A one-stop pharmacology shop

The Guide to PHARMACOLOGY portal

Most medicines are chemical substances that work by interacting with specific target proteins in the body. The International Union of Basic and Clinical Pharmacology (IUPHAR) and the British Pharmacological Society (BPS) have joined forces to develop the Guide to PHARMACOLOGY (www.guidetopharmacology.org), a portal to information on the targets of licensed drugs and other targets of current research interest, such as those linked to human disease. Over the next 3 years, with support from the Wellcome Trust, IUPHAR and BPS, the Guide to PHARMACOLOGY portal will be expanded to cover all the targets of current licensed drugs and those with potential to be targets of future therapeutics. Our goal is to provide scientists, doctors, allied professions and the general public with a ‘one-stop shop’ source of information on how drugs work, and to help researchers to design experiments using the appropriate reagents.

The revolution in genomics and molecular genetics has led to the identification of many novel approaches to the development of new medicines. However, there is an urgent need for an accessible and authoritative online synopsis of the complete landscape of existing and future drug targets, to foster innovative drug discovery and provide an integrated educational tool for academia, industry and the interested public.

We are creating a resource which will enable researchers and students to exploit the full potential of the considerable amount of information on drug action available in the published literature, by providing curated information on the properties of existing and future drug targets. It is intended that the novice researcher (or those conducting investigations into new areas) could identify pertinent literature, clarify nomenclature issues, categorize the available assays and identify the most useful experimental tools (including chemical tools, drugs and radioligands) and procedures. Key data are presented in a standardized and structured format, which can be analysed to form new hypotheses, validate conclusions and guide future research.

Guide to PHARMACOLOGY: background and content

In 2011, the BPS and IUPHAR joined forces to develop a new online portal, the Guide to PHARMACOLOGY, with the aim of providing an open-access resource covering all aspects of pharmacology for student and professional pharmacologists, industry experts and the interested public. The first version of the Guide to PHARMACOLOGY integrates information on drug targets from two established resources: the BPS Guide to Receptors and Channels (GRAC) and IUPHAR-DB.

Since 2004, the BPS has published the Guide to Receptors and Channels (GRAC) as a supplement to the British Journal of Pharmacology, freely available in print and online, and updated every 1–2 years. GRAC is a compendium of pharmacological data, presently providing information on the properties of over 1800 established, or potential, drug targets, the key licensed medicines and experimental drugs that act on them and recommended reading lists for newcomers to each field.

In a parallel and, until recently, largely separate effort, the IUPHAR Committee on Receptor Nomenclature and Drug Classification (NC-IUPHAR, www.iuphar-db.org/nciuphar.jsp) has developed the IUPHAR Database (IUPHAR-DB, www.iuphar-db.org), an open-access expert-curated database of the properties of human and rodent receptors and other drug targets. NC-IUPHAR acts as the scientific advisory and editorial board for the database, and its network of over 700 specialist advisors (organized into about 60 subcommittees) contribute expertise and data.

IUPHAR-DB provides detailed, expert-driven, manually curated annotation of the primary literature on the pharmacological, chemical, genetic, functional and pathophysiological properties of 630 G-protein-coupled receptors (GPCRs), nuclear hormone receptors, and voltage- and ligand-gated ion channels. The information provided includes quantitative
data on their interactions with over 3250 bioactive molecules, such as endogenous ligands, licensed drugs and key pharmacological tools (e.g. experimental tool compounds and imaging reagents). Developed under the auspices of NC-IUPHAR, IUPHAR-DB is an authoritative reference and educational resource for pharmacologists, clinicians and allied disciplines.

The first milestone in the development of the Guide to PHARMACOLOGY was the construction of an open-access online database version of the 5th (2011) edition of GRAC2, the GRAC Database (www.guidetopharmacology.org/GRAC/), integrated with information from IUPHAR-DB and accessible via the Guide to PHARMACOLOGY portal.

GRAC provides expert summaries of the key properties of a wider range of targets than IUPHAR-DB, covering GPCRs, ion channels, nuclear hormone receptors, catalytic receptors, transporters and enzymes. The database version of GRAC adds value to the printed compendium, by providing hyperlinks from drug targets to corresponding entries in other relevant databases, and to citations in PubMed. Each of the approximately 3000 unique drugs, endogenous substances and radioligands described in GRAC is now fully annotated with manually curated two-dimensional chemical structures, calculated physicochemical properties, the IUPAC name, synonyms and hyperlinks to relevant external chemistry databases.

Thus IUPHAR-DB and GRAC may be considered two complementary resources for pharmacological information, both linked and searchable via the Guide to PHARMACOLOGY portal.

Information on chemical substances in the Guide to PHARMACOLOGY

The Guide to PHARMACOLOGY currently lists over 5000 distinct chemicals acting with a range of different actions at targets, including agonists, antagonists, allosteric modulators, substrates, products, inhibitors and blockers. These molecules range from simple biogenic and synthetic organic chemicals to natural products and peptides. Information provided about chemicals includes two-dimensional structures, calculated physicochemical properties, synonyms, selectivity data at targets and links to external chemistry databases and to co-crystallized three-dimensional structures in the Protein Data Bank. An important recent addition is the curation of the sequences and post-translational modifications of >600 endogenous peptides as well as structural information for >600 synthetic peptides, modified forms and toxins. The database search interface allows for navigation of the chemical structure space covered by the IUPHAR and GRAC databases through text, identity, similarity, substructure and SMARTS-pattern queries.

Expert-driven annotation

IUPHAR-DB is maintained by a team of curators, with guidance from NC-IUPHAR and its network of contributors, providing expert-driven annotation of the pharmacology of drug target systems from peer-reviewed primary literature sources, linked to citations in PubMed. Subcommittees of NC-IUPHAR are responsible for developing the nomenclature for each drug target family and compiling data to be included in the database. Where no relevant subcommittee exists, data are captured by the curators or individual experts and peer-reviewed by at least two external referees.

The production of the GRAC compendium is overseen by a group of editors who contact NC-IUPHAR subcommittees and individual experts to compile lists of the key ligands and references and provide summaries of target families. The data in both resources are reviewed at regular intervals (at least yearly) by GRAC editors, NC-IUPHAR subcommittees and other contributors and updated as necessary.

Towards the future

Now, with support from the Wellcome Trust and shared funding from BPS and IUPHAR for 3 years, the Guide to PHARMACOLOGY will be further developed as a comprehensive, accurate and freely accessible online source of information on the properties of drug targets and the substances that act upon them. Our vision is to provide a unique authoritative global resource intelligible to all members of the scientific community to maximize our expanding knowledge of how druggable
genes affect health and disease and to discover new ways to diagnose, treat and prevent illness. As such, we aim to provide:

- a freely available, accurate, regularly updated source of information on the human targets of all current licensed medicines, as well as likely future targets, to foster innovative drug discovery and provide an integrated educational tool for academia, industry and the interested public

- an entry point into the pharmacological literature for basic and clinical scientists from other disciplines

- rich annotation of each drug and its target(s), together with expert summaries of the properties of target protein families, presented in a concise user-friendly format

- a catalogue of the key pharmacological tools for the study of each drug target, with accurate quantitative and chemical information from the primary research literature, curated by experts

- human-centric data, placed in context with data from commonly used model species, supporting a translational approach to pharmacological research

- links to disease information, assisting the selection of targets and drugs for the development of new approaches for the treatment and diagnosis of disease

- extensive links from individual targets and drugs to other online resources providing information on genomics, genetics, medicinal chemistry, disease relevance and structural biology

- support for education by providing online training materials such as tutorials, guidelines and recommended reading.

