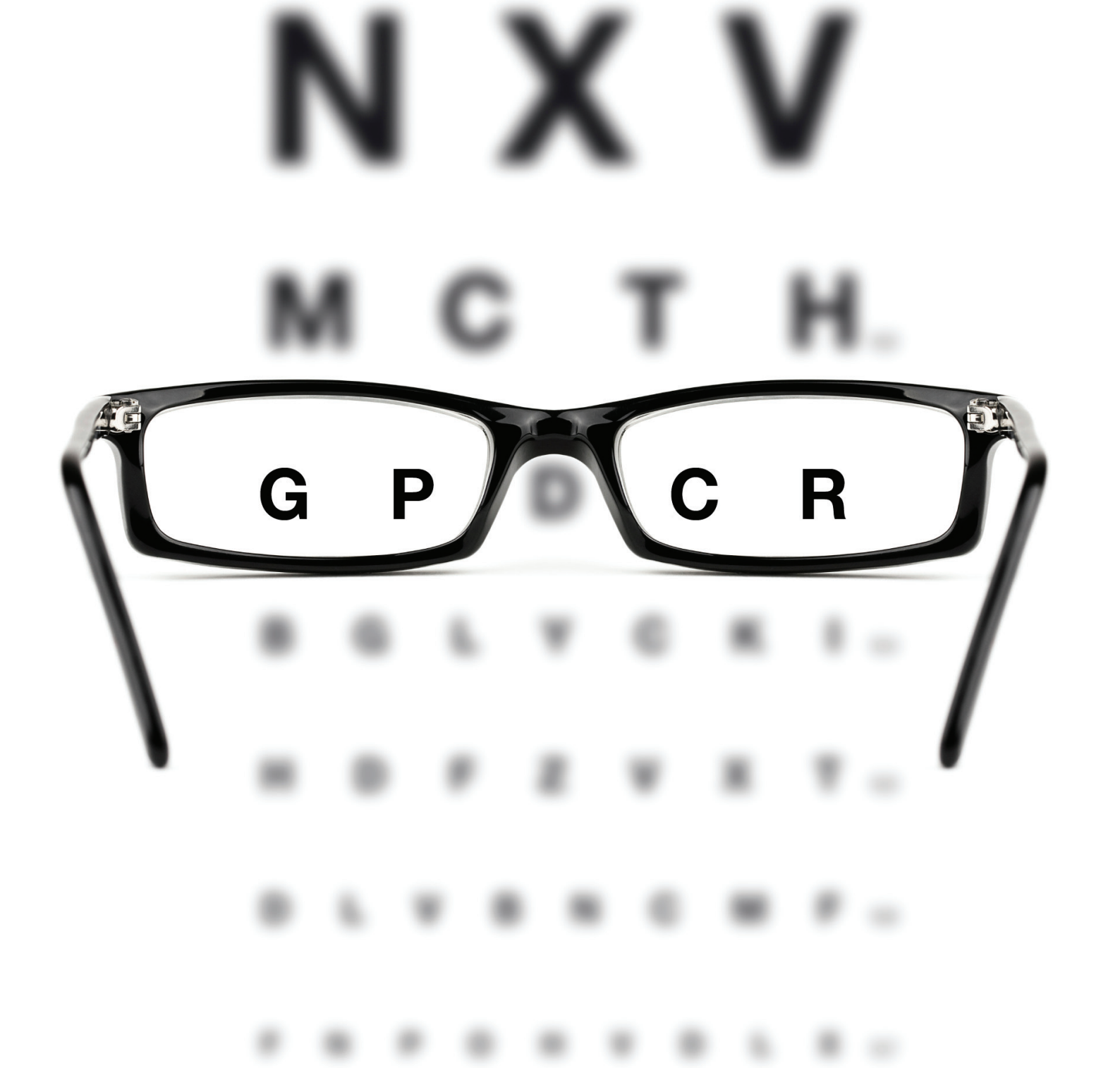
PHARMACOLOGY MATTERS

BRITISH PHARMACOLOGICAL SOCIETY
Today's science, tomorrow's medicines

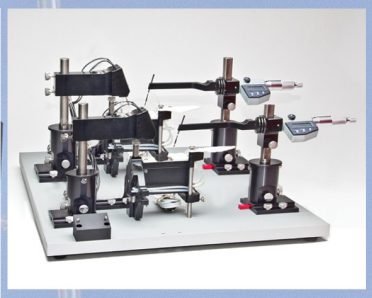
ISSN No: 1757-8175
Volume 6, Issue 1 - April 2013



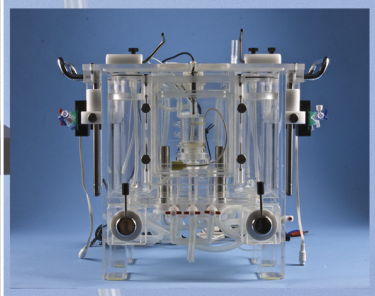
International collaboration | GPCR research | Nobel Prizes | pharmacology blogs

World Precision Instruments

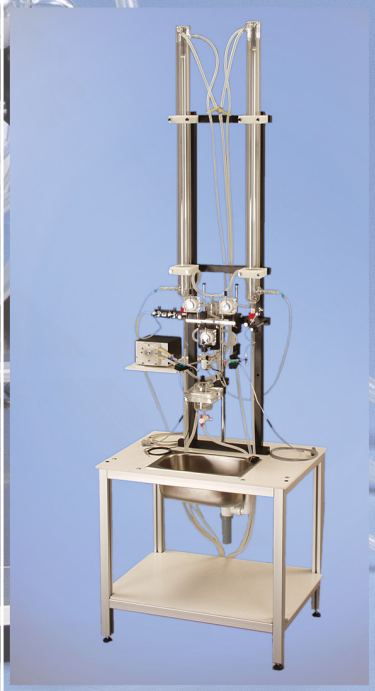
Take a *closer look* and find all the instruments you need for your Research at *WPI*:



- Horizontal Tissue Bath



- Compact Langendorff System



- Langendorff System
- Isolated Perfused Organ System

for detailed information and to download your free copy of our current catalogue please visit

www.wpi-europe.com

World Precision Instruments
1 Hunting Gate
Hitchin, Hertfordshire SG4 0TJ

Tel +44 (0)1462 424700
Fax +44 (0)1462 424701
E-mail wpiuk@wpi-europe.com

Guest Editorial

Robin Plevin
Editor, Pharmacology Matters

The 2012 Nobel Prize for Chemistry was shared by Robert Lefkowitz and Brian Kobilka in the field of G-protein coupled receptors (GPCRs). GPCRs are an area of intense interest for many BPS members and it is fitting that in this issue we review the impact these award winning discoveries have made. Articles from The Leicester Group, Fiona Marshall (Heptares Therapeutics Ltd) and Margaret Cunningham, one of our young pharmacologists, reflect the widespread interest and activity in this field.

It is useful to remember that GPCRs were not the only area of Pharmacology to be the subject of recent Nobel awards. The 2011 prize for medicine was awarded partly for the discover of the Toll-like receptors, a key class of receptor which has opened the way up for understanding innate immunology and its relevance for pharmacology. Clare Bryant's article The Toll of the Nobel, looks back on that award on P14.

The Presidents of BPS and ASPET introduce *Pharmacology Research & Perspectives*, our joint open access journal, on P5 and you can catch up on all other BPS activities with updates from our Chief Executive, Meetings, Education and the Young Pharmacologists throughout this issue.

This issue focuses on the impact of GPCRs on pharmacology and the pharmacologists whose work encompasses them. I do hope you enjoy the insight provided by these excellent articles.

Robin

Contents

Cover credit: iStockphoto

Your BPS

Jonathan Brüün
BPS Chief Executive

A very warm welcome to you all.

For the uninitiated, this section (formerly *'A View from…'*) is my opportunity to let you know about developments in your Society, and at your head office in London. So I should begin by highlighting one of the major developments in that area – your HQ now has a name: The Schild Plot.

As part of the 2013 *'Your BPS'* campaign – a programme of events and activities aiming to prioritise engagement with our members – BPS members were invited to suggest a name for the building at 16 Angel Gate, which the Society has owned since 1994. The campaign certainly caught the attention: 59 nominations were received in total from a whole range of members, from undergraduate students to retired pharmacologists. A shortlist of four final contenders was decided upon by BPS Council before members and over 800 attendees at the BPS Annual Meeting in December picked their favourite.

So, where did the name come from? In the middle of the last century, BPS member Heinz Otto Schild successfully described the body's response to drugs using a type of graph now known as 'the Schild plot'. 'The Schild Plot' was inspired by this pharmacological achievement and emerged as a clear winner. Thanks to Noël Harris, University of Northampton and Roland S. G. Jones, University of Bath for a great suggestion, and to all who voted to get *'Your BPS'* up and running.

Photo from left to right: Jono Brüün, Humphrey Rang, Noël Harris, and Roland S. G. Jones

Whenever you see *'Your BPS'* in 2013, there will be a chance for interaction: from nominating inspirational figures in pharmacology for the launch of a BPS 'Hall of Fame' in September, to providing photography to illustrate a new BPS calendar – just two of the activities planned for later this year. At the core of the campaign, though, will be a membership-wide survey to assess the needs of pharmacologists today, and understand what more the Society could be doing to support them.

Looking ahead, 2013 will see the BPS supporting and leading the pharmacologists of the future with a portfolio of online careers information for A level students and undergraduates, which will be hosted on our existing blog site www.pharmacologynow.org. We will also continue to represent the pharmacology community by contributing to government's Life Sciences Strategy, with sector partners, and through the collaborative work of the Drug Discovery Pathway Group, a BPS initiative which involves over 20 Learned Societies from the sector.

At the time of writing, we have less than a month to go until the joint meeting hosted by BPS and the American Society for Pharmacology & Experimental Therapeutics (ASPET) at Experimental Biology 2013, in Boston, USA. Highlights will include the Sir James Black Honorary Lecture by Nobel Prize winner and recent BPS honorary fellow Professor Robert J. Lefkowitz as well as a welcome reception to launch the Societies' new open access journal *Pharmacology Research & Perspectives*.

Finally, I would also like to highlight two announcements affecting the BPS team, both of which will have taken place by the time this edition of *Pharmacology Matters* goes to print.

The first concerns our Deputy Chief Executive, Kevin Kearns, who after service of almost 6.5 years, has elected to leave the Society in order to focus his career on freelance project-related work. Kevin contributed substantially to the BPS, not least as regards the development and management of the Society's finances and governance, and will have worked with many of those reading this magazine over that time. I'm sure you will therefore join me in thanking Kevin for his service, and wishing him well for the future.

We are seeking a replacement in Kevin's role, and will keep you in touch with developments.

Becky Hughes will also be leaving the BPS Meetings & Events team at the end of March – literally for pastures new! She will be spending this summer teaching horse riding at a US summer camp, with plans to teach equestrianism full-time. Becky has been a big part of the success of our Meetings programme in recent years, and I'm sure she'll flourish in her new endeavours.

Becky's replacement as Events Officer will be Helen To, who joins us from the Institute and Faculty of Actuaries where she has worked as Events and Communities Assistant for the last two years. We're looking forward to welcoming Helen to the team and I'm sure she and Karen Schlaegel, our Head of Meetings, will continue to ensure we deliver an outstanding service in that important part of the Society's activities.

I hope you enjoy this GPCR-themed edition of *Pharmacology Matters*.

International collaboration, a vital component of scientific progress

John Lazo
ASPET President

Phil Routledge
BPS President

John S. Lazo, PhD is currently the President of the American Society for Pharmacology and Experimental Therapeutics (ASPET). In addition, he is the Associate Dean for Basic Research and the Harrison Distinguished Professor in the Department of Pharmacology at the University of Virginia School of Medicine. He is also holds a secondary appointment in the Department of Chemistry.

Phil Routledge, OBE, MD, FRCP, FRCPE, FRCGP, FBTS, FBPharmacolS, FFPM is currently the President of the British Pharmacological Society (BPS). Phil is also Professor of Clinical Pharmacology at the Department of Pharmacology, Therapeutics & Toxicology within the School of Medicine at Cardiff University.

Alexander Fleming, a Scotsman, is credited with the discovery of penicillin in 1928, and Howard Florey (an Australian pharmacologist and pathologist), Ernst Chain (a German-born biochemist) and their colleagues with identifying its potential role as an antibacterial agent. Reducing this proposal to practice, however, only occurred when the Englishman, Norman G. Heatley travelled to the USA, and scientists in Merck and Company and E.R. Squibb and Sons eventually became involved collaboratively. Production was facilitated by the large-scale deep fermentation process designed by the American engineer, Margaret Hutchinson Rousseau. An American chemist, John C, Sheehan, then successfully synthesised penicillin in 1957, laying the foundation for the future production of many effective penicillin analogues[1]. As a result of these individuals and their international collaborations, perhaps the most important class of life-saving antibiotics are now available to millions of people worldwide. This is only one of numerous examples of how joint international ventures advance pharmacology.

ASPET has long demonstrated its commitment to promoting international collaboration. In 1929 the Society was involved with other FASEB organizations in hosting the *Thirteenth International Physiological Congress* (held in Boston) and when the *First International Pharmacological Meeting* was held in Stockholm, Sweden, in August 1961, ASPET members were well represented among the 1500 delegates. Five years later, ASPET was involved in the founding of the International Union of Pharmacology (IUPHAR) now called the International Union of Basic and Clinical Pharmacology[2].

BPS with over 3000 members from 60 countries worldwide considers itself to be a truly international organization. BPS has a strong culture of collaboration, both nationally and internationally. In 1984 we hosted the *9th IUPHAR* congress in London, which attracted 4,369 scientists from 68 countries and, more recently, the *5th EPHAR* congress (2008) in Manchester. Like ASPET, BPS is a member of IUPHAR and was also involved in the founding of the Federation of European Pharmacological Societies (EPHAR) in 1990 and the European Association of Clinical Pharmacology and Therapeutics (EACPT) in 1993.

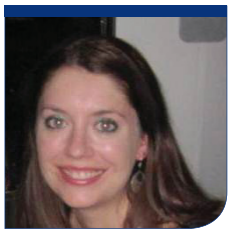
Good communication internationally between learned scientific societies stimulates the collaborative links that can accelerate the development of pharmacological agents from conception to clinical use. Our members believe that the only way to grow is to experiment. We are delighted that our two Societies have therefore decided to jointly launch an open access online-only journal *Pharmacology Research & Perspectives (PR&P)*. This journal will publish original research and reviews in pharmacology, clinical pharmacology and therapeutics, perspectives on these topics, and articles on education related to these areas. The open access approach will allow a rapid and efficient publication process to be followed by access via PubMed Central immediately after publication. We begin accepting manuscripts for *PR&P* in April 2013 and we warmly welcome Dr Mike Curtis, a longstanding BPS member, as the journal's first Editor.-in-Chief.

The history of penicillin illustrates the importance of interdisciplinary teams in advancing science. We are therefore pleased that the launch of *PR&P* will occur at *Experimental Biology 2013* in Boston, when pharmacologists, anatomists, biochemists, nutritionists, pathologists, physiologists as well as scientists from many other disciplines will be meeting to share ideas and hopefully develop new and productive collaborations, achieving together what they could not do alone.

References

1. Selections from *Discoveries in Pharmacology*. Eds MJ Parnham & J Bruinvels. Elsevier, Amsterdam (1987)
2. Parascandola J. A Brief History of ASPET on Its Centennial Anniversary, *Molecular Interventions* 2007; 7: 288-30.

Just the tonic for GPCR research – the 2012 Nobel Prize for Chemistry



Liz Rosethorne
Novartis Institute for Biomedical Research

Robin Plevin
Editor Pharmacology Matters

RP: I would like to welcome you to a *Pharmacology Matters* round table discussion, which focuses on the 2012 Nobel Prize in the area of G protein-coupled receptors (GPCRs). With me today are John Challiss (JC), Andrew Tobin (AT) and Gary Willars (GW), who host the bi-ennial BPS focused meeting on Cell Signalling, one of the most popular events in the BPS calendar. In the past this meeting has attracted key leaders in the GPCR field, including Brian Kobilka, who shared this year's Nobel Prize for Chemistry with Robert Lefkowitz. Also joining in today is Elizabeth Rosethorne (LR), the industrial representative of the Young Pharmacologists, who's also co-chairing the discussion. My name is Robin Plevin (RP). First of all John, it would be useful to give a little background as to the nature of the GPCR field at the time that Professor Lefkowitz began his research career.

JC: If my memory serves me correctly, Bob Lefkowitz published his first research paper around 1970. At that time our concept of a receptor as a physical entity was pretty rudimentary. Work by Sutherland and Rall had indicated what might lie beyond the initial ligand-receptor binding event and work by Rodbell's group strongly suggested that the 'receptor' and 'effector' (at the time only adenylate cyclase would have been considered an effector) were physically separate, but interacted with each other directly or indirectly. What Lefkowitz realised was that to make progress in understanding receptors beyond the purely pharmacological, we would need methods to 'see' receptors. His early papers focused on the relatively new technique of radioligand binding, initially to characterize ACTH binding to its receptor in the adrenal cortex.

GW: Lefkowitz's clinical speciality was cardiology and very early on he made a decision to focus on adrenoceptors, because of their clinical relevance and the availability of well-characterized agonist and antagonist ligands that could distinguish adrenoceptor subtypes. In developing radioligand binding methods (alongside other groups, including that of Steve Nahorski here in Leicester), a number of fundamental discoveries were made, for example, how guanine nucleotides affect agonist-receptor binding and, following on from Rodbell's work, the concept of guanine nucleotide binding (G) proteins modulating receptor affinity for its ligand.

JC: Throughout his career Lefkowitz has been a leading player in developing conceptual and mathematical models that account for GPCR behaviours, beginning with his seminal work at the start of the 1980s with Andre DeLean and others to introduce the ternary complex model.

RP: Andrew I know you're interested in more direct biochemical approaches used.

AT: Yes, I think all of the novel pharmacological findings of Lefkowitz and his collaborators, which at this time included Brian Kobilka, were in some respects fantastic bonuses along his primary path to isolate biochemically the β-adrenoceptor. This was achieved in the early 1980s when a homogeneous, active adrenoceptor was isolated. Perhaps a greater breakthrough came with the cloning of the β2-adrenoceptor in 1986. Rhodopsin had been sequenced by Edman degradation some years earlier, but that wasn't possible for non-visual GPCRs. It must have been a true eureka moment for the Lefkowitz lab that the β2-adrenoceptor and rhodopsin shared both sequence homology and topological similarity with respect to the seven transmembrane-spanning domains, and the realisation that the adrenoceptor was in the same gene family as rhodopsin. That, I think we all know from Lefkowitz's subsequent descriptions was a very big surprise.

RP: So how was the breakthrough followed up?

JC: The 1986 paper opened the way for an intense period of GPCR cloning: the Lefkowitz lab published almost the entire family of adrenoceptors. This flow of information quite quickly led to a transition from a pharmacological appreciation of GPCR diversity to a molecular biological/genetic understanding. The beauty and universality of the GPCR seven transmembrane domain structure was revealed, as was a clear indication of the true diversity of this receptor superfamily.

RP: That advance must have had implications for industry. Liz, would you like to comment?

LR: Yes, the biggest breakthrough in terms of drug screening and development was the ability to study receptors in isolation. Up until this point, a lot of the characterisation had been done in isolated mammalian tissues and organ bath experiments, which come with their own inherent problems, including low throughput and correlating potency of drugs in animals with that in human. The ability to clone and express human receptors led to detailed studies of mechanisms of action, as well as the use of high throughput screening to assess hundreds of thousands of compounds against a particular receptor.

GW: Another important development that followed the initial burst of GPCR cloning was the genetic manipulation of receptors. This enabled Lefkowitz, Kobilka and other groups to explore in molecular detail ligand-receptor and receptor-G protein interactions and led to a number of surprising breakthroughs. For example, the concept of constitutively-active GPCRs and the realization that many antagonists were actually inverse agonists, able to decrease the basal activity of a receptor. An obvious application of this would be to select inverse agonists over neutral antagonists where a disease was caused by increased constitutive activity of a particular GPCR.

LR: It also explained some of the things we'd been seeing in our clonal cell lines – constitutive activity when the receptor is over-expressed. Because of this, we've had to reclassify the way we think about ligands. Instead of thinking in simple terms of agonist versus antagonist; we now have a whole range of efficacies from positive to negative that will have an effect in disease.

RP: If we can now return to the basic understanding of GPCR function in relation to receptor desensitization.

JC: Many pharmacologists probably recognise Lefkowitz's lab first and foremost for its pioneering work with regard to receptor regulation. It was known from the early 1970s that rhodopsin was phosphorylated following light activation and Lefkowitz, with his clinical background, also appreciated that tachyphylaxis was a significant problem with regard to particular drug therapies, so a natural extension of his GPCR work was to seek more molecular explanations of how receptors become desensitized.

RP: Andrew, can you add to that?

AT: This again was seminal work initiated with Jeff Benovic who was working in the Lefkowitz group at the time. They had this notion, as John has just described, that phosphorylation of the receptor was important for receptor desensitization. Jeff managed to purify the β-adrenergic receptor kinase (βARK, now known as GRK2) and was able to reconstitute it, along with the receptor and G protein in a phospholipid vesicle, expecting it to uncouple receptor from G protein. They found that the more they purified the kinase the better it phosphorylated the receptor, but the less well it uncoupled receptor from G protein, suggesting that they were missing something. Around that time visual arrestin was identified as interacting with rhodopsin and the Lefkowitz lab hypothesised that there was an arrestin-like molecule more widely associated with other GPCRs. They got hold of visual arrestin, found that it did indeed uncouple the receptor, albeit less well than visual arrestin uncouples rhodopsin, and that led them to clone the first non-visual arrestins as components of the desensitization machinery. GRKs and arrestins – job done!

GW: Of course the role of arrestins eventually proved to be far more complex than we first thought. Arrestin bound to the phosphorylated receptor not only provides a docking linker for components of the pathway that turn off signalling, but can also scaffold other signalling pathways to the receptor. The Lefkowitz lab again made, and continues to make, game-changing discoveries in this alternate, G protein-independent signalling by GPCRs.

RP: How does that discovery relate to the concept of agonist 'bias' in signalling?

LR: We're starting to understand the idea that activating one particular pathway might lead to a beneficial effect while activation of a second pathway might lead to unwanted side-effects. If it is possible to develop a drug that would only activate the beneficial signalling pathways and not the potential side-effect pathways this would lead to better drugs with better safety profiles.

GW: The μ-opioid receptor is good example here, where the suggestion is that you wish preferentially to activate the G protein-dependent pathway to develop anti-nociceptive properties, whereas the arrestin scaffold and receptor internalization pathways you perhaps don't want to activate and therefore a G protein signalling favouring biased agonist could be useful. However, I guess for a lot of therapeutic cases from an industry perspective, you're not so certain which signal transduction pathways you might want to selectively activate/inhibit?

LR: No, because this is such a novel idea, until we start to look at biased signalling in either primary human tissues, or in animal models we are not going to know which pathway we need to target. However, the availability of biased ligands for GPCRs has opened new avenues for industry to exploit in terms of drug discovery, as has the discovery of allosteric ligands, which bind to an alternate site to the endogenous ligand to modulate the activity of the receptor.

RP: I think now that the GPCR story has perhaps come full cycle with the recent breakthrough work from the Kobilka lab in the area of crystallizing GPCRs.

JC: Absolutely. This was a masterstroke by the Kobilka group and one or two other groups around the world who have been ambitious enough to take on this massive challenge. The possibility of high quality structural information on GPCRs first came to the community's attention with the 2000 paper by Krzysztof Palczewski's lab reporting a rhodopsin structure at pretty good resolution. However, it was the first Kolbilka papers in 2007/2008 that really blew people's socks off. There was a general feeling that GPCR research had taken an enormous leap forwards.

RP: There were some hurdles to be jumped to actually make that breakthrough?

AT: Well, I think 'hurdles' is quite an interesting word in this context - I'd have thought 'mountains' would probably be more appropriate. I think that Brian Kobilka himself described it as irrational optimism, this particular project. To obtain the first β-adrenoceptor crystals the Kobilka lab in collaboration with others had to incorporate a staggering number of innovations, not least engineering the receptor so that it could be crystallized by either incorporating T4-lysozyme in place of the third intracellular loop, or generating an antibody fragment that stabilized the receptor structure – these approaches together with defining the correct lipids that can adopt a cubic lipid phase within which the crystals actually form were crucial advances. In Kobilka's subsequent structure of the active conformation of the β-adrenoceptor in complex with a $G\alpha_s$ protein he had to make another remarkable innovation, this time generating antibodies in llamas – so called nanobodies - that stabilize the active β-adrenoceptor/ $G\alpha_s$ complex. So yes, maybe a mountain range is probably the better way to describe it.

JC: It's amazing how things advance so quickly; it seems as though *Nature* and *Science* are now regularly publishing new GPCR crystal structures and not only using conventional crystallography methodologies, it looks as if Nuclear Magnetic Resonance (NMR) is catching up to some extent in providing more dynamic information about GPCR structure.

AT: I think that's right because one of the big problems with the GPCR crystal structure is the very properties which make them attractive to biology, namely the conformational flexibility of GPCRs, makes them really tough targets for the structural biologists. Locking down this conformational flexibility is one solution, but John's quite right in saying that the next set of biophysical techniques to be applied to GPCRs will actually be able to better interrogate their conformational landscapes.

RP: Finally, I'd like to bring up another aspect of GPCR structure-function – the issue of their quaternary structure.

AT: I think that we would all accept that class C GPCRs exist as dimers. The lab of Jean-Philippe Pin and others provided really nice evidence to show that the $GABA_B$ receptor is a constitutive dimer of $GABA_{B1}$ and $GABA_{B2}$ subunits, with one *7TM* monomer binding ligand leading to a transactivation of the other *7TM* monomer and G protein activation. However, the big question is whether class A GPCRs will form dimers. The work of Brian Kobilka, particularly that in collaboration with Roger Sunahara, has involved the reconstitution of single GPCRs into nanoparticles with a single G protein molecule. They were able to reconstitute receptor pharmacology perfectly and provide a strong case for a functional monomeric GPCR.

GW: Does that mean that dimers don't exist? Of course not. There is a wealth of evidence that favours the existence of GPCR dimers and higher order oligomers. How important quaternary GPCR structure might be in regulating the pharmacology of ligands *in vivo* is presently completely unknown – this is one of the many challenges on the horizon in GPCR research.

RP: Thank you all for your participation today.

Elizabeth Rosethorne is an Investigator at the Novartis Institutes for Biomedical Research in Horsham, UK, working in the Respiratory Disease Area. Much of her research focuses on GPCR pharmacology, with a particular emphasis on biased signalling and the kinetics of intracellular signalling mechanisms.

John Challiss is Professor of Molecular & Cellular Pharmacology at the University of Leicester. He has been involved in signal transduction research for over 25 years and his lab focuses increasingly on vascular GPCR signalling and regulation in health and disease.

Andrew Tobin is a programme leader with the MRC Toxicology Unit at Leicester and also holds a University Chair in Cell Biology. His research focuses on the mechanisms of regulation of GPCRs and how GPCR signalling impacts on physiological responses.

Gary Willars is a Senior Lecturer in the Department of Cell Physiology and Pharmacology at the University of Leicester. His current research focuses on allosteric regulation and the role of ligand structure and processing in determining signalling outcomes and receptor trafficking.

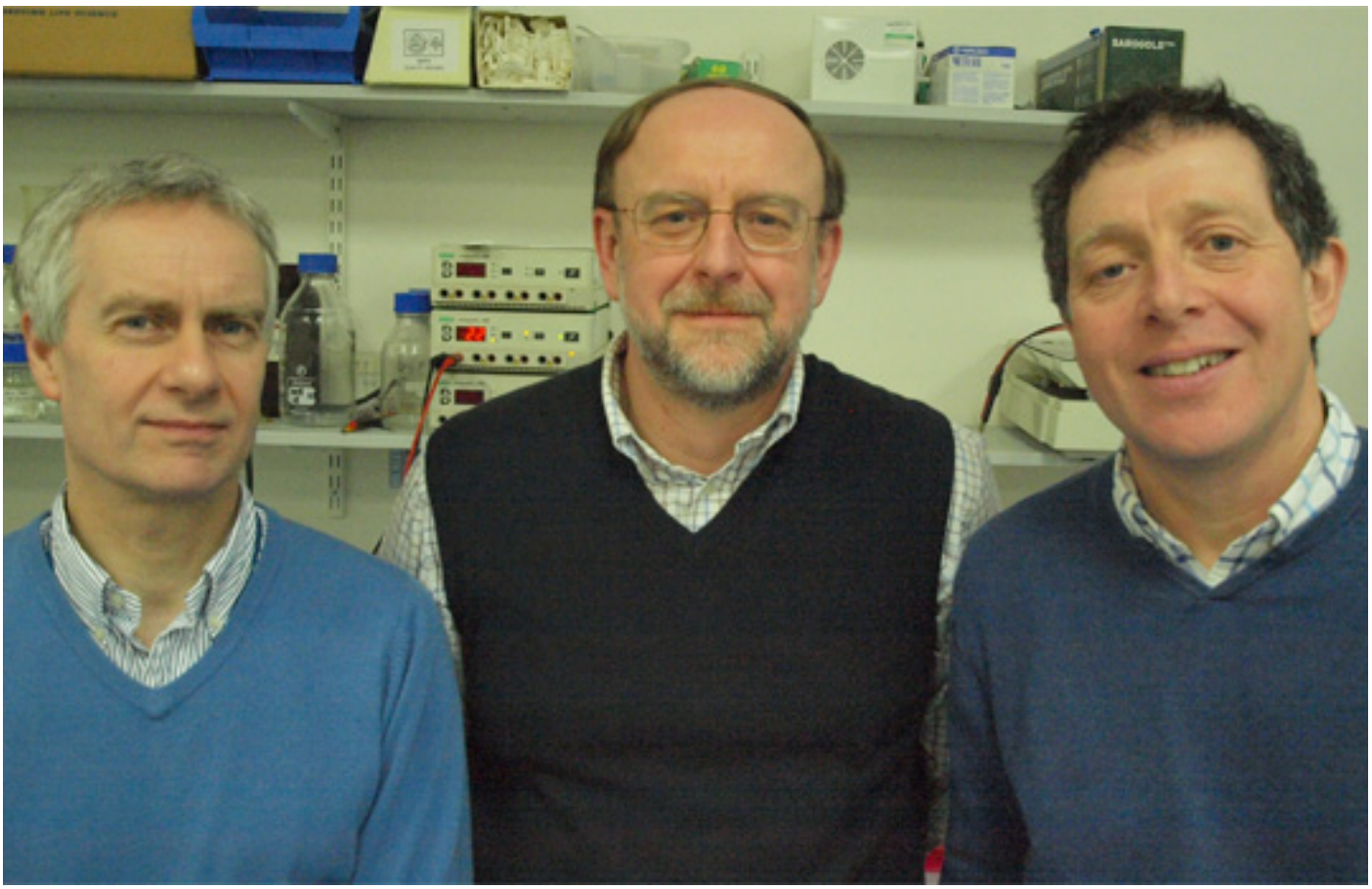


Photo from left to right: Gary Willars, John Challiss, Andrew Tobin

From Nobel Prizes to GPCR drug discovery

Fiona H. Marshall
Heptares Therapeutics Ltd

Fiona is a cofounder and Chief Scientific Officer of Heptares Therapeutics Ltd, a G-protein-coupled receptor (GPCR) drug discovery company that uses a novel structure based drug discovery approach utilizing stabilized receptors (StaRs). She has over 20 years experience in genomic-based drug discovery with particular expertise on GPCRs. She spent 12 years at GlaxoSmithKline, where she held a number of senior positions including Head of the Department of Molecular Pharmacology. Her group was responsible for the discovery of the $GABA_B$ receptor heterodimer, the identification of RAMPs, the cloning of the CGRP and adrenomedullin receptors, the identification of the nicotinic acid receptor and the deorphanization of GPR41 and 43. She was Director of Discovery Pharmacology, Europe, for Millennium Pharmaceuticals and then spent several years as an independent consultant to a variety of venture capital and biotech companies. She is currently Chair of the CRUK Drug Discovery Committee and Vice-chair of the Wellcome Trust Seeding Drug Discovery Committee.

The history of drugs directed at GPCRs dates from the ancient use of plant derived substances through to today's synthetic compounds designed by computers to fit perfectly into pockets within the receptor. For the last 40 years the research of Robert Lefkowitz and Brian Kobilka which led to the 2012 Nobel prize for chemistry has driven new approaches in drug discovery at this important family of proteins.

The first drugs directed at GPCRs were discovered by people experimenting with plant substances for both medicinal use as well as for their mind altering properties. Opioids, cannabinoids and the alkaloids such as atropine and hyoscine from deadly nightshade and henbane were used by the ancient Greeks and Romans. In the early 1900s work by researchers such as John Langley led to the appreciation that the effects of such drugs were mediated by 'receptive substances' present in tissues. Bioassays using isolated tissues in organ baths were established and used by pharmaceutical companies to screen for bioactive substances. A highly effective approach was to test analogues of natural hormones which had improved properties with respect to selectivity and metabolic stability. This approach was used successfully to discover drugs such as the beta blockers including propanolol by Sir James Black (Black, 1989) and subsequently the longer-acting beta agonists such as salbutamol for the treatment of asthma. A similar strategy was also successfully used for the peptide angiotensin receptor. Here small molecules were designed which mimicked the 3-dimensional structure of the angiotensin peptide leading to the approval of the first angiotensin receptor blocker (ARB) losartan for the treatment of hypertension (Timmermans *et al*, 1991). The majority of GPCR drugs on the market today derive from these approaches.

In the late 60s and early 70s Lefkowitz (Lefkowitz *et al*, 1970) in the USA and Humphrey Rang and William Paton (Rang and Paton, 1965) in the UK developed radiolabelled versions of adrenocorticotrophin hormone, catecholamines and atropine and showed that these could bind specifically to receptors in tissues. Radioligand binding assays soon replaced bioassays as the screen of choice by pharmaceutical companies. Libraries of compounds could be tested for their ability to displace hormone binding from membranes. These assays were more robust than many tissue bioassays and could produce accurate measures of drug affinity. They could also be run in higher throughput as microplate assays were established coupled to automated cell harvesters that could separate bound from free ligand. Binding assays were used effectively to improve on existing GPCR drugs, resulting for example in the discovery of further ARBs with improved potency and duration of action compared to losartan. Other drugs discovered using radioligand binding to tissues include the neurokinin NK1 antagonists eventually marketed for chemotherapy-induced nausea.

In 1986 the cloning of the β2-adrenergic receptor by Kobilka and Lefkowitz heralded a new age in GPCR research and strategies for drug discovery (Dixon *et al*, 1986). Cloning of the first receptor required a Herculean effort in purifying sufficient protein from native tissue to allow protein sequencing and subsequent cloning of the entire gene sequence. Once the first receptor was cloned it was then possible to use low stringency hybridization approaches to search for related sequences. The GPCR superfamily began to emerge and it was soon realised that the similar 7-transmembrane domain structure present in rhodopsin was common across a very large family of related proteins. For some receptor families that had been extensively characterised by pharmacology, receptor cloning provided the molecular confirmation of existing pharmacological classification. In some cases cloning identified additional receptor subtypes not shown by pharmacology – for example the histamine H_4 receptor (Nguyen *et al*, 2001). In a few cases such as the $GABA_B$ receptor the suggestion of pharmacological subtypes failed to materialise into different molecular targets. It now appears likely that differences in pharmacology were due to interactions with accessory proteins (Schwenk *et al*, 2010).

The availability of cloned receptors enabled pharmaceutical companies to screen compounds on human receptors rather than animal tissue. This proved important for several receptors such as the neurokinin NK1 receptor and the β3 receptor where compounds showed significant differences in activity between human and rodent receptors. Recombinant DNA technologies also led to a switch from binding assays to functional assays in cells as the preferred screening platform. Such assays could be run in high throughput allowing companies to screen millions of compounds at the start of drug discovery programmes. GPCR drugs identified following HTS campaigns include Pfizer's CCR5 antagonist – Maraviroc for HIV infection (Wood and Armour, 2005) and Merck's dual orexin antagonist Suvorexant for insomnia (Cox *et al*, 2010). Unfortunately HTS approaches have led to a gradual increase in the molecular weight and lipophilicity of GPCR

targeted drugs (Congreve *et al*, 2011), properties which result in an increased likelihood of toxicity and a higher attrition rate during development (Empfield and Leeson, 2010). GPCR drugs derived from HTS such as the CGRP antagonist talcagepant and the orexin receptor antagonist almorexant are examples of compounds derived from HTS screens that have failed during development for off-target toxicity.

In addition to studying GPCRs directly, Lefkowitz and colleagues also identified the role of interacting proteins including G protein receptor kinases and β-arrestin. This led to the discovery that GPCRs could signal through β-arrestin independent of G protein signalling and that some agonist ligands could bias the receptor towards one pathway or another. Biased ligands may have an improved safety profile in the case where undesirable side effects are mediated by a different signalling pathway (Whalen *et al*, 2011). This approach is underway to develop better tolerated opioid agonists for pain treatment.

The use of molecular techniques to study GPCR structure function in Lefkowitz's lab led to the identification of constitutively active mutants (CAMs) by Susanna Cotecchia and others (Lefkowitz *et al*, 1993). This led to the recognition that antagonists could be neutral or inverse agonists and that these differences could have consequences for drug discovery. For example, different antipsychotic profiles are found for antagonists vs inverse agonists at dopamine receptors (Strange, 2008) whilst cannabinoid neutral antagonists may have improved side effects over inverse agonists (Janero, 2012). Inverse agonists have been identified to specifically target receptors with high natural levels of constitutive signalling such as the histamine H_3 receptor (Schwartz, 2011) and ghrelin receptor (Holst *et al* 2003). CAMs have also been exploited by pharmaceutical companies to screen for ligands at orphan receptors as screening can be carried out in the absence of a ligand.

Despite the many developments outlined above GPCR drug discovery been hampered by the lack of detailed structural insight compared to soluble targets such as kinases. In addition modern techniques in drug discovery including biophysical methods and fragment screening require purified stable proteins. Kobilka and colleagues have provided many breakthroughs in this area in particular with the development of ligand affinity methods for protein purification and the use of fusion proteins to assist in the crystallization of receptors. These developments led to the first high resolution crystal structure of the β2 receptor from Kobilka in collaboration with Ray Stevens team at the Scripps published in 2007 (Cherezov *et al*). These methods have been complemented by the ability to stabilise receptors for purification and structural studies (Tate and Schertler, 2009). More than 15 GPCR structures have been solved enabling pharmaceutical companies to use computer based virtual screening to generate starting points for drug discovery (Langmead et al, 2012) and to used structure based design to find more potent and selective drugs with improved physicochemical properties (Congreve *et al*, 2011). The structure of the active complex of a GPCR with the cognate G protein from Kobilka (Rasmussen *et al*, 2012) further enables computational approaches to drug design by providing an understanding of the changes which occur during activation and how these may be differentially stabilised by the binding of agonist or antagonist drugs.

References

Black J. Drugs from emasculated hormones: the principle of syntopic antagonism. *Science*. 1989; 245:486-93.

Cherezov V, Rosenbaum DM, Hanson MA, Rasmussen SGF, Thian FS, Kobilka TS, Choi H, Kuhn P, Weis WI, Kobilka BK *et al.*: High-resolution crystal structure of an engineered human β2-adrenergic G protein-coupled receptor. *Science* 2007; 318:1258-1265.

Congreve M, Langmead C, Marshall FH. The use of GPCR structures in drug design. *Adv Pharmacol*. 2011; 62:1-36.

Cox CD, Breslin MJ, Whitman DB, Schreier JD, McGaughey GB, Bogusky MJ, Roecker AJ, Mercer SP, Bednar RA, Lemaire W, Bruno JG, Reiss DR, Harrell CM, Murphy KL, Garson SL, Doran SM, Prueksaritanont T, Anderson WB, Tang C, Roller S, Cabalu TD, Cui D, Hartman GD, Young SD, Koblan KS, Winrow CJ, Renger JJ, Coleman PJ. Discovery of the dual orexin receptor antagonist [(7*R*)-4-(5-chloro-1,3-benzoxazol-2-yl)-7-methyl-1,4-diazepan-1-yl][5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl]methanone (MK-4305) for the treatment of insomnia. *J Med Chem*. 2010;53:5320-32.

Dixon RA, Kobilka BK, Strader DJ, Benovic JL, Dohlman HG, Frielle T, Bolanowski MA, Bennett CD, Rands E, Diehl RE, Mumford RA, Slater EE, Sigal IS, Caron MG, Lefkowitz RJ, Strader CD. Cloning of the gene and cDNA for mammalian beta-adrenergic receptor and homology with rhodopsin. *Nature* 1986; 321:75-9.

Empfield JR, Leeson PD. Lessons learned from candidate drug attrition. *IDrugs*. 2010; 13:869-73.

Holst B, Cygankiewicz A, Jensen TH, Ankersen M, Schwartz TW. High constitutive signaling of the ghrelin receptor–identification of a potent inverse agonist. *Mol Endocrinol*. 2003;17:2201-10.

Janero DR.Cannabinoid-1 receptor (CB1R) blockers as medicines: beyond obesity and cardiometabolic disorders to substance abuse/drug addiction with CB1R neutral antagonists. Expert Opin *Emerg Drugs*. 2012;17.

Langmead CJ, Andrews SP, Congreve M, Errey JC, Hurrell E, Marshall FH, Mason JS, Richardson CM, Robertson N, Zhukov A, Weir M. Identification of novel adenosine A(2A) receptor antagonists by virtual screening. *J Med Chem*.2012; 55:1904-9

Lefkowitz RJ, Cotecchia S, Samama P, Costa T. Constitutive activity of receptors coupled to guanine nucleotide regulatory proteins. *Trends Pharmacol Sci*. 1993; 14(8):303-7.

Lefkowitz RJ, Roth J, Pastan I. Radioreceptor assay of adrenocorticotropic hormone: new approach to assay of polypeptide hormones in plasma. *Science* 1970; 170:633-5.

Nguyen T, Shapiro DA, George SR, Setola V, Lee DK, Cheng R, Rauser L, Lee SP, Lynch KR, Roth BL, O'Dowd BF. Discovery of a novel member of the histamine receptor family. *Mol Pharmacol*. 2001; 59:427-33.

Paton WD and Rang HP. The uptake of atropine and related drugs by intestinal smooth muscle of the guinea-pig in relation to acetylcholine receptors. *Proc R Soc Lond B Biol Sci*. 1965.

Rasmussen SG, DeVree BT, Zou Y, Kruse AC, Chung KY, Kobilka TS, Thian FS, Chae PS, Pardon E, Calinski D, Mathiesen JM, Shah ST, Lyons JA, Caffrey M, Gellman SH, Steyaert J, Skiniotis G, Weis WI, Sunahara RK, Kobilka BK. Crystal structure of the β2 adrenergic receptor-Gs protein complex. *Nature* 2011; 477:549-55.

Schwartz JC. The histamine H_3 receptor: from discovery to clinical trials with pitolisant. *Br J Pharmacol.* 2011;163:713-21.

Schwenk J, Metz M, Zolles G, Turecek R, Fritzius T, Bildl W, Tarusawa E, Kulik A, Unger A, Ivankova K, Seddik R, Tiao JY, Rajalu M, Trojanova J, Rohde V, Gassmann M, Schulte U, Fakler B, Bettler B. Native GABA(B) receptors are heteromultimers with a family of auxiliary subunits. *Nature* 2010; 465:231-5.

Strange PG. Antipsychotic drug action: antagonism, inverse agonism or partial agonism. *Trends Pharmacol Sci.* 2008; 29(6):314-21

Tate CG, Schertler GF. Engineering G protein-coupled receptors to facilitate their structure determination. *Curr Opin Struct Biol.* 2009; 19:386-95

Timmermans PB, Carini DJ, Chiu AT, Duncia JV, Price WA Jr, Wells GJ, Wong PC, Wexler RR, Johnson AL. Angiotensin II receptor antagonists. From discovery to antihypertensive drugs. *Hypertension.* 1991; 18:136-42.

Whalen EJ, Rajagopal S, Lefkowitz RJ. Therapeutic potential of -arrestin- and G protein-biased agonists. *Trends Mol Med.* 2011; 17:126-39.

Wood A, Armour D. The discovery of the CCR5 receptor antagonist, UK-427,857, a new agent for the treatment of HIV infection and AIDS. *Prog Med Chem* 2005; 43:239-71.

BPS BRITISH PHARMACOLOGICAL SOCIETY
Today's science, tomorrow's medicines

About the BPS

With over 3,000 members, the British Pharmacological Society (BPS) is the primary learned society in the UK concerned with research into drugs and the way they work. Its members teach and carry out research in higher education, the pharmaceutical and biotechnology industries, hospitals, and health services. Many members play a key role in teaching medical students the principles of pharmacology, which underpin safe and effective prescribing in the NHS. Others are responsible for the clinical trials that translate new medicines from molecule to society.

Join us

If you are interested in networking with our members and strengthening our community, you should identify which of the individual categories you are eligible to apply for:

Full Member
For Pharmacologists and Clinical Pharmacologists.
Standard Tariff - £90

Associate Member
Open to individuals having a professional interest in pharmacology or a closely related subject who do not have the necessary qualifications to become Members.
Standard Tariff - £60

Postgraduate Member
Open to individuals studying for higher degrees in pharmacology, or closely related subjects. Also open to clinicians in training who have a specific interest, or intend to follow a career in clinical pharmacology.
Standard Tariff - £20

Undergraduate Member
Open to individuals studying for degrees in pharmacology and other undergraduates whose courses include a substantial pharmacology component. Also open to medical students at any stage of training.
Standard Tariff - Free

CLICK Become a member
www.bps.ac.uk/members

Benefits:

- free or discounted registration to BPS scientific meetings including *Pharmacology 2013*
- enjoy access to the full online versions of our journals: *British Journal of Pharmacology* and *British Journal of Clinical Pharmacology*
- become eligible for bursaries and travel grants to attend meetings in the UK and overseas
- apply for prestigious study awards and prizes such as the A J Clark Studentships and Wellcome Prize Medal
- receive regular editions of *Pharmacology Matters*, the BPS magazine
- opportunities to contribute to furthering pharmacology, across a range of activities through the Society's committees, special interest groups and working parties

Follow us:

Facebook
Twitter
YouTube

Contact

Paul Tizard
Membership & Awards Officer
Tel: +44 (0) 20 7239 0171
E-mail: membership@bps.ac.uk

How GPCRs changed my life

Margaret Cunningham
University of Bristol

A candid insight into the progression of an early career GPCR researcher: from bedpan* to bench side

Margaret studied for her undergraduate degree in Biochemistry and Pharmacology at the University of Strathclyde. She was awarded the British Pharmacological Society (BPS) AJ Clark PhD studentship (2006-2009) to work in the laboratory of Professor Robin Plevin at the University of Strathclyde investigating the molecular pharmacology and traffic of the Proteinase-activated receptor (PAR) family. Margaret joined Dr Stuart Mundell as a British Heart Foundation (BHF) funded post-doctoral researcher in 2010, where she continues her research examining the regulatory mechanisms controlling platelet GPCR function.

Similar to most pharmacologists, I didn't really appreciate the first time I was introduced to G-protein coupled receptors (GPCRs); it was during my undergraduate degree when I was given an array of unpronounceable agonists and antagonists to test in the guinea pig ileum organ bath preparation. At the time of the practicals, like most students in the class, I remember being more concerned with the dark art of serial dilutions and striving to not mess up or kill the tissue (which routinely happened) in order to get perfect text book dose response curves (which were rarely achieved). It was actually my biochemistry lectures that sparked my interest in the GPCR field, delivered by the late Dr Eve Lutz**. Dr Lutz would often enthusiastically incorporate current examples of relevant areas in the field of GPCR regulation to bolster her lecture series encompassing gene expression and protein function. Dr Lutz also encouraged me further by inviting me to join the university's Pharmacological Society as an undergraduate member and attend Cell Biology research seminars. This early exposure to research stimulated my interest further and I was able to get a summer student placement in the laboratory of Professor Plevin's studying the intracellular signalling in response to protease-activated receptor-2 (PAR_2), (Goon Goh *et al* 2008). Some might say that the grey of Professor Plevin's hair grew exponentially with the period of time I spent in his laboratory that summer. However, that said, it was there where my "love affair" with the mighty GPCR was born.

During that summer and early autumn, many external guest speakers were invited to present at the Cell Biology seminar program at the University of Strathclyde. One of particular significance for me was a presentation given by Professor Graeme Milligan (University of Glasgow) detailing the concept of GPCR dimerisation. After that seminar and following extensive perusal of the literature surrounding this area of research, I approached Professor Plevin with a proposal to explore the PAR family further in relation to their potential to form functional dimers as a potential PhD project. I still remember the chuckle Professor Plevin let out as I sat opposite him delivering my spiel like an excitable child high on E-numbers… an irrepressible trait that remains with me still. It was at that meeting we decided to submit my proposal for consideration for a British Pharmacological Society (BPS) AJ Clark PhD Studentship award and fortunately I was successful.

Prior to starting my PhD, on reflection, it was clear that certain technical aspects of my PhD project would be difficult to undertake solely at the University of Strathclyde. This was a blessing in disguise as I was then able to then go on and collaborate with a number of other great laboratories including those of Professor Graeme Milligan and Professor Gwyn Gould (University of Glasgow) and Dr Joris Robben (RUNMC, Nijmegen, Holland). During this period I learned the importance of not being too proud to admit the limitations of my own capabilities, and if needed, to collaborate with those best placed in the field to learn from and gain the necessary skills first hand. The application of all of these skills enabled me to confidently investigate both dimerisation and intracellular trafficking of the PAR family in extensive detail.

Over the course of my three years I was able to explore the regulation of PAR_4 trafficking to demonstrate functional heterodimerisation between PAR_2 and PAR_4 as a critical regulator in anterograde traffic and signal transduction of PAR_4. This work was published last year in the Journal of Biological Chemistry (Cunningham *et al* 2012). The data that I generated from my project enabled me to attend the 2009 Molecular Pharmacology Gordon Research Conference in Italy. It was at this meeting where I was finally given the opportunity to put faces to the names of the researchers whose research I had followed ardently in the years prior to and during my PhD. What can I say, it's not every day you find yourself lost in the medieval town of Barga with a Nobel laureate-to-be, Professor Robert Lefkowitz. Star struck, I did what any self respecting GPCR groupie would do… I respectfully asked that his wife take a picture of me standing in the presence of her husband, the Godfather of GPCRs. Shameless I know! On a not-so-shameless note, the meeting gave me insight into the very latest unpublished research steering the GPCR field at an international level at that time and I got to meet many leaders in the field. This confirmed within me the desire to continue my work in this particular area following completion of my PhD.

For my first postdoctoral position I have relocated to Bristol to work in the laboratory of Dr Stuart Mundell (BPS Novartis prize winner 2010) as part of the Bristol Platelet Group (www.bristolplatelets.org) at the University of Bristol. So far my research in the Mundell lab has involved investigating the regulatory mechanisms that underlie PAR and purinoreceptor function in platelets (Nisar and Cunningham *et al*, 2012 and Cunningham *et al* 2013a). Through an on-going collaborative effort involving both Dr Mundell and Dr Nisar, as part of a Genotype and Phenotype of Platelets (GAPP) consortium# led by Professor Steve Watson (University of Birmingham), I have been fortunate to be involved in vital translational research investigating patients displaying bleeding tendencies where mutations with key platelet GPCRs have been identified (Cunningham et al 2013b). Prior to my move to Bristol, most of my training up until that point involved the use of *In vitro* cell based systems using over-expression of receptors to provide mechanistic

insight into receptor regulation. Here, this work has enabled me to be involved in studies that explore native GPCR function in patient platelets and to investigate novel mutations in GPCRs which may possibly be linked to human pathologies.

Moving to Bristol was a period of many new beginnings for me. I was taking my initial step onto the ladder of academic research in my first postdoctoral position and impending motherhood for the first time. There is no denying that maintaining that all important harmonious work/life balance has been an immense challenge. One thing I recognized was the need to have proper mentorship, someone to go to for advice who had similar experiences and had progressed in science irrespective of family commitments. For me, the BPS mentorship scheme I have been actively involved in has been an invaluable help throughout this period.

Perhaps I wouldn't say that GPCRs changed my life, but the research I have been involved in since my summer project certainly opened my eyes to the diversity that encompasses GPCR research. A spark ignited early enough in my studies to mark the beginning of an enjoyable research career, which I continue to make steady progress in to this day.

Footnotes

*Margaret supported her undergraduate studies by working in an old people's home where she used a lot of bed pans

**Eve Lutz died Saturday 20th August 2011. She was the first person to clone the VIP_2 receptor (Lutz *et al* 1993 and 1999)

The GAPP Consortium exists as a collaboration between research groups at the University of Bristol, University of Birmingham and the University of Sheffield

References

Cunningham MR, McIntosh KA, Pediani JD, Robben J, Cooke AE, Nilsson M, *et al*. Novel role for proteinase-activated receptor 2 (PAR2) in membrane trafficking of proteinase-activated receptor 4 (PAR4). *J Biol Chem* 2012; 287(20): 16656-16669.

Cunningham MR, Nisar SP, Cooke AE, Emery ED, Mundell SJ. Differential endosomal sorting of a novel P2Y(12) purinoreceptor mutant. *Traffic* 2013b.

Cunningham MR, Nisar SP, Mundell SJ. Molecular mechanisms of platelet P2Y12 receptor regulation. *Biochem Soc Trans* 2013a; 41(1): 225-230.

Goon Goh F, Sloss CM, Cunningham MR, Nilsson M, Cadalbert L, Plevin R. G-protein-dependent and -independent pathways regulate proteinase-activated receptor-2 mediated p65 NFkappaB serine 536 phosphorylation in human keratinocytes. *Cell Signal* 2008; 20(7): 1267-1274.

Lutz EM, Shen S, Mackay M, West K, Harmar AJ. Structure of the human VIPR2 gene for vasoactive intestinal peptide receptor type 2. *FEBS* Lett 1999; 458(2): 197-203.

Lutz EM, Sheward WJ, West KM, Morrow JA, Fink G, Harmar AJ. The VIP2 receptor: molecular characterisation of a cDNA encoding a novel receptor for vasoactive intestinal peptide. *FEBS* Lett 1993; 334(1): 3-8.

Nisar SP, Cunningham M, Saxena K, Pope RJ, Kelly E, Mundell SJ. Arrestin scaffolds NHERF1 to the P2Y12 receptor to regulate receptor internalization. *J Biol Chem* 2012; 287(29): 24505-24515.

Professor Robert Lefkowitz and Dr Margaret Cunningham

The Toll of the Nobel

Clare Bryant
University of Cambridge

The award to Lefkowitz and Kobilka was not the only recent Nobel Prize of significance to pharmacology. In this article Clare Bryant reminds us of the recent breakthrough in immune biology, which has implications for the understanding of a novel class of receptors and their role in disease.

Clare Bryant is Reader in Immunopharmacology at the University of Cambridge. She has worked on Pattern Recognition Receptor pharmacology for several years. Her research group studies how Pattern Recognition Receptors influence the host immune response to bacterial infection and on determining the molecular mechanisms of agonism, antagonism and inverse agonism at these receptors.

In 2011 the Nobel prize in Physiology or Medicine was divided and awarded to three recipients: Ralph Steinman, Bruce A. Beutler and Jules A. Hoffmann. Ralph Steinman was awarded the prize "for his discovery of the dendritic cell and its role in adaptive immunity" whilst Bruce A. Beutler and Jules A. Hoffmann were awarded theirs "for their discoveries concerning the activation of innate immunity". Sadly Ralph Steinman died two days before the announcement and, in a very unusual step, the committee still awarded him the prize.

So why was a Nobel prize awarded for the activation of innate immunity and why would it be of interest to pharmacologists? Up until the late 90s there was a key gap in our understanding of how specific immunity against a pathogen was generated. It was well accepted that the host could indeed mount a pathogen-specific immune response to control infection, but no one knew how the host initially detected pathogens or whether this was then linked to the adaptive immune response mediated through antigen presentation to T-cells. In 1989, however, in his paper "Approaching the Asymptote?" introducing the Cold Spring Harbor Symposium on Immune Recognition, Charlie Janeway wrote "I believe it is safe to state that our understanding of immunological recognition is approaching some sort of asymptote". Immunologists had long known that receptors existed on T-cell and B-cells. These cells could recognize any purified protein, but they were unable to generate an immune response to them unless the proteins were mixed with an adjuvant, such as Freunds, which contains killed *Mycobacterium tuberculosis* organisms (Janeway called this the immunologist's "dirty little secret"). In his paper Janeway hypothesized that there were a family of innate immune receptors or Pattern Recognition Receptors (PRRs) that recognized particular pathogen associated molecular patterns (PAMP) associated with pathogens, such as the *M. tuberculosis* molecules in Freunds, and this would provide the "*second signal*" for T-cell and B-cell activation.

Much work followed addressing Janeway's hypothesis. Cytokines commonly provide the "second signal" to accompany antigen presentation to drive adaptive immunity and one transcription factor, nuclear factor kappa B (NFκB), was known to be important in the gene transcription of many cytokines. Activation of the interleukin-1 receptor, for example, stimulates NFκB to induce the production of many cytokines. Gay and Keith, in 1991, noted the similarity of the signaling or Toll/Interleukin-1 receptor (TIR) domain of the interleukin-1 receptor to the signaling domain of the *Drosophila* Toll receptor. Toll activates the transcription factor Dorsal-related immune factor which is the fly NFκB homologue. Lamaitre and Hoffman, in 1996, showed that flies carrying a mutation in Toll lacked resistance to fungal infection, thus identifying the first PRR. Medzhitov and Janeway cloned the first human Toll-like receptor (TLR) in 1997, TLR4, although the ligand for this receptor was unknown. Activation of a hybrid version of this TLR, lacking the extracellular domain of the receptor, triggered NFκB activation. A potential source for Janeway's "second signal" was therefore identified and supported his PRR hypothesis. Beutler, using positional cloning, showed that the chromosome locus in mice resistant to lipopolysaccharide (LPS), the active component of Gram-negative bacteria, contained a mutation in the TLR4 gene that prevented it from functioning and thus the first mammalian PAMP receptor was identified. Work from the laboratory of Shizuo Akira using mice where TLR4 was "knocked-out" confirmed TLR4 as the PRR for LPS and furthered showed that these mice, whilst completely resistant to LPS, were more susceptible to Gram-negative bacteria than wild-type mice showing the importance of this receptor in helping the host to control bacterial infection. TLR4 did not detect Gram-positive bacteria suggesting the potential of receptor subtypes able to respond specifically to different pathogens. Indeed, other TLRs were subsequently identified as receptors for different families of bacteria, viruses and a class of endogenous proteins called danger molecules or DAMPs. Identification of the adaptor proteins and associated signaling pathways stimulated by TLRs rapidly followed.

Since this seminal work over 10,000 papers have been published on TLRs and other families of PRRs have been identified including RIG-Like Receptors and Nod-Like Receptors. The receptors for many pathogens have now been identified, although a number of PRRs still remain as orphan receptors. It is clear from the numerous studies using knock-out mice, many of which were generated in the Akira laboratory, that the PRRs are absolutely required to control infections. Mutations in PRRs have also been identified in people. Some PRR mutations predispose humans to serious childhood infections, for example a mutation in TLR3 leads to severe HSV infections. Some people are born with PRR mutations that render them constitutively active, for example

in NLRP3, which leads to patients suffering from generalized inflammatory syndromes. Generally the phenotypes of people with PRR mutations are less severe than those seen in "knock-out" mice. It also appears that patients with PRR mutations who survive childhood do not appear to suffer form severe infections in adult life, which leads to some interesting immunological questions that are currently unresolved.

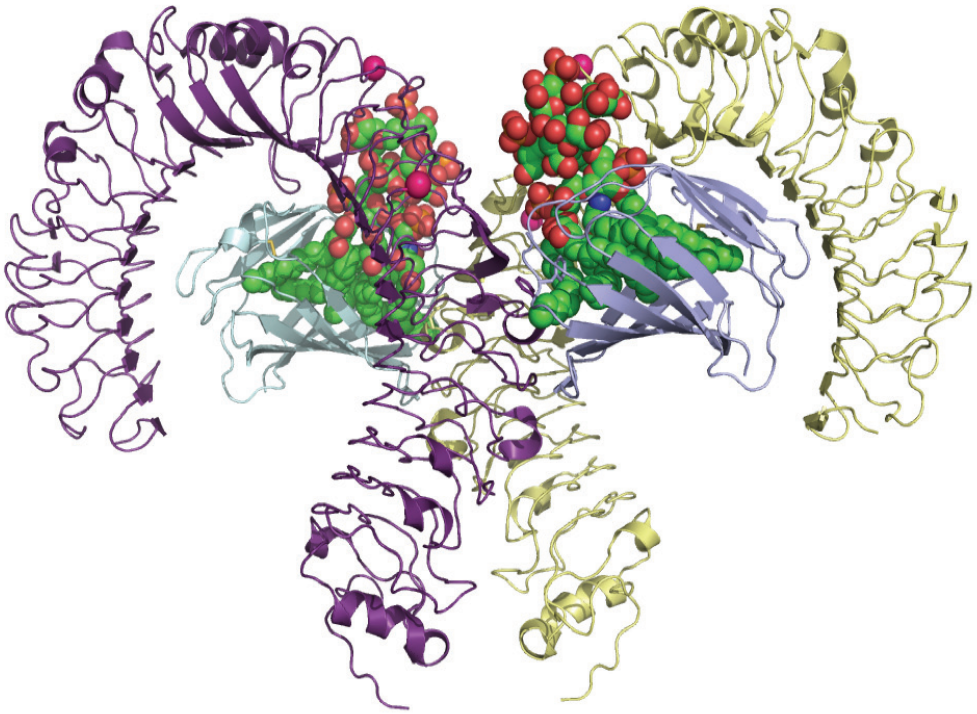
These and other studies bring the PRRs to the fore as a key area of pharmacological research which is yet to be fully developed. Recent data has emerged on the potential association between mutations in PRRs and a wide range of diseases from cancer to allergy and diabetes suggesting that therapeutic targeting of these receptors is likely to be rewarding. Pioneering work by Lee, Wilson and Segal have led to crystal structures of the extra-cellular domains of many of the ligand-bound TLRs now being available. Agonist-bound TLRs form dimeric structures. The availability of the crystal structures makes therapeutic targeting of PRRs a realistic prospect. Indeed some compounds have already been developed to target specific TLRs. Eritoran is a TLR4 antagonist that has been tested in human sepsis clinical trials and monophosphoryl lipid A, a partial agonist at TLR4, has been developed as an adjuvant in the Gardasil cervical cancer vaccine.

Despite these advances there are still major gaps in our fundamental understanding of basic pharmacological concepts for these receptors such as how full, partial or inverse agonism occur. This is likely due to the structural complexity of not only the TLRs, but also the arrangement of their downstream signaling proteins.

One of the TLR signaling complexes has been crystallised (MyD88 in association with IRAK4; the Myddosome) and it forms an unusual oligomeric complex suggesting PRR signaling is achieved by a series of complicated macromolecular interactions. This structural complexity is nicely illustrated by considering how LPS, a full agonist, activates TLR4. LPS first binds to two proteins (LPS binding protein and CD14) to facilitate ligand presentation to the TLR4/MD2 receptor complex. LPS then binds to MD2/TLR4 which then dimerises with a second TLR4/MD2 complex (Fig 1a). Dimerisation of the LPS-TLR4/MD2 complex then recruits the adaptor proteins Mal and MyD88 to then go on and, presumably, form the Myddosome signaling complex (Fig 1b). A second signaling pathway is also activated (through Tram and Trif) but we do not know whether the proteins in this pathway also form a macromolecular complex. How these kind of complex protein rearrangements may change to facilitate partial agonism remains to be determined.

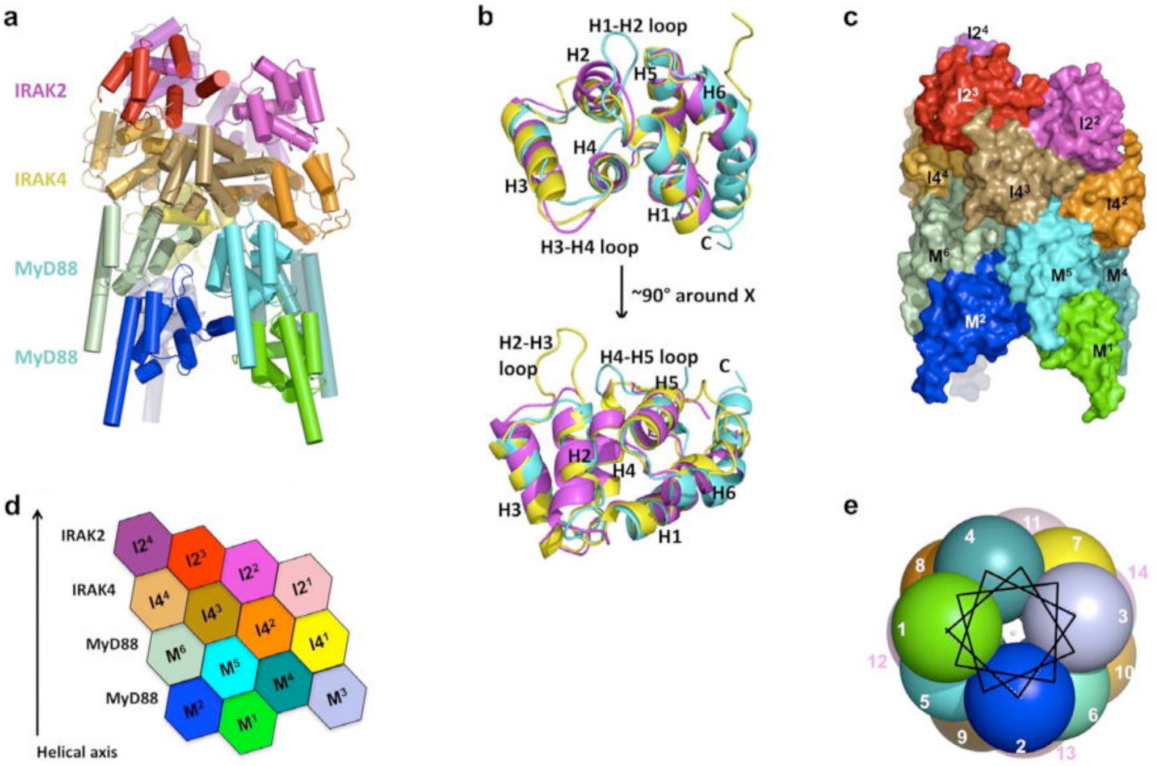
On reflection the award of a Nobel prize for the discovery of PRRs was unsurprising. Janeway's hypothesis was a critical original idea in immunology and PRRs appear to provide the missing link between innate and adaptive immunity. How the PRRs interface with adaptive immunity is currently an area of intensive research and likely to lead to new therapeutic targets to treat diseases associated with chronic inflammation as well as infection. The molecular mechanisms by which the host detects pathogens is now solved, but how this impacts on the treatment of disease is just beginning to emerge.

Fig 1a.



Structural model of the LPS bound dimeric TLR4/MD2 complex (Bryant *et al*, 2010; Nat Rev Microbiol. 2010 8:8-14)
http://www.nature.com/nrmicro/journal/v8/n1/abs/nrmicro2266.html

Fig 1b.



Structural representations of the Myddosome complex (Lin *et al*, Nature, 2010 465: 885–890)
http://www.nature.com/nature/journal/v465/n7300/full/nature09121.html

Further reading relating to the pharmacology of TLRs

Bryant CE, Spring DR, Gangloff M, Gay NJ. The molecular basis of the host response to lipopolysaccharide. Nat Rev Microbiol. 2010 8:8-14

Gay NJ, Gangloff M, O'Neill LA. What the Myddosome structure tells us about the initiation of innate immunity. Trends Immunol. 2011 32:104-9.

References

C. A. Janeway, Jr. Approaching the Asymptote? Cold Spring Harb Symp Quant Biol 1989; 54 Pt 1, 1

Gay NJ and Keith FJ. Drosophila Toll and IL-1 receptor. *Nature* 1991;351, 355-6

Lemaitre B, Nicolas E, Michaut L, Reichhart JM, Hoffmann JA. The dorsoventral regulatory gene cassette spätzle/Toll/cactus controls the potent antifungal response in Drosophila adults. *Cell* 1996; 86, 973-83

Medzhitov R, Preston-Hurlburt P, Janeway CA. A human homologue of the Drosophila Toll protein signals activation of adaptive immunity *Nature* 1997; 388, 394-7

Poltorak A, He X, Smirnova I, Liu MY, Van Huffel C, Du X, Birdwell D, Alejos E, Silva M, Galanos C, Freudenberg M, Ricciardi-Castagnoli P, Layton B, Beutler B. Defective LPS signaling in C3H/HeJ and C57BL/10ScCr mice: mutations in Tlr4 gene. *Science* 1998; 282, 2085-8

Hoshino K, Takeuchi O, Kawai T, Sanjo H, Ogawa T, Takeda Y, Takeda K, Akira S. Cutting edge: Toll-like receptor 4 (TLR4)-deficient mice are hyporesponsive to lipopolysaccharide: evidence for TLR4 as the Lps gene product. *J Immunol* 1999; 162, 3749-52

Zhang SY, Herman M, Ciancanelli MJ, Pérez de Diego R, Sancho-Shimizu V, Abel L, Casanova JL. TLR3 immunity to infection in mice and humans. *Curr Opin Immunol* 2013; 25(1)19-33

Bell JK, Askins J, Hall PR, Davies DR, Segal DM. The dsRNA binding site of human Toll-like receptor 3 *Proc Natl Acad Sci* 2006; USA. 103, 8792-7

Park BS, Song DH, Kim HM, Choi BS, Lee H, Lee JO. The structural basis of lipopolysaccharide recognition by the TLR4-MD-2 complex *Nature* 2009; 458, 1191-5

Yoon SI, Kurnasov O, Natarajan V, Hong M, Gudkov AV, Osterman AL, Wilson IA. Structural basis of TLR5-flagellin recognition and signaling. Science 2012; 335, 859-64
Lin SC, Lo YC, Wu H. Helical assembly in the MyD88-IRAK4-IRAK2 complex in TLR/IL-1R signalling. *Nature* 2010; 465, 885-90

Education: an update

Jess Strangward
BPS Head of Education

> ‘I want to be a doctor, but not the sort of doctor who makes people better, the sort who invents new medicine’
>
> Future pharmacologist, aged 8

At the BPS office we know when spring has sprung as it’s time for the UCAS (Universities and College Admissions Service) fairs across the country. At the London event 16,000 students came through the door. We distributed over 500 pharmacology leaflets and spoke to scores of students who were considering pharmacology as a degree. We also spoke to potential medical students to impress on them the importance of pharmacology as a key component of their future studies and to ensure BPS is on their radar! We are planning to attend the Bristol UCAS fair and will be sending materials to one in Manchester. UCAS fairs offer a timely opportunity to speak directly to young people looking for a career in science.

It was interesting to see the political decisions taken over the past few years making an impact. As the students entered the fair they were confronted by a student financing stand (I’ve never seen one so prominently placed before). Previously, students wanted to know more about what subjects they could study but now the focus is on the skills they will gain and the jobs available at the end. One girl seemed convinced that, if she didn’t get into medicine, university wasn’t going to be the best career choice. This is when our careers resources and our experience can really make a difference. Young people’s knowledge of the diverse range of careers associated with science can sometimes be very limited and it’s useful for us to share the career profiles of some our members. Fortunately it is easy to help potential students understand pharmacology’s relevance to the world of work – we will always be searching for new medicines.

Prescription for success

“*What work experience should I do?*”. This is a question that we’re asked more and more on Facebook and via email. It’s a tricky one to answer and we are in the process of developing a list of members who would be willing to take on work experience students. Some students do manage to gain work experience but for those who live in remote areas this isn’t always feasible. It can be particularly tricky for keen science focused students to demonstrate their commitment when entering the world of labs - it isn’t necessarily straightforward for the uninitiated. The problem continues into the undergraduate realm where it is vital to keep building your skills set. This is the reason why BPS is committed to providing vacation bursaries to enable students to take on a summer research project. These allow students to develop not only their lab skills but understand the research environment and the collaborative process of science.

If you have an idea about how we can help students demonstrate their commitment to pharmacology that doesn’t necessarily include work experience, please get in touch:

education@bps.ac.uk

Pharmacology in the Wild

BPS was a major sponsor at the Brighton Science Festival that ran throughout February. Our topics spanned from Science of Honey to Personalised Medicines. Our audience numbers never dropped below 60 and peaked at 125. There was a raft of interesting questions from the audience to keep our speakers on their toes. After our final talk, Inside Shakespeare’s Cabinet with Professor Rod Flower, we were travelling on the train back to London and happened to see a young boy sat with his father reading our ‘How do Drugs Work?’ leaflet and asking lots of questions. It kept him occupied for a full hour (not sure dad thanked us for that!) and even if that young boy doesn’t go on to study pharmacology he might start to look at his medicine cabinet a little differently.

PharmacologyNOW

Over the coming months the BPS Education team will be looking for contributors for our new website that will host our careers and teachers resources and be the ‘friendly face of pharmacology’. We are searching for short, pithy blogs that can be about anything from your favourite receptor to comments on a current news article. We will also be looking for longer pieces that give a deeper insight into pharmacology that might be of interest to the general public.

Let us know if you want to be involved!

education@bps.ac.uk

Why blog about pharmacology?

Jenny Koenig
Editor, Pharmacology Matters

You've got three papers and a grant application to write, a thesis to examine and more admin than you could possibly ever get through. So why might you want to blog? Probably more to the point does anyone ever read blogs?

There is a lot of very worthy writing about how important outreach is and how it is a scientist's duty to communicate their work to the public. My reading of the blogosphere suggests that it is safe to say that most bloggers don't blog out of a sense of duty: they do it because they enjoy it and are enthusiastic about their work. Jon Copley in his blog[i] on *SciConnect* points out more advantages: *"gaining broader perspectives of research problems or issues"* and *"reaffirming motivation in our research / boosting our morale"*. Furthermore there is that elusive "impact" required for research proposals: the site statistics generated automatically by blog websites such as Wordpress and Blogger can tell you how many people have visited, which can be useful ammunition. Interestingly Jon points out that if the effort is shared between all the members of a research group then the effort by any one individual can then be realistic. Certainly collaborating with others is a good way of keeping the blog posts coming, whilst not making it too onerous and time-consuming.

David Nutt is a great example of a blogger who has something to say and wants to share his ideas. He relates pharmacology to the wider issue of policy and there is a strong argument that scientists should be aware of and be thinking about and communicating their ideas and views on policy issues. His is one of the few primarily drug-related blogs, which he writes with collaborators at the Independent Scientific Committee on Drugs[ii]. This is an interesting combination of explanations of the basic science and research on mainly drugs of abuse along with implications for public policy and legislation.

Often it is the comments at the end of a blog post that can be more interesting and insightful than the blog post itself. In fact, you could argue that a good blog post is one that stimulates discussion. One such insightful comment was the argument that doing outreach work benefits your career because it raises your profile, people notice you and remember you and you then get invited to give talks. To quote :

*"… I got to know the senior faculty really well through doing outreach – and you can never underestimate the importance of someone knowing your name. Years later I get emails out of the blue recommending that I apply for prestigious fellowships because people *remember* who I am and what I work on – outreach is a profile raising activity, why does no-one ever mention that?*

Having a reputation for being able to communicate well means I am often invited to give talks about my research … As an early-career researcher this is a massive advantage."

The first thing that became apparent when I started hunting for blogs about pharmacology was that there are very few that are entirely devoted to the subject. There is, however, a lot written about pharmacology in blogs and it is hidden amongst other writing. Here are a few that caught my eye[1].

Many of the general science blog sites contain some excellent writing. Philip Strange's recent blog about phenylbutazone entering the human food chain as a contaminant in horsemeat[iv] provided me with a nice, relevant link for my students currently studying drugs for inflammation. This is at the *Occam's Typewriter* site where there is plenty of other good reading, though not a lot of it is pharmacological.

There are also some amazing student-run magazines with associated blogs such as the Aberdeen-based *AU Science Magazine*[v] and the Cambridge-based *BlueSci*[vi]. *AU magazine* delves into the resources of the University of Aberdeen's Special Collections and the result is a fascinating article on the history of drug-making beautifully illustrated with images from the collections.

The medical research charities have good blogs themselves and also link to a lot of interesting writing. Cancer Research UK in particular have articles about clinical trials for example an article on trastuzumab emtansine (T-DM1) for treatment of HER2-positive breast cancer[vii] whilst the Wellcome Trust had, amongst others, a nice article on the development microneedles for delivery of vaccines without the need for trained personnel or cold storage[viii].

There are a number of general science blogs which have pharmacologically-inclined articles. David Kroll's *take as directed* blog, part of *PLOS* blogs[ix], covers a range of topical issues and the *Naked Scientists* have a selection of medicine-related articles[x] as well as podcasts. Many universities have set up blogs that cover all of their research but the Michigan State University Department of Pharmacology & Toxicology have established their own blog – one of the few to focus specifically on pharmacology and apparently written by their own academic staff. It is unusual for someone to blog anonymously, but the *Helpful Poisons* blogger does just that with some fascinating, largely historical, accounts of poisons used as medicines[xi].

For me, some of the most powerful blogs are those where the scientists talk about their own experiences and explain why they do their research. The story of Diane Kelly is told as a podcast[xii] of a talk she gave and the enthusiasm with which she speaks about her work bowls you over. She addresses the issue of animal dissection with incredible honesty and you get a sense that this is not just some cold scientific fact being delivered but a real person telling a fascinating story that gives you an insight into what makes her tick. Nature's *SpotOn* website[xiii] has a strand on story-telling as a science communication tool and has a number of other examples that really make an impact.

[1] I'm sure I didn't find all blogs about pharmacology, so if I've left any out please do forgive me.

It is this enthusiasm that keeps bloggers blogging. Katie Griffiths has her own blog *The Molecular Circus*[xiv] and says that one thing that keeps her going is the responses she gets from readers, both in the comments on the blog and on Twitter. **Twitter is an important way of publicising a blog – in fact it is critical**.

Heather Doran in addition to writing for *AU Science Magazine* has her own blog. She agrees that getting feedback from readers is inspiring – read her blog article *Why get involved in 'Public Engagement' and 'Science Communication'?*[xv] She's also had useful comments about her research from someone completely outside her field, which she wouldn't have received otherwise. Her writing about being a research student, *Things I wish I had known when I started my PhD*[xvi] is recommended reading for other graduate students!

Finally, you've written that blog but how do you get people to find it and read it? This is where Twitter comes into its own. Using Twitter professionally would be the subject of a whole article in its own right, but luckily for me Heather Doran[xvii] and Professor Dorothy Bishop[xviii] have beaten me to it!

[i] http://www.sciconnect.co.uk/blog/2012/07/can-outreach-make-you-a-better-scientist-2/

[ii] http://drugscience.org.uk/blog/

[iii] http://scientopia.org/blogs/scicurious/2012/06/06/on-outreach-somethings-got-to-give/

[iv] http://occamstypewriter.org/irregulars/2013/02/19/the-bute-in-horsemeat/

[v] http://ausm.org.uk

[vi] http://www.bluesci.org

[vii] https://scienceblog.cancerresearchuk.org/2012/06/06/asco-2012-a-new-treatment-for-her2-positive-breast-cancer/ Interesting that the Nature Medicine blog had an article about the same topic. http://blogs.nature.com/spoonful/2013/02/antibody-drug-combo-approved-for-fighting-breast-cancer.html

[viii] http://wellcometrust.wordpress.com/2013/02/22/microneedles/

[ix] http://blogs.plos.org/takeasdirected/2011/07/15/the-whole-herb-and-nothing-but-the-herb/

[x] http://www.thenakedscientists.com/HTML/features/q_subject/164,407/nocache/1/

[xi] http://www.helpfulpoisons.blogspot.co.uk

[xii] http://storycollider.org/podcast/2012-09-30

[xiii] http://www.nature.com/spoton/2013/02/spoton-nyc-telling-stories-the-power-of-personal-stories-in-science/

[xiv] http://themolecularcircus.wordpress.com

[xv] http://sciencehastheanswer.blogspot.co.uk/2011/10/why-get-involved-in-public-engagement.html

[xvi] http://sciencehastheanswer.blogspot.co.uk/2012/01/things-i-wish-i-had-known-when-i.html

[xvii] http://sciencehastheanswer.blogspot.co.uk/2012/04/how-to-use-twitter.html

[xviii] http://deevybee.blogspot.co.uk/2011/06/gentle-introduction-to-twitter-for.html

Meetings: an update

Karen Schlaegel
Head of Meetings and Events

Professor David Webb
Vice President-Meetings

We would like to thank everyone who took the time to complete the Meetings survey at the end of last year. We found the results very valuable and are delighted to report that BPS meetings are perceived as offering high quality and relevant content, with 90% of our respondents telling us they would recommend BPS meetings to their colleagues. Oral and poster communications, plenary lectures and the networking element of the meetings were also all rated very highly. Furthermore, we are delighted about the numerous positive comments on the organization of our meetings, which is perceived to have improved and gained in professionalism.

We were interested to see that winter is still the preferred timing for our Annual Meeting for the majority of respondents (it seems that it is only BPS (meetings) staff who would prefer a quieter run up to Christmas…). Most voted to stick with the current three day format.

There are clearly two camps within the Society when it comes to picking the location of the meeting: with about half of respondents voting to stay in London and the other half preferring to hold the meetings both in and out of London. We hope that the planned membership survey will bring some clarity on this issue.

While we appreciate that attending our free annual meeting is a great membership benefit we are conscious of increasing costs – particularly of unused lunches that regularly get wasted. We were therefore delighted that a majority of respondents stated that they would be happy to contribute to the costs of the meeting. BPS Meetings Committee feels strongly that introducing a (nominal) fee would significantly reduce wastage. Given the very positive comments about the Winter Meetings, we also feel confident that the meeting is good value! In line with the general strategy of the Society, we would always look for ways to keep costs, especially for student delegates, to an absolute minimum and we would, of course, continue to provide bursaries. Having said this, we can confirm that *Pharmacology 2013* will remain free to attend for our members.

Work commitments, and increasing costs of travel and accommodation, were named as the most important factors making attendance at meetings more difficult. BPS continues to offer bursaries to members presenting at the meeting, with priority given to student members and members from developing countries. We hope that this helps our members address these issues.

We are already busy preparing for *Pharmacology 2013* and hope that we can make it a still bigger and better meeting! We have had to close registrations early two years in a row so we are very pleased to announce that we have secured a larger area at the QEII. The space offers a larger lecture theatre, more space for networking, refreshments, exhibition and posters, and the meeting will now 'only' be spread over two instead of three floors which should make it easier to locate and access lectures - even though most delegates now know their way around the maze that is the QEII!

Many thanks also to the delegates who completed the feedback survey for the 2012 Winter Meeting. It's fair to say that the survey results mirrored the very positive comments collated in the video available on our website (bit.ly/XsjgII). Delegates clearly enjoyed the photo booth (we have the evidence!) and the Treasure Hunt received positive feedback from both delegates and exhibitors. We have decided to keep these elements and will advertise them more widely for *Pharmacology 2013*. The networking area, sponsored by our publishers Wiley-Blackwell, hosted, amongst other things, the first Pharmacology Corner. The event proved popular and we hope that it will continue to form an integral part of the meeting.

The programme for *Pharmacology 2013* is now available (www.bps.ac.uk/meetings/13a5092985f) and we are looking forward to a broad range of exciting science:

Tuesday 17 December

- Animal research in the UK - what is the EU Directive doing for us?
- Integrating pharmacology and chemistry to maximize benefits and minimize risks for nanomedicine development
- New insights into serotonin receptor modulation and signalling – in association with the International Society for Serotonin Research
- Specialist Registrar training session

Wednesday 18 December

- Inflammasome: a key immune defender with a sinister side
- Paracetamol poisoning in the UK - where are we now and what's the future?
- Pharmacology and OMICS technology

Thursday 19 December

- Neuropharmacology and psychiatric disorders
- New pharmacological targets in the microcirculation – in association with the British Microcirculation Society
- Drug Discovery of the Year: The Key Role of Pharmacology

We are also listening to the constructive criticism we have received, and will be implementing the following changes for this year's meeting:

- All symposia will be breaking for their 30-minute tea and

coffee break at the same time. This should make it easier for delegates to move between sessions as well as facilitate networking

- There will be a 30-minute dedicated lunch break
- The clinical poster session will run in parallel with one of the basic poster sessions. The original slot always clashed with the Wednesday morning symposia. This will now enable the clinical pharmacologists to attend the sessions and we are hoping that it will create an even livelier poster session, assisting the exchange between basic and clinical presenters
- The Annual General Meeting will be moved from Thursday to Wednesday and we hope that this will encourage and enable more members to attend
- Symposia on Thursday will start at 9:30 – starting half an hour later will hopefully increase attendance numbers on the third day and be particularly welcomed by those who attended our Annual Dinner the night before!
- We will award a prize for the best poster on each day and will make the announcement at the end of each day, rather than after the meeting
- The BPS education team is also working on a number of new initiatives – all will be revealed in due course!

There are still eight months to go, but we hope that you have already saved *Pharmacology 2013* in your diaries. We look forward to welcoming you from 17—19 December 2013 in London – if not before at one of our other meetings or workshops.

As always – if you have any comments or ideas, please do not hesitate to contact Karen at the BPS office (ks@bps.ac.uk).

Rod Flower gives a talk in pharmacology corner at the Winter Meeting 2012

Clinical poster session at the Winter Meeting 2012

Japanese Society of Clinical Pharmacology and Therapeutics Annual Meeting

Professor David Webb
Vice President-Meetings

Several BPS members (John Cockcroft, Simon Maxwell, John Petrie and myself) were invited by the President of the Japanese Society of Clinical Pharmacology and Therapeutics (JSCPT), Professor Shinichiro Ueda, to join their 33rd Annual Meeting in Okinawa, Japan (29 November to 1 December 2012). The theme of the meeting was "Clinical pharmacology as sensible clinical practice: from population-based evidence to personalised medicine" and attracted 1,800 delegates from Japan, Korea and other parts of Asia.

We contributed to several joint symposia between BPS and JSCPT as chairs and lecturers. On the first day, I was involved in a symposium *From Bench to Bedside; Endothelin and Vascular Disease*, and John Cockcroft and John Petrie were involved in a joint symposium on *Investigator Initiated Clinical Research: the More Regulation, the More Reliability?* highlighting some of the difficulties raised for UK researchers by the European Clinical Trials Directive. John Cockcroft was also involved in a joint symposium on *Biomarkers for Atherosclerotic Disease*, talking about the difference between atherosclerosis and arteriosclerosis. In addition, I gave a Presidential Invited Lecture on *British Pharmacological Society: Past, Present and Future*.

On the second day, John Petrie was involved in a symposium on *Clinical Studies of Diabetic Cardiovascular Complications*, talking on cardiovascular outcome and anti-diabetic complications. On the final day, Simon Maxwell joined a symposium on *Clinical Pharmacology as a Speciality: Too Young to Die 2012*, and spoke on teaching safe and effective prescribing to medical students and junior doctors.

Shinichiro Ueda spent time in Glasgow in the 1990s, working with John Petrie and myself, and one of our other co-chairs was Shigeru Kageyama, who worked with John Cockcroft in Colin Dollery's department at the Hammersmith Hospital. It was good to renew our links. The Korean Society of Clinical Pharmacology and Therapeutics, led by Professor Sang-Goo Shin, was also a guest at this meeting, and it is clear that Asian clinical pharmacology is in extremely good health, and aiming to be internationally competitive in clinical trials.

We were made extremely welcome in Okinawa, and enjoyed some excellent science. There was also a very enjoyable social programme, much consumption of alcohol, a series of interesting musical experiences, the celebration of Christmas Japanese-style, and a wide variety of fish (both to eat and view – the latter at the Okinawa Churaumi Aquarium and Naha Fish Market). The provision of interpreters, and a programme in English, allowed us to fully engage in the meeting, much of which was anyway delivered in English. Refreshed by the meeting, its semi-tropical setting, and the tremendous welcome and support provided by Professor Ueda, I very much hope we will be able to generate similar collaborative ventures with Asian clinical pharmacology in the near future.

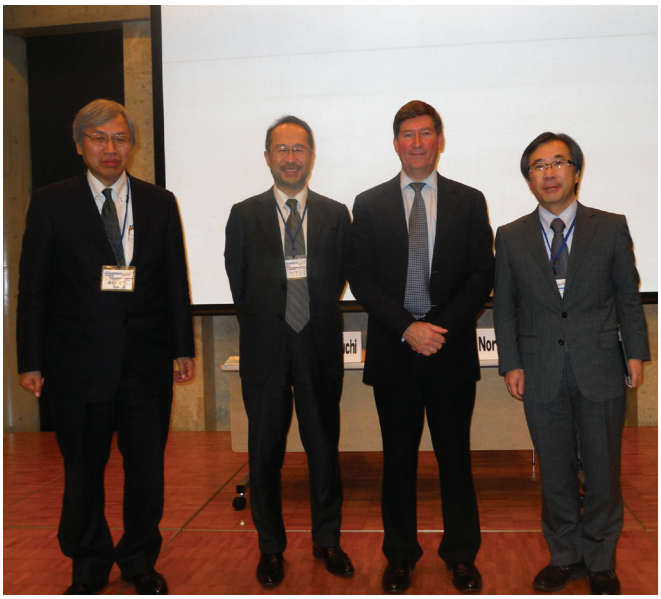


Photo from left to right: Professors Takashi Miyauchi, Noriaki Emoto, David Webb and Hiroshi Watanabe. Professors Miyauchi and Emoto are organizing the ET-13 meeting in Tokyo (8–11 September 2013).

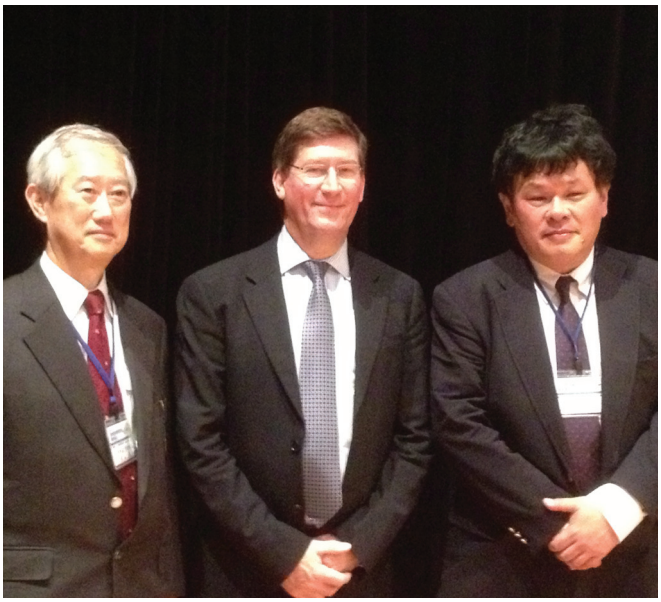
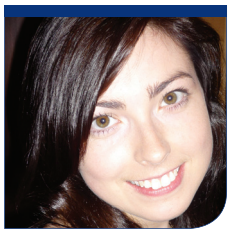


Photo from left to right: Professors Shigeru Kageyama, David Webb and Shinichiro Ueda.

Young Pharmacologists: an update



Hannah Watson
Editor, Pharmacology Matters

Hannah Watson is a foundation year one doctor currently working in NHS Grampian. She graduated from the University of Edinburgh in 2012 with an MBChB and BMedSci in Pharmacology. She has been a member of the Young Pharmacologists Committee and on the Editorial Board for Pharmacology Matters since 2010.

Last year was an exceptional year for the Young Pharmacologists with a number of great achievements to our name. Highlights include contributing to discussions that shaped BPS' 5-year strategy, continuation of fundraising efforts to provide bursaries for African Scientists to attend IUPHAR 2014 and the acceptance of a symposium *Stem Cells-Pharmacology and Therapeutics* to EB2013.

The year ended on a high with the incredible success of the BPS Winter Meeting held in London at the Queen Elizabeth II Conference Centre. The Young Pharmacologists were thoroughly involved with the academic and social opportunities the conference provides. We hosted a Welcome Reception at SixtyOne Whitehall, which was by all accounts enjoyed by those who attended. It was a sophisticated event honoured by our keynote speaker, the inspirational Professor Humphrey Rang, musical entertainment from Daryl Kellie and delightful canapés! It really was an enjoyable evening.

"It was a great chance to catch up with old friends and make new ones!" Maria Fernandes

The Young Pharmacologists Committee would like to show our appreciation to our demitting Chair, Professor Jane Mitchell. Jane has shown a great deal of dedication to the role and there is no doubt that our successes are directly related to her input and professional guidance. In her time as Chair, she was pivotal to the progression of our activities. Thank you, Jane, for your dedication!

Following on, the Committee is excited to welcome Professor Tim Warner as the newly appointed Chair. We all greatly look forward to working alongside him. Welcome to the Committee!

EACPT Summer School 2013, Edinburgh

This event is being hosted by the RCPE and supported by BPS. The event will encourage and provide a networking event for Young Clinical Pharmacologists from across Europe. There is an exciting group of keynote speakers and there are bursaries available for BPS members presenting a poster at the meeting. Early Bird registration is open until Sunday 19 May 2013.

Pharmacological Societies

Following on from the last update, we are still encouraging Young Pharmacologists to set up Pharmacology Societies/Clubs at their institutions if there is not already one. This is a great way to meet with like-minded individuals to discuss current pharmacology topics, collaborate with research and so forth. Importantly, it will also be a CV booster! If you would like to know more about setting up a Pharmacology Society or have questions about anything mentioned in this issue please contact Hazel (hom@bps.ac.uk) at the BPS office.

Photo from left to right: Liang Yew-Booth, Maria Fernandes, Dan Reed, Jane Mitchell, Humphrey Rang, Liz Rosethorne and Oliver Keown.

BPS BRITISH PHARMACOLOGICAL SOCIETY
Today's science, tomorrow's medicines

EACPT

RCPE Royal College of Physicians of Edinburgh

4—6 July 2013, Edinburgh, UK
CPD approved by the RCPE (12 credits)

10th EACPT Summer School 2013, Edinburgh

Supported by BPS and hosted by RCPE, the programme will consist of keynote presentations on all aspects of clinical pharmacology by invited expert speakers, workshops, poster presentations, free communications and social events. There will be a strong interactive element and the opportunity for delegates to network with the speakers.

Bursaries are available

Keynote speakers:

Ingolf Cascorbi, University of Kiel
Adam Cohen, Centre for Human Drug Research, Leiden
Garret FitzGerald, University of Pennsylvania
Sir Michael Rawlins, NICE
Sir Kent Woods, MHRA

Confirmed speakers:

Amrita Ahluwalia, Barts and the London School of Medicine and Dentistry
Jeff Aronson, University of Oxford
Nick Bateman, Royal Infirmary of Edinburgh
Morris Brown, University of Cambridge
Jamie Coleman, University of Birmingham
James Dear, University of Edinburgh
Michael Eddleston, University of Edinburgh
Gary Ford, Newcastle University
Aroon Hingorani, University College London
Simon Maxwell, University of Edinburgh
Tom MacDonald, University of Dundee
Patricia McGettigan, Barts and the London School of Medicine and Dentistry
Ken Paterson, University of Glasgow
Munir Pirmohamed, University of Liverpool
Phil Routledge, Cardiff University
Donald Singer, University of Warwick
David Webb, University of Edinburgh
Martin Wilkins, Imperial College London
Ian Wilkinson, University of Cambridge

For more information or to register your interest please contact:
t: +44 (0)207 239 0176 e: meetings@bps.ac.uk w: www.bps.ac.uk

EDINBURGH INSPIRING CAPITAL

www.bps.ac.uk/meetings/139ba11a3ad

Women in Pharmacology role models

Chloe Rose
GlaxoSmithKline

Liz Mitchell, VP R&D Discovery Pipeline, GlaxoSmithKline (GSK), interviewed by Chloe Rose, currently an undergraduate pharmacology student doing an industrial placement as a clinical research scientist with GSK.

1. