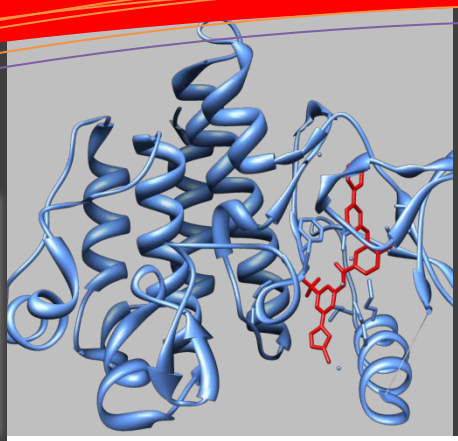
ISSUE 04 NOVEMBER 2013

The biannual newsletter from the IUPHAR Committee on Receptor Nomenclature and Drug Classification

NC-IUPHAR news



Featured in this issue

IUPHAR
International Union of Basic and Clinical Pharmacology

NC-IUPHAR Meeting Reports

Edinburgh, 26-28 April, and Paris 11-13 October 2013

See pages 12 and 13 for more details

CAPE TOWN, SOUTH AFRICA
WCP2014
17TH WORLD CONGRESS OF BASIC & CLINICAL PHARMACOLOGY

17th World Congress of Basic and Clinical Pharmacology

Cape Town, South Africa, 13-18 July 2014

Robert Lefkowitz, Nobel Laureate for Chemistry in 2012, is to open WCP2014

http://www.wcp2014.org

See pages 13 and 17 for more details

A message from the Chairman

The Guide to PHARMACOLOGY and its 'snapshot' little brother, the *Concise Guide to PHARMACOLOGY 2013/2014*.

We are engaged in a major task: How can we define all the main receptor and drug targets coded by the human genome, and put them in a database freely accessible to all? Even more important, link them to therapeutics and pharmacological target validation.

The availability of the grant by the Wellcome Trust, with support from IUPHAR, the British Pharmacological Society (BPS) and our sponsors (thanks!) has allowed us to have 5 curators working on the pharmacology of these targets, and this power, coupled to the multiple expert subcommittees, allows a new vision on target validation.

The immense recent growth of knowledge about drug targets, with their crystal structures, has been a huge help to drug discovery and while IUPHAR classifications are regularly used, we are able to try to be proactive including targets, and contacting experts. There is an immense way to go, but the objective is defining most of the potentially druggable sites encoded by the human genome. In order to do this we are changing the 'brand name' of the IUPHAR-database, IUPHAR-DB, to 'guidetopharmacology.org' to signify the broad approach we wish to take, without losing the rigour and organisation of IUPHAR-DB, managed by Tony Harmar and his curating team. This is also signalled by a change of colour from red and white to blue and white (www.guidetopharmacology.org), although as a Sunderland Football Club supporter, I think this is a backward step. Nevertheless, since the last newsletter we have made some real progress.

First, in a major collaboration with the BPS, we have been able to make their publication, the *Guide to Receptors and Channels* (GRAC) into a database form, merge some aspects with Guide to PHARMACOLOGY and in December, publish it as a 'snapshot' of the current state of nomenclature in the *British Journal of Pharmacology*: this is the *Concise Guide to PHARMACOLOGY 2013/2014 (more details on page 15).* This was due to a massive amount of work over the summer by the GRAC editors: Steve Alexander and John Peters, and Tony Harmar and his team. The transporters are covered for example.

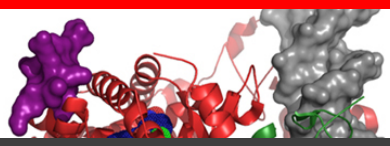
Second, a parallel effort by Doriano Fabbro, with Elena Faccenda as curator, has produced a complete database of kinases - with their pharmacology, thanks also to Discoverx, Millipore and Reaction Biology: visit it on www.guidetopharmacology.org. Chris Southan, as a new member of the database team, adds his strong bioinformatic and chemistry experience to our structure/activity curation. We now have 2485 proteins presently in the database, with 6064 ligands, 559 approved drugs.

However we still need more expert text in the database, covering the physiology and pathophysiology, and the translational work available to consider if the target has therapeutic utility. We hope to cover epigenetic targets and non-coding RNAs, in alliance with HGNC. The more analytical approach of NC-IUPHAR continues and we have documents on allostery and biased signalling in the pipeline. With ASPET and the BPS we are setting educational initiatives.

Another major event is the World Congress of Pharmacology (WCP 2014) in Cape Town in July 2014: there is a very exciting program, so please mark this in your calenders. Look forward to seeing you there!

This gives us an opportunity to thank our subcommittees (all 80!, and our reviewers). We are a public service, and for that we need the public - please help our efforts by contacting the curators on: enquiries@guidetopharmacology.org

Michael Spedding, Chairman of NC-IUPHAR



IUPHAR/BPS
Guide to PHARMACOLOGY

...incorporating IUPHAR DATABASE
International Union of Basic and Clinical Pharmacology

About the IUPHAR Database and Guide to PHARMACOLOGY

The IUPHAR/BPS Guide to PHARMACOLOGY portal (http://www.guidetopharmacology.org) is being developed to assist research in pharmacology, drug discovery and chemical biology in academia and industry, by providing: [1] an authoritative synopsis of the complete landscape of current and research drug targets; [2] an accurate source of information on the basic science underlying drug action; [3] guidance to researchers in selecting appropriate compounds for *in vitro* and *in vivo* experiments, including commercially available pharmacological tools for each target; and [4] an integrated educational resource for researchers, students and the interested public.

The IUPHAR/BPS Guide to PHARMACOLOGY portal has been online since December 2011. The current release of the database (October 2013) integrates data from two sources. The first of these is the IUPHAR Database (IUPHAR-DB; http://www.iuphar-db.org), which provides in-depth, integrative views of the pharmacology, genetics, functions and pathophysiology of important target families, including G protein-coupled receptors (GPCRs), ion channels and nuclear hormone receptors (NHRs). The second is the BPS 'Guide to Receptors and Channels' (GRAC), a compendium, previously published in print, providing concise overviews of the key properties of a wider range of targets than those covered in IUPHAR-DB, together with the endogenous ligands, experimental drugs, radiolabeled ligands and probe compounds, with recommended reading lists for newcomers to each field.

Developed under the auspices of the IUPHAR Committee on Receptor Nomenclature and Drug Classification (NC-IUPHAR), the resource is an authoritative reference and educational resource for pharmacologists, clinicians and allied disciplines. All data in IUPHAR-DB can now be accessed through the IUPHAR/BPS Guide to PHARMACOLOGY.

An update from the Database Team

Some developments since the November 2012 newsletter:

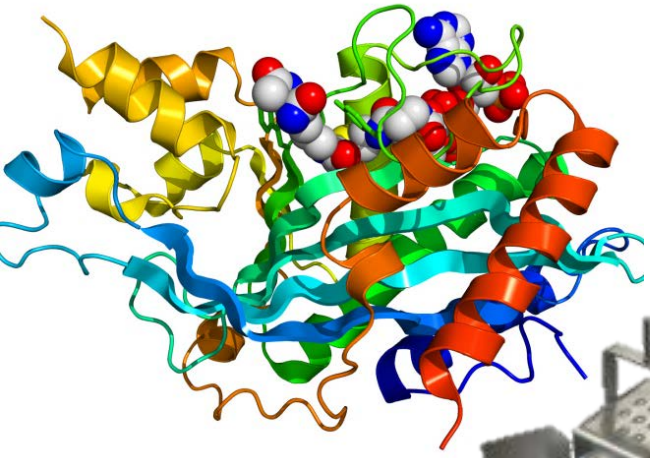
- ***Web site*:** The new IUPHAR/BPS Guide to PHARMACOLOGY web site was launched in July;
- ***New NC-IUPHAR Subcommittee Chairs:*** Girolamo Calò (Neuropeptide S), Raul Gainetdinov (Dopamine), Sadashiva Karnik (Angiotensin), Jérôme Leprince (QRFP), Martin Michel (β_3-adrenoceptor), Manuel Tena-Sempere (Kisspeptin).
- ***Database updates: GPCRs:*** α-Adrenoceptors, Adenosine, Apelin, Bombesin, Complement peptide, Formylpeptide, Free fatty acid, Galanin, Ghrelin, Hydroxycarboxylic acid, Leukotriene, Metabotropic glutamate, Neurotensin, Neuromedin U, Neuropeptide S, P2Y, Prokineticin, Prostanoid, QRFP, Relaxin family peptide, Somatostatin receptor 2 (sst2 receptor), Tachykinin, Thyrotropin-releasing hormone, Trace amine,; *VGICs;* CatSper and Two-Pore, Cyclic Nucleotide-Regulated, Transient Receptor Potential.
- ***Full annotation of the Adhesion Class GPCRs:*** Many thanks to Helgi Schiöth who oversaw the full annotation of all the adhesion class GPCRs, working with members of the Adhesion GPCR consortium, including Jörg Hamann and Tobias Langenhan.
- ***Annotation of kinases (see page 3) and proteases/hydrolases:*** the database now includes pages with genomic and structural information for 175 proteases and 14 hydrolases with activity records in ChEMBL. Detailed ligand activity (K_i or IC_{50}) mapping has been curated for 46 proteases and 14 hydrolases for either approved prodrugs, drugs, clinical candidates or selected research compounds.

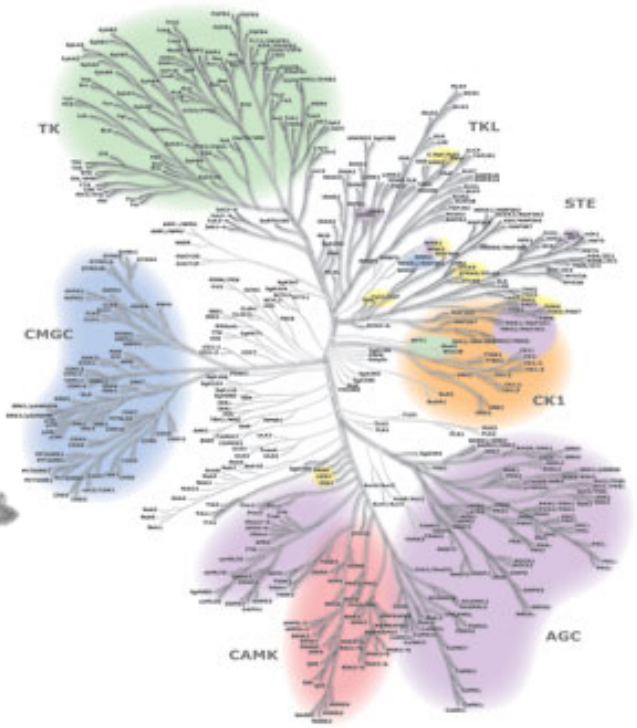
Database statistics

Target class	Number of targets
7TM receptors	400
G protein-coupled receptors including orphans	394
Orphan G protein-coupled receptors	130
Other 7TM proteins	6
Nuclear hormone receptors	48
Catalytic receptors	223
Ligand-gated ion channels	84
Voltage-gated ion channels	142
Other ion channels	49
Enzymes	1008
Transporters	503
Other protein targets	28
Total number of targets	2485

Chemical class	Number of ligands
Synthetic organics	3504
Metabolites	550
Endogenous peptides	687
Other peptides including synthetic peptides	1089
Natural products	161
Antibodies	10
Inorganics	55
Others	8
Approved drugs	559
Withdrawn drugs	11
Drugs with INNs	857
Radioactive ligands	550
Total number of ligands	6064

Number of synonyms	51189
Number of binding constants	41116
Number of binding constants excluding kinase screens	9909
Number of references	21774





In the spotlight...

Protein kinases

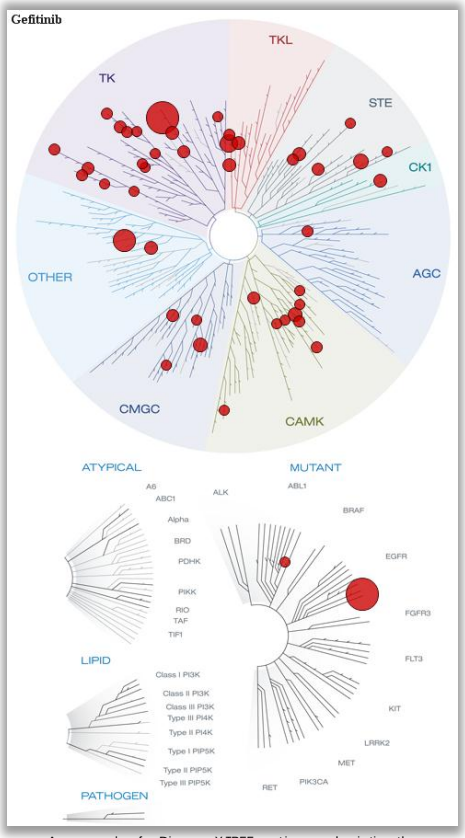
New kinase section in the database!

What is included:

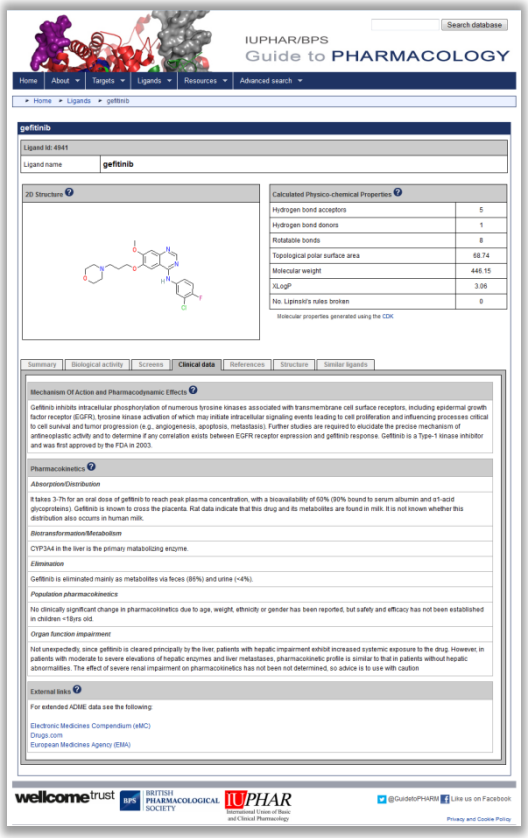
- Coverage in the database is now complete for all the human protein kinases and selected lipid kinases, including genomic and structural information for all the kinases;
- Structural information on all the ligands, ligand synonyms, approved drug status, International Nonproprietary Names (INNs), and external chemistry related database links
- Additional information is provided on the 24 clinically-used kinase inhibitors (including summaries of clinical use and ADME data);
- Selected bioactivity data for approved kinase inhibitors;
- Data from published screening assays by DiscoveRx, EMD Millipore and Reaction Biology are also included for 71, 158 and 176 kinase inhibitors, respectively. DiscoveRx data include links to their TREE*spot*™ visualisation tool.

EMD MILLIPORE

REACTION BIOLOGY CORP.



An example of a DiscoverX TREE*spot* image depicting the coverage for Gefinitib across the kinome. The larger the spot, the higher the affinity for the kinase



The ligand page for Gefitinib on the IUPHAR/BPS Guide to PHARMACOLOGY, open on the 'Clinical data' tab.

AN OVERVIEW OF KINASES

Doriano Fabbro

PIQUR Therapeutics AG

Kinases belong to a large and diverse superfamily of enzymes and members of the eukaryotic protein kinase (ePK) family are responsible for mediating and controlling the majority of complex signalling events in eukaryotic cells.

Reversible phosphorylation, where kinases transfer the gamma phosphate of ATP to hydroxyl groups of various substrates including lipids, sugars or amino acids plays an essential role in most, if not all, cellular signalling influencing almost every cellular process (including regulation of the cell cycle, growth, apoptosis and signal transduction). In eukaryotes, reversible protein phosphorylation is often transient and is performed by ePKs on Ser, Thr or Tyr residues and the respective phosphatases, which remove the phosphate.

At the latest count, the human kinome contains 566 ePK genes. There are two main classes of human protein kinases: the protein tyrosine kinases (PTKs) which phosphorylate Tyr and the Ser- and Thr-specific kinases (STKs) which phosphorylate Ser and/or Thr residues on protein substrates. Whilst there are a few dual-specificity protein kinases (phosphorylating both Tyr and Thr), the majority of ePKs are STKs. This is reflected in the ratio of cellular phosphorylation of pSer : pThr : pTyr = 1000 : 100 : 1. Although only a minor number of substrates are phosphorylated by PTKs, the importance of tyrosine phosphorylation is profound. Many gain of function (GOF) and/or loss of function (LOF) mutations are found in PTKs which have, therefore, long been considered as important drug targets.

The ePK domain is the most abundant catalytic domain in the eukaryotic genome and the overall structural organization of the kinase domain is highly conserved. The catalytic function of ePKs is confined to a ~300 amino acid domain, which provides all of the machinery required for phosphorylation of proteins on Ser, Thr and/or Tyr residues. Of special note is the so-called “gatekeeper” residue which controls access to the “back-pocket” of the kinase ATP binding site, since this residue is often mutated in kinase alleles resistant to inhibitors.

