmaceutical drugs/targets and of cellular mechanisms in health/disease, we must combine results from both to predict new multi-drug therapies. They show that there are serious current obstacles to such prediction, but that introducing new systematic practices would facilitate this opportunity. The team are also working on a number of publications in 3Q17. The list includes our biennial database publication in *Nucleic Acids Research*, a write-up of the SynPHARM project, a *Current Protocols in Bioinformatics* invitation, a paper on the RDF project, as well as invitations from ACS Omega and *ChemMedChem*.

Finally, Simon Maxwell and John Szarek continue to spearhead the development of the IUPHAR Pharmacology Education Project (PEP; http://www.pharmacologyeducation.org/), an education portal that is closely linked with the GtoPdb. It provides access to high quality training in the principles and techniques of basic and clinical pharmacology, and was publicly released at Experimental Biology 2016. PEP links to ligand and target entries in GtoPdb, and we have recently included reciprocal links from GtoPdb back to PEP.

Further details about the recent activities of NC-IUPHAR, updates and developments to GtoPdb and GtoImmuPdb, activities of the database team, and 'Hot Topics' in pharmacology, can be found in the guidetopharmacology blog which allows the database team to share feature developments, technical updates, articles or events at a greater level of detail and cross-linking than shorter postings typical of our social networking sites (guest posts are welcome).

Support for the ongoing efforts of NC-IUPHAR and the GtoPdb Team come from a long-standing endowment (NC-IUPHAR), Servier (for NC-IUPHAR meetings), the British Pharmacological Society (database staff salaries) and the Wellcome Trust (database staff salaries). The financial aspects of these arrangements are dealt with separately by IUPHAR and the University of Edinburgh.

Organisation of NC-IUPHAR

Core Committee

The Core Committee of NC-IUPHAR, comprising the Executive Committee and Core Members is listed in

Appendix I. The biannual core NC-IUPHAR meetings are 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

To broaden the expertise of the core committee, there are a number of corresponding members (see Appendix I). Corresponding members further increase the global representation of NC-IUPHAR and can be invited to attend selected meetings of NC-IUPHAR according to the meeting themes. They include representatives of the major pharmaceutical companies. We welcome our new corresponding members, Philippe Delerive (France), Patrick Sexton (Australia) and Katerina Tiligada (Greece).

Evolving Pharmacology Group

Anthony Davenport leads a group which monitors the 'de-orphanisation' of GPCRs and evolving pharmacology of drug targets in general. Particularly important and timely breakthroughs are included in the Hot Topics section of the database along with email alerts.

Clinical Translational Pharmacology Group

To provide advice on the translational aspects of drug target pharmacology, a subgroup (see Appendix I) of clinical pharmacologists discuss how best to respond to the wishes of our clinical colleagues and to translate activity at drug target sites to clinical efficacy.

Database contributors and NC-IUPHAR subcommittees

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, finalising documents and the website pages. However, we encourage postdocs to join 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 NC-IUPHAR is 79. The subcommittees meet to establish consensus on classification, and to ensure that the NC-IUPHAR guidelines are complied with. We now have >90 subcommittees.

Full details of NC-IUPHAR membership and oversight committees, *Concise Guide to PHARMACOLOGY* contributors, and Database contributors and NC-IUPHAR subcommittee membership can be found online at http://www.guidetopharmacology.org/GRAC/ContributorListForward

Acknowledgements

We are very grateful to our funders and sponsors. We are also immensely grateful for the work done by our colleagues in NC-IUPHAR and all the contributing chairs and subcommittee members. 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 (please contact: enquiries@guidetopharmacology.org).

This report was compiled by Steve Alexander and Adam Pawson | September 2017