Exploring new targets

We are aiming to provide quantitative pharmacological information on all of the (human) targets of current prescription medicines and other likely targets of future small-molecule drugs. We currently provide detailed information on all of the approximately 220 GPCRs for which endogenous ligands have been identified, all 48 nuclear receptors and many voltage- and ligand-gated ion channels and encoded by the human, rat and mouse genomes, together with information on the key properties of ‘orphan’ GPCRs, other ion channels, transporters, catalytic receptors and selected enzymes. This set of targets currently includes about half of the targets of licensed medicines in use today. We are expanding the resource to provide curated information on a further ~900 targets so that the completed resource would contain detailed information on all the human targets of current prescription medicines (about 435 human genes\(^3\)). We will also provide basic information on the pharmacological properties of a further approximately 620 genes that are likely targets of future medicines, as defined by published screening literature.

Working towards accurate online chemical information

We aim to ensure that the structures and nomenclature of the chemical substances in the Guide to PHARMACOLOGY are correct, working in collaboration and sharing our data with the providers of other databases such as PubChem\(^1\), ChemSpider\(^2\), DrugBank\(^6\) and the Human Metabolome Database\(^7\). Databases of chemical information extracted from the literature frequently contain errors and ambiguities,
which tend to proliferate between databases when the content is downloaded and reused. Reliable information on the properties of drug targets and the substances that act on them is crucial to the productivity of the academic, biotechnology and pharmaceutical sectors in developing new medicines. A carefully curated core set of pharmacological tools with unambiguous structural information would be valuable to researchers selecting reagents for use in their research, avoiding the use, for example, of the wrong stereoisomer of a drug in an experiment.

Establishing a ‘gold standard’ set of recommended pharmacological tools

A major goal for the future is to help researchers to choose appropriate reagents for in vitro and in vivo experiments from the plethora of substances used in the literature. We are working towards providing a ‘gold standard’ set of readily available recommended pharmacological tools for each target (licensed drugs, commercially available experimental compounds, radioligands and imaging reagents). Desirable properties include high potency/affinity in commonly used experimental species, selectivity for the appropriate target type, appropriate pharmacokinetic properties (e.g. good bioavailability, suitable for oral dosing, appropriate half-life, first-order elimination kinetics, no auto-induction of enzymatic biotransformation and lack of pharmacokinetic interactions with other drugs).

Providing information on clinically used drugs

A resource linking information on the clinical uses of drugs to pre-clinical data and rigorously defined chemical structures would be valuable to basic and clinical scientists worldwide. For each clinically used drug listed in the Guide to PHARMACOLOGY, we are working to provide a brief summary of therapeutic uses of the drug (e.g. for atorvastatin ‘a competitive inhibitor of 3-hydroxy-3-methylglutaryl-CoA reductase used in the treatment of hypercholesterolaemia’), guided by a panel of eminent clinical pharmacologists from NC-IUPHAR (the Clinical and Translational Pharmacology Group). Consistent with the international focus of the IUPHAR Database and Guide to PHARMACOLOGY Portal, we are using the World Health Organization (WHO) database of International Nonproprietary Names (INN: www.who.int/medicines/services/inn/en/) and the WHO Anatomical Therapeutic Chemical (ATC) classification (www.whocc.no/atc) as the basis for the classification of clinically used drugs. Further information on clinical pharmacology is provided through links to DrugBank, which contains extensive information on therapeutic indications, absorption, metabolism, excretion and toxicity.

How you can help

We welcome contributors! Although we already cover about half of the targets of prescription medicines in IUPHAR-DB and GRAC, delivered through the Guide to PHARMACOLOGY portal, there are many important areas that we do not yet cover. Over the next 3 years, our goal is to add about 900 new targets, including all the targets of prescription medicines and other targets of interest (such as those that are the targets of drugs in clinical trials or which show up in screening studies). Many of the targets to be added are enzymes and other proteins involved in human biochemical processes, some of which have been widely studied by scientists. In order to maximize their potential as future drug targets, we need to ensure that the Guide to PHARMACOLOGY covers all relevant aspects. To do this, we will need guidance from experts to help us curate and display the kind of data and information that our users would expect. If you would like to contribute your expertise to our effort, please contact us at enquiries@guidetopharmacology.org.

References