Aberrant kinase function, such as hyperactivity or overexpression plays a role in a wide variety of diseases including cancer, inflammatory diseases, diabetes, atherosclerosis, and immunological disorders. Despite a third of all protein targets under investigation in the pharmaceutical industry being protein or lipid kinases, their full potential remains to be fully exploited.

KINASE INHIBITORS

Potent but non-selective tool molecules such as staurosporine led to the initiation of drug development efforts which culminated in the approval of the first kinase inhibitor, Imatinib (CGP57148, STI571, Glivec, Gleevec), for the treatment of chronic myelogenous leukemia (CML) in 2001. Since then, 24 small molecule kinase inhibitors have been approved by the FDA, the majority being for the treatment of cancer with a minor number approved for other indications.

Continued on page 05...

ABOUT THE AUTHOR

Doriano Fabbro Chief Scientific Officer at Piqur Therapeutics AG, received his Ph.D. in cell biology and biochemistry at the University of Basel, where he worked afterwards for 12 years as Group Leader in Molecular Tumor Biology. In 1991, he joined the Oncology Group of Ciba-Geigy Basel. After the merger of Ciba-Geigy with Sandoz in 1996 he served at Novartis, he served as Head of Drug Discovery for Oncology until 2005, and then as Head of Kinase Biology until 2012. Doriano has contributed to the discovery and development of various protein kinase inhibitors for the treatment of cancer; *e.g.* Midostaurin®, Glivec®, Afinitor®, and Tasigna®. Doriano is author in more than 200 publications and numerous patents in the area of protein kinases regulation, structure, screening and drug discovery. He has been honored with the Novartis Oncology President's Award (2005).

Doriano Fabbro

Continued from page 04...

Although the structural determinants of kinase inhibition by small molecules binding to the ATP-binding site is well understood the selectivity and the limited set of chemical entities targeting the ATP-binding site, have become the major issues in kinase drug discovery.

Traditionally, drug discovery has used in vitro biochemical- and cellular assays followed by *in vivo* clinical studies to assess drug efficacy. There are many different ways to measure biochemical protein kinase activity (such as detection of radio labelled transfer of phosphate to the substrate, ATP consumption or ADP production measurement, TR-FRET, peptide array-based, micro fluidic technologies, and label free analysis).

Cellular assays show similar diversity, focused on measuring target modification (by Western blot, phospho-ELISA and reversed-phase arrays, for example) or changes in downstream signalling. Combining these various techniques gives a readout of in vitro kinase activity and the effect of inhibitors, and can be used to reveal on- and off-target effects. Such systematic inhibitor profiling has provided novel ways to better define the selectivity profile of drug candidates and has revealed previously unidentified mechanisms of action. But, despite this enhanced profiling of drug candidates, it still proves very difficult to align these results with their potential toxological effects and clinical efficacy in patients, meaning that many potential research leads fail in pre-clinical stages of development. Recent progress in molecular profiling in conjunction with precision medicine will further our understanding and allow better assessment and prediction of efficacy/toxicity of these inhibitors in disease models (pharmacokinetics/pharmacodynamics) and patients. The prospect of using kinase inhibitors against diseases other than cancer may also be enhanced by such improved understanding.

Approved kinase inhibitor drugs (as of July 2013)

Approved Drug	Drug Target	Approved Disease Indications
Imatinib (STI571, Glivec, Gleevec)	ABL, PDGFR, KIT	CML, Ph+ B-ALL, CMML, HES, GIST
Gefitinib (ZD1839, Iressa)	EGFR	NSCLC
Erlotinib (OSI-774,Tarceva)	EGFR	NSCLC, pancreatic cancer
Sorafenib (BAY 43-9006, Nexavar)	VEGFR2, PDGFR, KIT, FLT3, BRAF	RCC
Sunitinib (SU11248, Sutent)	VEGFR, KIT, PDGFR, RET, CSF1R, FLT3	RCC, imatinib resistant GIST
Lapatinib (GW2016, Tykerb)	EGFR, ERBB2	BC
Dasatinib (BM-354825,Sprycel)	ABL, PDGFR, KIT, SRC	CML
Nilotinib (AMN107,Tasigna)	ABL, PDGFR, KIT	CML
Everolimus (Rad001, Afinitor, Votubia, Certican)	mTOR	RCC, SEGA, Transplantation
Temsirolimus (CCI-779, Torisel)	mTOR	RCC
Crizotinib (PF-02341066, Xalcori)	MET and ALK	NSCLC with ALK translocations
Vandetanib (ZD6474, Caprelsa)	RET, VEGFR1-2, FGFR, EGFR	MTC
Ruxolitinib (INC424, Jakafi)	JAK2	IMF with JAK2V617F
Vemurafenib (PLX4032, RG7204, Zelboraf)	BRAF	m-melanoma with BRAFV600E
Axitinib (AG013736, Inlyta)	VEGFR, KIT, PDGFR, RET, CSF1R, FLT3	RCC
Regorafenib (BAY 73-4506, Stivarga)	VEGFR2, Tie2	CRC, GIST
Pazopanib (GW-786034, Votrient)	VEGFR, PDGFR, KIT,	RCC
Tofacitinib (CP-690550, Xeljanz Tasocitinib)	JAK3	JAK3
Cabozantinib (XL184, BMS907351, Cometriq)	VEGFR2, PDGFR, KIT, FLT3,	MTC
Ponatinib (AP24534, Iclusig)	ABL	T315 resistant CML
Bosutinib (SKI-606, Bosulif)	ABL	CML resistant/ intolerant to therapy
Dabrafenib (Tafinlar)	BRAF	m-melanoma with BRAFV600E
Trametinib (Mekinist)	MEK	m-melanoma with BRAFV600E
Afatnib (Gilotrif, Tomtovok, Tovok)	EGFR	NSCLC with EGFR activating mutations

Abbreviations: BC (breast cancer), CML (chronic myelogenoue leukemia), GIST (gastrointestinal stromal tumor), HES (hypereosinophilic syndrome), IMF (idiopathic myelofibrosis), m-melanoma (malignant melanoma), MTC (medullary thyroid cancer), NSCLC (non-small cell lung cancer), Ph+ B-ALL (Philadelphia chromosome positive B cell acute lymphoblastic leukemia), RA (rheumatoid arthritis), RCC (renal cell carcinoma), SEGA (subependymal giant cell astrocytoma), AZ (AstraZeneca), BI Boehringer Ingelheim), GSK (GlaxoSmithKLine), OSI (OSI Pharmaceuticals).

The curatorial assignment of primary or secondary target proteins as causative for the kinase inhibitor molecular mechanism of action is particularly complex. This is principally due to: a) dependence of *in vitro* cross-reactivity rankings on the assay conditions; b) difficulties of verifying and relating the implied polypharmacology to *in vivo* efficacy and; c) the clinical importance of tumor-specific somatic variants or fusion proteins in these targets. The target listing in the table above has been carefully selected and approved by our consultant experts but is, by definition, subject to these caveats.

PROFILE

Former Edinburgh University pharmacology graduate and Database Curator for IUPHAR-DB

Rebecca Hills, Consultant, Just::Health Communications, Putney, London

A 3-month stint during my Pharmacology honours year working on a project for the IUPHAR receptor database threw me to the world of receptor nomenclature, scientific writing, editing, and digital publication. Upon graduation I started working for Professor Harmar, (who heads up the database team in Edinburgh) as Database Curator on a full-time basis, where I remained for nearly 3 years. Working alongside the Database Developer, I undertook literature reviews of receptor families and their ligands (inputting findings into the database), commissioned and edited reviews from key opinion leaders, and liaised on a regular basis with the IUPHAR nomenclature committee with progress reports.

Wanting to build on this editorial experience, I moved to scientific publisher Elsevier in London, where I worked on their high-profile research review journals *Trends in Pharmacological Sciences*, *Trends in Neurosciences* and *Trends in Biochemical Sciences*. Elsevier provided me with rigorous training in editing scientific articles as well as proofreading; this improved my eye for detail (so, if there are any mistakes in here – tsk!) as well as my writing ability, which has stood me in good stead not only for all my future roles to date but also for everyday life. My extensive knowledge of receptor nomenclature also came in very handy for my work on the three aforementioned titles, although I am not sure my somewhat strict approach made me too popular with the authors!

A move to the BMJ Group's Evidence Centre took me away from print and back to digital publication, and also from research to clinical publication. In the Evidence Centre I worked as a Content Editor for a collection of online resources communicating evidence-based information to clinicians and patients.

I enjoyed editing, and of course science, but I wanted a job that allowed me to venture out of the office. I knew of friends working for so-called "med ed agencies" who were travelling all over the place and I decided to investigate. I landed a job working as a Project Manager for a leading medical communications agency called Synergy, offering scientific, editorial and creative input to medical education projects across multiple disease areas.

Clients included some of the biggest pharmaceutical companies in the world, and I was instrumental in the delivery of educational programmes aimed at healthcare professionals. Projects included running sponsored satellite symposia at large congresses as well as standalone CME (continued medical education)-accredited meetings. This involved everything from developing the meeting objectives and agenda, creating PowerPoint slides, coordinating the design of the meeting branding, sourcing speakers and a chairperson, liaising with audiovisual crews and congress secretariats, through to taking minutes and writing meeting reports. Disease areas I worked on included vaccination, rheumatoid arthritis and skin diseases such as psoriasis and chronic hand eczema. It was a really hands-on role; every month or so I was out of the office, and I was lucky enough have the opportunity to travel to far flung places such as Taiwan, Mexico and Dubai.

Whilst I still very much enjoyed working in medical education, I was interested to explore a public-focused way of working. Around a year ago I moved to an agency called Just::Health Communications, an independent healthcare communications agency specialising in public relations, medical education and policy relations. I am a Consultant and work directly with three high-profile clients on their PR and medical education programmes in the UK and Europe – a combination of educating healthcare professionals (as at Synergy), as well as public relations, which (so far!) has included "selling in" press releases on new survey data to medical and consumer media. I work on smoking cessation, hepatitis C and pain management, and I still get out of the office regularly, with client visits around the UK and Europe.

Outside work, I write a blog, which combines my love of writing and communications with food, travel and photography.

ABOUT THE AUTHOR

Rebecca Hills is a former curator for IUPHAR-DB who joined the database team after graduating at the University of Edinburgh. Rebecca tells us about her career experiences since leaving IUPHAR-DB.

students and post-docs corner

STUDENT EXPERIENCES

Share your experiences with us!
Tell us about your experiences while studying pharmacology, about your projects and future career ambitions, and we'll publish them in future newsletters.
enquiries@guidetopharmacology.org

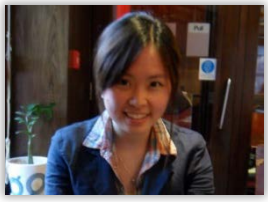
Veny Lukito, Third year pharmacology student, University of Edinburgh

Currently I am a final year Pharmacology undergraduate at the University of Edinburgh. From June to August 2011 I undertook a summer placement with the IUPHAR-DB. During this placement, my task was to improve the information of endogenous peptides acting on human, mouse and rat GPCRs. The genetic sequences, post-translational modifications, genetic precursors governing the peptides syntheses as well as the physiological functions of the peptides were investigated through various peer-reviewed papers. Additionally, the structural and functional levels of endogenous peptides were explored to a greater extent based on genetic differences in human, mouse and rat.

Even though it was not a lab-based project, I found this work very interesting mainly because of its implications on the future development of IUPHAR-DB. Besides more information became updated on the database, readers can appreciate the clinical relevance of endogenous peptides and the GPCRs involved. Also, the information updated can facilitate research which concentrates on synthetic ligands that mimic or modify the actions of some endogenous peptides.

Through this project I have acquired vast knowledge on the latest pharmacological development of GPCRs and some skills that are essential for my academic performance and future career. Examples include the ability of critical thinking and some skills for problem solving. More importantly, this placement has assured me that research is the path that I want to be involved in the future and encouraged me to further my study in the drug discovery area.

Finally, I would like to thank the Wellcome Trust for the support given during those 8 weeks of my summer placement. Also, I would like to express my gratitude towards the opportunity given by Professor Tony Harmar to make some contributions to his work as well as Joanna Sharman, Chido Mpamhanga, Adam Pawson and Vincent Bombail for their help and support during the completions of the project.



Veny

Veny is now doing an MSc degree in Integrative Neuroscience at Edinburgh University.

Jasmine Macgilchrist, Third year pharmacology student, University of Bath

Currently, I am a third year pharmacologist at the University of Bath doing a 12 month placement supervised by Professor Mark Lindsay. In the third year of the course, the majority of students in my year either have done a paid placement in industry or a 12 month project in a university.

My project involves work in bioinformatics, using a database to look at differences in miRNA expression levels. miRNAs are small non coding RNAs which inhibit protein translation through binding to the 3' UTR region of mRNA, causing either degradation through fully complementary Watson crick base pairing or translation inhibition through partial complementarity. Many miRNAs have unknown functions, however, in the past twenty years roles have been implicated in aging, cancer and development, indicating the importance of miRNAs in disease and physiology.

Compared to the first two years of my undergraduate pharmacology degree, this work has proven to be completely different! The work is all computer based compared with the lab based work done in my first two years. Due to the freely accessible use of the database, I am able to work anywhere with the data, limited solely by the amount I can download on the internet bandwidth I am using. A lot of the work is data downloading, analysis, target searching and genome analysis. Hopefully in the next couple of months I will be submitting a paper.

I find my project quite exciting to be working in an area that is rapidly expanding, due to the human genome project. I highly recommend a placement year as part of a degree, as it gives a good idea of what the world of work is like in your chosen degree programme. My placement year has given me a feel for what I am working towards when studying for my degree and it is a completely different experience to going to lectures, tutorials and practical classes. Doing a placement in bioinformatics has helped me determine what type of work I'd like to do once I've graduated, which a year ago I had no clue!

Jasmine

ABOUT THE AUTHOR

Antony Williams is the VP of Strategic Development and Head of the eScience team at the Royal Society of Chemistry. He spent over a decade in the commercial scientific software business, worked in Fortune 500 industry in the USA and in academia as a lab manager. He was trained as an NMR spectroscopist by training and has authored over 130 peer-reviewed publications and multiple review articles and book chapters. He continues to focus his passion for providing access to chemistry-related information to the masses with the RSC-eScience team and innovate novel approaches for improved access to chemical data online. He can be found as the ChemConnector on the social networks.

Antony Williams

PROFILE OF THE ROYAL SOCIETY OF CHEMISTRY

A recent meeting took place between the NC-IUPHAR database team and David James (Executive Director, Strategic Innovation, RSC), Jonathan Brüün (Chief Executive, BPS) and Katherine Richardson (Head of Communications and Membership at BPS) to explore links between the IUPHAR/BPS Guide to PHARMACOLOGY, and both RSC and ChemSpider as the RSC's new open innovation e-platform for early stage drug development.

The Royal Society of Chemistry - Serving the Diverse Needs of the Chemistry Community Through eScience Initiatives

Antony J. Williams (email: williamsa@rsc.org)
Royal Society of Chemistry,
Department of eScience,
904 Tamaras Circle, Wake Forest, NC-27587

The Royal Society of Chemistry (RSC) is one of the world's primary learned societies focused on the mission of "advancing the chemical sciences". In recent years the society has invested in the development of a number of eScience initiatives including the award-winning Project Prospect for semantic mark-up of scientific publications and ChemSpider, one of the chemistry community's primary online resources. Today RSC is executing on a number of strategic initiatives to support their mission and this short article provides an overview of some of these efforts.

ChemSpider is a free, online chemical database offering access to molecular structures, nomenclature and chemical synonyms, physical and chemical properties, spectral data, synthetic methods, safety information for over twenty six million unique chemical compounds sourced and linked out to almost four hundred separate data sources on the web. ChemSpider has become one of the primary chemistry internet portals but is not just a search engine layered on terabytes of chemistry data but is also a crowdsourcing community for chemists. Users can add their own data and layer on annotations and assist in the curation and annotation of records. Indeed, an increasing proportion of the chemistry community has been forthcoming in adding information including new chemical structures, associations between structures and publications, addition of analytical data such as spectra and, especially, the curation of chemical identifiers and property data. This has helped move ChemSpider from being one more large online public chemical compound databases to being a rich resource of increasingly curated data.

ChemSpider has been described as the "Google for Chemistry" and a "Wikipedia for chemists". By aggregating data and linking it together using a chemical structure as the primary record in the database, ChemSpider has been able to link together many resources such as Wikipedia, PubChem, the ChEBI (Chemical Entities of Biological Interest) database from the European Bioinformatics Institute) [8], chemical vendors, a patent database, and both open and closed access chemistry journals. Where possible, each chemical record retains the links out to the original source of the material thereby associating a microattribution. These links allow a ChemSpider user to source information of particular interest, including where to purchase a chemical, toxicity and metabolism data and so on. Aggregating that level of connected information via a classical search engine, like Google, would be very time consuming. However, ChemSpider also has a number of advantages over a simple Google search. The variety of information about a compound provided at ChemSpider is really very hard to match on any other free web site especially since the data continue to be validated, updated and expanded by practicing chemists. ChemSpider also provides links to many other online sources including Google Books, Scholar and Patents, and an ever-increasing number of government, commercial and academic databases. We have also integrated to an array of RSC Databases, our books index and the RSC publishing website.

The closest comparison in terms of validated and crowd-sourced contributions to the domain of chemistry are the chemical pages in Wikipedia; however, Wikipedia has information on far fewer compounds (around 10,000) and supports only text searching not structure searching.

Continued on page 09...

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One of the primary objectives for the RSC is to advance the chemical sciences. This is not only in terms of researchers but also to provide tools with the intention of training the next generation of chemists. To support this mission RSC developed the Learn Chemistry platform (http://www.rsc.org/learn-chemistry) to provide a central access point and search facility to access various chemistry resources. The Learn Chemistry wiki integrates to ChemSpider to provide access to data and information that is delivered at a level most appropriate to students in their last years of school, and first years of university (ages 16-19). The resource is an interactive resource and allows students to answer a variety of quiz questions, and allowing chemical educators to contribute to the content. In parallel to the Learn Chemistry wiki the ChemSpider team also manages the development of the SpectraSchool website (http://spectraschool.rsc.org/), a website to learn about various forms of spectroscopy, specifically 1D NMR, mass spectrometry, infrared and UV-Vis spectroscopy. Users have the opportunity to display the various forms of spectral data associated with a number of common organic molecules but also provides a quiz-based mode where the user is shown a number of spectra of various types from which the user has to determine what the chemical compound is. The spectroscopy data are hosted in the ChemSpider database as the central repository of analytical data.

ChemSpider "web services" provide programmatic access to ChemSpider and allows for instrument vendors to utilize the data for the purpose of structure identification. This opportunity in particular is being used for the purpose of compound identification by mass spectrometry. The data are also available to the Open PHACTS project (http://www/openphacts.org), a project funded by the Innovative Medicines Initiative, and ChemSpider is one of the key participants in the project. We will also be supporting the PharmaSea project for helping to identify new natural products from the ocean (http://www.pharma-sea.eu/) and, ultimately, to host some of the data associated with the resulting chemical compounds.

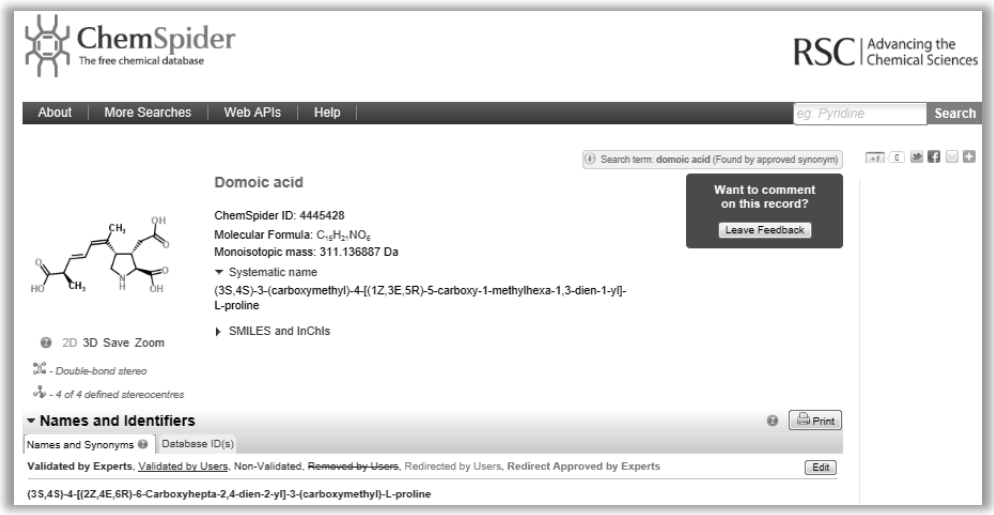

Figure 1: The header of the chemical record for Domoic Acid (http://www.chemspider.com/4445428) in ChemSpider. The entire record spans multiple pages including links to patents and publications, pre-calculated and experimental properties and links to many data external data sources and informational websites.

One of the most critical projects that the RSC-eScience team is progressing now is the UK centric Chemical Database Service (http://cds.rsc.org) offering access for academic scientists to a suite of commercial databases and services, with additional development to create a chemistry data repository to take place. These databases include reaction databases, thermophysical and crystallographic data and various other forms of information including available chemicals from vendors.

The services include prediction algorithms for physicochemical properties, NMR spectroscopy prediction, systematic nomenclature generation and various other facilities. These capabilities have been delivered in the first few months of the project and the future developments include extension into providing a repository for research data utilizing our experience in data management for chemistry. In this way scientists will be able to host their data in the cloud and will be able to share data collaboratively, under embargo or publicly, if they choose. This five year project will require that the challenges of complex data management for the chemical sciences be addressed, that the complexities of data licensing and sharing be navigated, and that the appropriate tools for searching and displaying the myriad forms of information be developed.

Continued on page 10...

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The most active development projects at present from the eScience group will dramatically extend the reach and utility of the data for the community as well as providing deep integration into our scientific article archive. The DERA project (Digitally Enabling the RSC Archive) will extract data from the entire RSC archive of over 300,000 articles – chemical compounds, reactions, spectral data, property data and so on. The data will then be made available to the community via the appropriate interfaces. ChemSpider Reactions, intended to be the largest freely accessible database of chemical syntheses, will unveil in April 2013 with over ½ a million reactions and will be the host for all reactions extracted from the archive. ChemSpider will be the home for all spectroscopic data and is expected to host over 300,000 spectra by May 2013. Property data will be used to underpin the development of predictive models that will be served up to the community to utilize, to validate, to provide feedback and to, hopefully, improve by contributing their own data. As these technologies develop we will be extending our data models to include the handling of materials-based data that cannot necessarily fit the existing model of ChemSpider and its requirement for well-defined chemical structures.

Conclusion

The eScience group at the Royal Society of Chemistry is active in a number of groundbreaking projects to facilitate access to chemistry related for the community. The ChemSpider database is one of the premier chemistry sites on the internet and its initial focus on small organic chemical compounds has been extended into supporting chemical reactions, analytical data (specifically spectroscopy) and other forms of chemistry data. The engagement of the user community to participate as data depositors and curators extends access to chemistry data outside of the realm of published articles that is presently dealt with by the abstracting services. Increasingly we are seeing chemists publish their chemical compounds, related syntheses and spectral data to one of our databases and as the push todays Open Data continues, especially driven by the expectations of the funding agencies also encouraging Open Access publishing. While we are still in early years of community access to the Big Data of chemistry, the RSC-eScience group, and the many development projects it is involved with, intends to provide a global chemistry hub as a foundation of this changing world of data access.

Visit the ChemConnector Blog at http://www.chemconnectorblog.com

DID YOU KNOW?

IUPHAR-DB and the Guide to PHARMACOLOGY provide a wide range of information on ligand molecules

The IUPHAR Database and Guide to PHARMACOLOGY now contain over 6000 distinct ligand molecules, ranging from synthetic organic chemicals to natural products and peptides.

Information provided about ligands includes 2D structures, calculated physical-chemical properties, synonyms, selectivity data at targets and links to external chemical structure databases and to co-crystallised 3D structures in the Protein Data Bank.

An important recent addition is the curation of the sequences and post-translational modifications of >600 endogenous peptide ligands and well as structural information for >600 synthetic peptides, modified forms and toxins.

The database search interface allows for navigation of the ligand chemical structure space covered by the databases through text, identity, similarity, substructure and SMARTS-pattern queries.

About NC-IUPHAR

The IUPHAR Committee on Receptor Nomenclature and Drug Classification (NC-IUPHAR), founded in 1987, is chaired by Michael Spedding (France). NC-IUPHAR has the objective of issuing guidelines for the nomenclature and classification of all the (human) biological targets, including all the targets of current and future prescription medicines; facilitating the interface between the discovery of new sequences from the Human Genome Project and the designation of the derived entities as functional biological targets and potential drug targets; designating polymorphisms and variants which are functionally important; developing an authoritative and freely available, global online resource, the IUPHAR database (http://www.iuphar-db.org), which is now accessible via the Guide to PHARMACOLOGY portal (http://guidetopharmacology.org), with a remit to provide access to data on all known biological targets; 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 literature; provide an entry point into the pharmacological literature for basic and clinical scientists from other disciplines; provide an integrated educational resource with access to high quality training in the principles of basic and clinical pharmacology and techniques; foster innovative drug discovery.

Membership

Chair
Michael Spedding, France

Vice Chairs
Anthony Davenport, UK - Chairman Evolving Pharmacology
Anthony Harmar, UK - Database Chairman
Rick Neubig, USA - GPCRs
Eliot Ohlstein, USA - Editor

Members
Stephen 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

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, USA
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

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
Christopher Southan, Sweden – Cheminformatician/Database curator
Veronika Divincova, UK - Project Administrator
Matt Wright, UK - Representing HGNC

Past Chairs (ex officio)
Paul Vanhoutte, China
Robert Ruffolo, 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

Participants of the April 2013 NC-IUPHAR meeting in Edinburgh, Scotland (*meeting report on page 12*)

Ongoing and future NC-IUPHAR activities

- Wellcome grant projects
- Evolving Pharmacology – deorphanisation of GPCRs plus hot topics (web site); full list of GPCR orphans with
- Allosterism (and functional coupling) – applied to GPCRs, ion channels, nuclear hormone receptors and kinases
- Biased agonism and functional selectivity
- GPCR heterodimers – standards and lists
- Alternative splicing recommendations
- Biomarkers
- Target validation
- Gene and protein lists for receptors and all drug sites coordinated between HGNC and NC-IUPHAR – with epigenetic consideration
- Antibodies – collaboration with Marie-Paule Lefranc at IMGT
- Interaction with the IUPHAR immunopharmacology section
- Cyclases and Phosphodiesterases
- Epigenetics, list of targets and pharmacological difficulties
- Non-coding RNAs – with HGNC – list with pharmacological difficulties
- Proteases and Hydroiases
- Pattern recognition receptors
- Transporters
- Producing the *Concise Guide to PHARMACOLOGY* which replaces GRAC
- Education site

NC-IUPHAR Meeting Report April 2013

The Spring NC-IUPHAR meeting was held in Edinburgh from 26-28th April 2013. In addition to many of the core members of the committee being in attendance, we were delighted to be joined by members of the NC-IUPHAR Clinical Translational Pharmacology Group (Sir Colin Dollery, Alex Phipps and David Webb), and our special guests Rab Prinjha and Yoshikatsu Kanai.

The meeting began with a pre-meeting of the NC-IUPHAR Clinical Translational Pharmacology Group (CTPG). There was a discussion on the difficulties and opportunities of preclinical and clinical translational research via therapeutic areas. The Chairman noted that translation is one of the major problems for the industry and the importance of the ability to translate targets and accommodate data. It was highlighted that databases containing clinical translational data must be searchable in terms of pathways, crosslinking etc. and exploration of curation of drugs by disease classes is favourable. Contribution by experts in relation to a variety of data for our gold standard ligands was also discussed.

Alex Phipps presented on biomarkers and there were subsequent discussions on oncology perspective for translation medicine; diagnostics and population enrichment; and quantitative clinical pharmacology. There was a general discussion on target validation, future drug targets for inclusion in the database, and the translational aspects of protein kinases.

The CTPG meeting was followed by general discussions on the interactions between IUPHAR and the British Pharmacological Society. This was followed by the database meeting, during which the curators gave a presentation on the current status and recent developments of the IUPHAR database and Guide to PHARMACOLOGY portal. Following the presentation, a number of issues were discussed, including developing the Guide to PHARMACOLOGY portal as a knowledge base for academics and students, enhancing the usability of the resources and the future curation of new drug targets for inclusion in the databases. The database chairman Tony Harmar then gave a presentation on the database team's requirements and plans for the next 3 years from the start of the Wellcome Trust funding period on the 1st November 2012. There was a major discussion on website branding as we move forward. A number of action points were put in place.

On the Saturday, NC-IUPHAR Chairman Michael Spedding welcomed the participants, gave an overview on the activities and structure of NC-IUPHAR, and presented the main objectives of the meeting. The morning began by revisiting important issues raised during the database meeting on the Friday afternoon, followed by a number of discussions relating to important issues in pharmacology today. The main topics that were discussed included: the application of allostery to GPCRs, ion channels, nuclear hormone receptors and tyrosine kinases receptors; biased signalling (Rick Neubig); the status of the voltage- and ligand-gated ion channels subcommittees presented by Bill Catterall and John Peters respectively; a report on the activity of the Emerging Pharmacology Committee dealing with the status of orphan GPCRs (Anthony Davenport); and Editor's reports by Eliot Ohlstein and Ian McGrath on the status of manuscripts in the pipeline for *Pharmacological Reviews* and *British Journal of Pharmacology*. During the day we heard presentations from Helgi Schiöth on 'Adhesion GPCRs' and issue with nomenclature; Rab Prinkha gave an excellent overview of different epigenetic enzymes and their possible roles and on the status of the activity of the epigenetics subcommittee; and with respect to a new activity by NC-IUPHAR, Doriano Fabbro gave a presentation on the complete pharmacological classification of tyrosine kinase receptors and future plans to include these as targets in the IUPHAR database; Alex Phipps spoke on personalised medicine and gave a summary of his slides presented on Friday. There were discussion on progress on ncRNAs and targets for the database, and on alignment with the immunopharmacology section of IUPHAR.

The meeting concluded on the Sunday following a full morning session devoted to the NC-IUPHAR financial report by Urs Ruegg, discussions on development of the new education site, reactivation of the nuclear hormone receptor subcommittees, drug targets in epigenetics and transporters, links with pharmacology societies around the world, and the programme for the 17th World Congress of Basic and Clinical Pharmacology in Cape Town, South Africa in 2014.

Michael Spedding ended the meeting with a summary of the main points achieved at the meeting and action points. Finally, participants were reminded about the next meeting to take place in Paris, October 2013 and the Edinburgh meeting in April 2014.

APRIL ATTENDEES

Stephen ALEXANDER, UK
Helen BENSON, UK
Tom BONNER, USA
Jonathan BRÜÜN, UK
Anthony DAVENPORT, UK
Jamie DAVIES, UK
Veronika DIVINCOVA, UK
Sir Colin DOLLERY, UK
Sam ENNA, USA
Doriano FABBRO, Switzerland
Elena FACCENDA, UK
Anthony HARMAR, UK
Yoshikatzu KANAI, Japan
Janos KISS, Hungary
Chris LANGMEAD, Australia
Simon MAXWELL, UK
Ian McGRATH, UK
Rick NEUBIG, USA
Eliot OHLSTEIN, USA
Adam PAWSON, UK
John PETERS , UK
Alex PHIPPS, UK
Rabinder PRINJHA, UK
Urs RUEGG, Switzerland
Joanna SHARMAN, UK
Christopher SOUTHAN, Sweden
Helgi SCHIÖTH, Sweden
Michael SPEDDING, France
Davis WEBB, UK

OCTOBER ATTENDEES

Alison ABBOTT, Germany
Stephen ALEXANDER, UK
Helen BENSON, UK
Jonathan BRÜÜN, UK
Tom BURRIS, USA
William CATTERALL, USA
Arthur CHRISTOPOULOS, Australia
John CIDLOWSKI, USA
Anthony DAVENPORT, UK
Sam ENNA, USA
Doriano FABBRO, Switzerland
Elena FACCENDA, UK
Jörg HAMANN, The Netherlands
Anthony HARMAR, UK
Kozo KAIBUCHI, Japan
Marie-Paule LEFRANC, France
Ian McGRATH, UK
Rick NEUBIG, USA
Adam PAWSON, UK
Alex PHIPPS, UK
Joanna SHARMAN, UK
Christopher SOUTHAN, Sweden
Helgi SCHIÖTH, Sweden
Michael SPEDDING, France

CAPE TOWN, SOUTH AFRICA
WCP 2014
17TH WORLD CONGRESS OF BASIC & CLINICAL PHARMACOLOGY

9th ADRENOCEPTOR SATELLITE MEETING

Receptor structure changes the pharmacology paradigm

James Black Conference of the *British Pharmacological Society.*

Major Sponsor: National Research Foundation of South Africa

Kruger National Park, South Africa, 19-23 July 2014

Plenary speakers include Brian Kobilka (Nobel Laureate for Chemistry in 2012) and Arthur Christopoulos

NC-IUPHAR Meeting October 2013

Chairman's Overview of achievements at the Autumn NC-IUPHAR meeting held in Paris, France from 11-13 October 2013.

- **How can we define in a database all the main receptor and drug targets coded by the human genome? Even more important, link them to therapeutics and the holy grail: pharmacological target validation;**

The immense recent growth of knowledge about drug targets, with their crystal structures, has been a huge help to drug discovery, and IUPHAR classifications are regularly used, together with the database. We approach defining nearly all potentially druggable sites encoded by the human genome. However, drug discovery has not grown at the same rate as our knowledge of drug targets, and part of this is due to the exponentially-increasing number of drug variables, and receptor polymorphisms, which may be crucial in disease states, and also contribute to controversy. Controlling these variables by identifying them *via* groups of experts has been shown to be a first step in dealing with these difficulties: their work appears in the Guide to PHARMACOLOGY (www.guidetopharmacology.org). This is done by an expert-driven analysis, using our ~80 subcommittees – everybody is welcome to contribute! – this means you!

The IUPHAR database (IUPHAR-DB; www.iuphar-db-org) has been subsumed into this larger effort – the Guide to PHARMACOLOGY, necessary because of our wish to cover ALL potential drug targets. A collaboration with the British Pharmacological Society has also produced the Concise Guide to PHARMACOLOGY, the successor to the BPS Guide to Receptors and Channels (GRAC). There are now a total of 2485 proteins presently in the database, of which the 48 NHRs, 142 VGICs, 6064 ligands, 599 approved drugs, 550 radioactive ligands, 41000 binding constants, 374 targets with mapped approved drugs, ~450 kinases with pharmacology.

- **How to assess drugs in development;**

Summary of discussions: 555 effect mediating drug targets, of which 19 are new chemical entities, 4 new targets/year; Clinicaltrials.gov reports >143000 trials from 183 countries; Schiöth et al. have analysed the Centrewatch database; 555 established targets, 475 clinical trial targets; FDA approved agents: 86% are small molecule; monoclonal Abs 3%; Clinical trial agents: 63% are small molecules; monoclonal Abs 9%; Chris Southan's analysis: Schiöth et al. 481 approved; 3-way DrugBank/ChEMBL/TTD 352 incl. research targets; 202 TOAD set selected for IUPHAR (we have 148 already!).

- **We use an expert-driven system of subcommittees, but we need to add on all the data-trawling methods which make sense ;**

A strategy is set in place where we address the drugs in development in Alzheimer's and several examples (in conjunction with ECNP) in psychiatry, data trawling, and linking with expert subcommittees. Thus we would be able to regroup targets in target types but also by therapeutic indication. This would also be of great use to patient groups.

- **We are contracted to extending the database to the primary targets of prescribed drugs, by the Wellcome grant: how far can we go towards drugs in development and their targets? Can we also indicate which of these targets have failed?**

This will be answered by practically working on the Alzheimer's and ECNP example, opening the door to collaborations with more patient and clinical organisations.

- **How can we incorporate the large and expanded body of knowledge for antibodies and their targets?**

A collaboration is now established with Marie-Paule Lefranc who runs the main Ab database (IMGT). This is part of an extension into immunopharmacology for IUPHAR. Marie-Paule gave an outstanding presentation of the development of the IMGT database which has now become the largest DB for antibodies and their use. There is considerable synergy between the NC-IUPHAR DB and IMGT, so we will work on practical examples and inter-database links between Abs to their protein targets. An Ab subcommittee has been formed.

- **How can we incorporate data about biomarkers for these targets?**

Target-based biomarkers will be prioritized to be included in the target validation aspects to develop (Alex Phipps). A document produced by Chris Southan has been circulated.

- **We have succeeded in producing a complete database to kinases and their inhibitors;**

Thanks to Doriano Fabbro and our curator Elena Faccenda, the full pharmacology is presented for the kinases, and a series of publications have been prioritized.

- **Substantial progress has been made on proteases, hydrolases and their inhibitors;**

Thanks to our new curator, Chris Southan, an extended set of targets, drugs and inhibitors has been added, as well as a new subcommittee chair established.

- **We are reinitializing our nuclear receptor committees and re-addressing these drug targets;**

John Cidlowski and Tom Burris have joined our effort. New committees are being formed and key issues such as allostery, tissue selective isoforms of NHRs will be addressed.

- **Evolving pharmacology;**

Classification of ligands and receptors – new receptor nomenclature of adhesion GPCRs.

- **Allostery: finalisation of a major document;**

Allostery has been redefined operationally with the terms refined, including ALMAs (allosteric ligand-modifying Abs).

- **Creation of an education site for pharmacology;**

The IUPHAR educational website: Simon Maxwell is leading this effort. We will create a new teaching initiative for pharmacology set up by a collaboration between IUPHAR, BPS and ASPET in the form of a website, based at Edinburgh, supported by IUPHAR-DB. We define the modalities and synergies with NC-IUPHAR, IUPHAR-DB and IUPHAR/BPS Guide to PHARMACOLOGY.

- **The World Congress of Pharmacology (WCP 2014);**

Is in Cape Town next July; NC-IUPHAR members are giving six plenary lectures and organising six symposia.

- **Continuing our financial future while remaining a unique independent group, composed of both academic and industrial scientists: we thank our sponsors and the Wellcome Trust.**

We need your help! If you have some time and expertise to contribute to our endeavour, please contact us: enquiries@guidetopharmacology.org

Our global network of expert contributors

NC-IUPHAR Subcommittee Chairs

G protein-coupled receptors

5-Hydroxytryptamine: Nick Barnes, John Neumaier
α_1-adrenoceptors: Dianne Perez
Apelin: Anthony Davenport
Bombesin: Robert Jensen
Calcium-sensing: Ed Brown, Hans Bräuner-Osborne
Cholecystokinin: Laurence Miller
Dopamine: Raul Gainetdinov
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
α_2-adrenoceptors: Lutz Hein
β-adrenoceptors: Terry Hébert, Martin Michel
Bradykinin: vacant
Cannabinoid: Roger Pertwee, Allyn Howlett
Complement peptide: Peter Monk
Endothelin: Anthony Davenport
Free fatty acid: Leigh Stoddart
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: Mariapia Abbrachio, Geoffrey Burnstock
Platelet-activating factor: vacant
Prostanoid: Robert Jones
Relaxin-like: Nick Barker
Trace amine: Janet Maguire
Vasopressin and oxytocin: Bernard Mouillac
Adenosine: Adriaan Izjerman
Angiotensin: Karnik Sadashiva
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: Manuel Tena-Sempere
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: vacant
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

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

John Cidlowski and Thomas Burris (Liaisons for all NHR subcommittees)

Epigenetics

Rabinder Prinjha

Protein kinases

Doriano Fabbro

Non-coding RNAs

Matt Wright

Transporters

Stephen Alexander

Editors, Concise Guide to PHARMACOLOGY

Stephen Alexander, Anthony Harmar, John Peters

NEWS BITE

Nuclear Hormone Receptors (NHRs)

John Cidlowski and Tom Burris join NC-IUPHAR

We are delighted to announce that John Cidlowski and Tom Burris have agreed to serve as chair and vice chair respectively to liaise with the NHR subcommittees on behalf of NC-IUPHAR. We are looking forward to working with them to get the NHR entries in the database updated, and thank them for volunteering their time.

EXPERT DRIVEN ANNOTATION

The IUPHAR Database and Guide to PHARMACOLOGY Portal are maintained by a team of curators, with guidance from NC-IUPHAR and an international network of ~700 expert contributors, providing expert-driven annotation of the pharmacology of drug target systems from peer-reviewed primary literature sources.

A global knowledge environment for pharmacology students, academic and industrial scientists, and the interested public.

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.

Data are sourced from and referenced to the primary literature (peer-reviewed research publications rather than review articles), with links to citations in PubMed. Wherever possible, data are supported by more than one literature source. After review by the curators to ensure accuracy and consistency with the rest of the information in the database, the data are added to the development server.

After approval by NC-IUPHAR, the data are transferred to the public database. Data are reviewed at regular intervals (at least yearly) by subcommittees and other contributors and updated as necessary.

NC-IUPHAR UPDATE ON ORPHAN GPCRs

Recommendations for new pairings with cognate ligands

The Evolving Pharmacology Group of NC-IUPHAR, in collaboration with the British Pharmacological Society, BJP and GRAC, has a major initiative to monitor the 'de-orphanisation' of orphan GPCRs. Our recent review (G-protein coupled receptor list: recommendations for new pairings with cognate ligands) provides and update to reflect new pairing, and describes the criteria used to recommend the pairing of an orphan receptor with its cognate ligand(s).

Recommendations are made for new receptor names based on eleven pairings for class A GPCRs. A further thirty receptors are highlighted where pairing have been reported but further input is needed from the scientific community, particularly from pharmacologist to validate these findings. The review represents a spectrum of knowledge and a snapshot of current classification: Fifty-seven Class A receptors are still considered orphans and information is given where a significant phenotype has been reported in genetically modified mice. In Class B, six pairings have been described in a single publication, with twenty-eight still classified as orphans. Seven orphan receptors remain in Class C, with one pairing described by a single paper. Visit IUPHAR-DB for further information which has been updated this year to coincide with the review.

Anthony Davenport, Chair of the Evolving Pharmacology Group

Recent NC-IUPHAR related publications

The collaboration between NC-IUPHAR, the American Society for Pharmacology and Experimental Therapeutics (ASPET) and the British Pharmacological Society (BPS) allows NC-IUPHAR subcommittees to publish nomenclature reports in *Pharmacological Reviews* and 'state-of-the-field' reviews in *British Journal of Pharmacology*. A selection of the most recent NC-IUPHAR related articles are listed below.

IUPHAR review article published on the Complement peptide receptors.

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.

IUPHAR review update article published on orphan G protein-coupled receptors.

Davenport AP, Alexander SP, Sharman JL, Pawson AJ, Benson HE, Monaghan AE, Liew WC, Mpamhanga CP, Bonner TI, Neubig RR, Pin JP, Spedding M, Harmar AJ. (2013) International Union of Basic and Clinical Pharmacology. LXXXVIII. G Protein-Coupled Receptor List: Recommendations for New Pairings with Cognate Ligands. Pharmacol Rev. 65: 967-86.

IUPHAR review article published on new concepts in pharmacological efficacy at G protein-coupled receptors.

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

IUPHAR Database and Guide to PHARMACOLOGY articles published in the Nucleic Acids Research Database Issue.

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. Nucleic Acids Research Jan;41(Database issue):D1083-8.

Pawson AJ, Sharman JL, Benson HE, Faccenda E, Alexander SP, Buneman OP, Davenport AP, McGrath JC, Peters, JA, Southan C, Spedding M, Yu W, Harmar AJ and NC-IUPHAR. (2014) Nucleic Acids Research (Database issue). *In press*.

An article recently published in the magazine of the Biochemical Society describes the vision for the Guide To PHARMACOLOGY portal.

Pawson AJ, Sharman JL, Benson HE, Faccenda E, Spedding M, and Harmar AJ. (2013) The Guide to PHARMACOLOGY portal - a one-stop pharmacology shop. The Biochemist. 35 (1): 36-39.

NEWS BITE...*Launching in December 2013*

The *Concise Guide to PHARMACOLOGY 2013/2014*

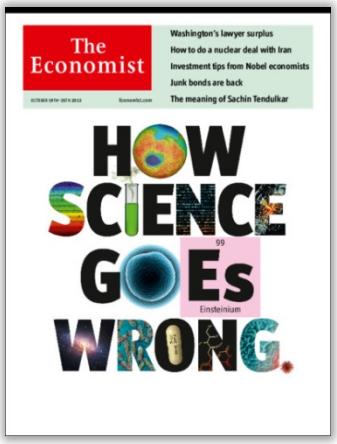
- Concise overviews of the key properties of over 2000 targets with pharmacology
- Links to open access knowledgebase of drug targets and their ligands (www.guidetopharmacology.org)
- Official IUPHAR classification and nomenclature for human drug targets
- Easy to use tables comparing related targets
- Produced in conjunction with NC-IUPHAR
- Links *via* www.guidetopharmacology.org to detailed views of target and ligand properties from the IUPHAR database
- Links to key literature
- Permanent, point-in-time record that will survive database updates
- Editors: Stephen Alexander, John Peters and Tony Harmar.

RESPONSE

A response to a recent editorial and article in *The Economist* (19th October 2013): THE ROLE OF NC-IUPHAR

Michael Spedding, Chairman of NC-IUPHAR

For some time now it has become clear that some papers published in high impact journals are just not repeatable. This is a problem for science as a whole, but which has become so serious that the front page of the Economist of October 19th carried the above figure (which captured my attention from the street, to buy the issue), with an editorial and an article: the last line of the editorial was: 'The false trails laid down by shoddy research are an unforgivable barrier to understanding'.



Very seductive ground-breaking science is difficult to judge, but can generate enormous costs if taken at face value. I am an industrial scientist and starting a research project based on high profile publications which aren't validated is risky. Thus several companies have started groups to validate critical studies, with only a quarter being validated (Prinz *et al*., 2011, Bayer Health Services). This isn't the science that we know ! (we trust). But we need to protect our young scientists from it. At the same time (17th October) *Nature* published a special issue entitled 'Impact', stating that evaluating research output and judging which work to fund is getting harder.

But this comes at a time when all our universities are totally taken up by the necessity to obtain a good Research Excellence Framework (REF) score which will be a major switch as to where the £1.6 billion distributed by the UK government, goes. Having papers published in high impact journals is an enormous magnet, with highly beneficial effects on subsequent careers and funding. However, in artificial re-engineered cells, the multiple variables which affect drug action may be very difficult to relate to more physiological (or pathophysiological) systems. It is the role of pharmacologists to ensure that these variables are well controlled. And NC-IUPHAR and the Guide to PHARMACOLOGY will start to include target validation criteria for our multiple receptor systems.

In this respect the San Francisco Declaration on Research Assessment (DORA) published general recommendation for all stakeholders in the research community (see: http://am.ascb.org/dora/) : Do not use journal-based metrics, such as Journal Impact Factors, as a surrogate measure of the quality of individual research articles, to assess an individual scientist's contributions, or in hiring, promotion, or funding decisions.

Getting into the highest impact journals requires 'remarkable' findings. But the distribution of citations in these journals is very skewed – probably for obvious reasons, as citations over time show the articles which are really useful, and the converse is also true. Furthermore getting into these journals condemns authors to suffering high failure rates, and consequently spending more and more effort on submitting rather than experimenting. The answer is quite simple : use the author's citations, in appropriate professional journals where the referees know the field, rather than the journal in which the article is published. High impact journals are fantastic reads, and of great value, but do not represent the full wealth of science.

However, there is another problem which faces the REF analysis : cooperation. In the authors opinion, a paper with multiple authors applying different techniques to a problem is more likely to lead to a breakthrough, which is reproducible, than the work of a single lab. However, in in some analyses of research productivity, only one lab gets the benefits : how can this help cooperative research?

Here NC-IUPHAR tries to use validated data, as we require replication before data are put into the database, and we use expert subcommittees who will only cite papers which have passed the test of time. This requires much work from our subcommittees but it leads to a more solid set of knowledge which is publically curated and available. Here, however, we have an issue with REF, as work on reviews and public databases is not rewarded: how can we validate data using experts if their work is not acknowledged? The ability to counter irreproducible research should be a criteria, based on the seriousness of the problem. Thus we are going to include target validation in the Guide to PHARMACOLOGY, as it develops. You can comment on tweet feed.

Prinz F, Schlange T, Asadullah K. Believe it or not: how much can we rely on published data on potential drug targets? Nat Rev Drug Discov. 2011 Aug 31;10(9):712. doi: 10.1038/nrd3439-c1.

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How can you contribute to NC-IUPHAR projects?

If you have some time and expertise – contact the curators at enquiries@guidetopharmacology.org

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The database team

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From left to right; Veronika Divincova (project administrator), Elena Faccenda (curator), Joanna Sharman (database developer), Adam Pawson (curator) and Helen Benson (curator); Edinburgh, Scotland

Chris Southan, cheminformatician/ curator; Göteborg, Sweden

...a parting thought

We welcome contributors!

Although we already cover about half of the targets of prescription medicines in the Guide to PHARMACOLOGY portal, there are many important areas that we do not yet cover. Moving forward, our goal is to add about 900 new targets (including all the targets of approved drugs). We have already made major advances on this, but 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

CAPE TOWN, SOUTH AFRICA
WCP 2014
17TH WORLD CONGRESS OF BASIC & CLINICAL PHARMACOLOGY

NC-IUPHAR at WCP2014

The 17th World Congress of Basic and Clinical Pharmacology takes place in Cape Town, South Africa, 13-18 July 2014.

There is a very exciting program and a number of NC-IUPHAR committee and subcommittee members, and affiliates are giving plenary lectures and symposia.

Plenary lectures by NC-IUPHAR affiliates:

IUPHAR's Analytical Pharmacology Lecture, **Arthur Christopoulos** - Adventures in allostery: From function to structure

Yoshikatsu Kanai - Amino acid transporters in oncology

Simon Maxwell - Challenges in training tomorrow's prescribers

Kozo Kaibuchi - Protein Phosphorylation in Signal transduction

Richard Neubig - Signal transduction in therapeutics

Doriano Fabbro - Tyrosine kinase inhibitors

Martin Michel - Autonomic pharmacology of the urogenital tract

Symposia including NC-IUPHAR affiliates:

Orphan G protein-coupled receptors- What are the new ligand and new drug targets? (Tony Harmar, Anthony Davenport, Janet Maguire, Stephen Alexander)

Structural Basis for Ion Channel Pharmacology (including Bill Catterall)

NC-IUPHAR and guide to pharmacology (Sir Colin Dollery, Michael Spedding, Tony Harmar, Simon Maxwell)

Update in geriatric pharmacology Optimal Prescribing in Older Patients: The challenge of Multiple Comorbid Conditions and Polypharmacy (including Darrell Abernethy)

Evolution, sport and modern diseases (including Michael Spedding)

Emerging Drug Targets (including Richard Neubig)

Glucocorticoids: new insights into mechanisms of action (including John Cidlowski)

Epigenetic mechanisms in cell- and drug-based heart failure therapies (including Lutz Hein)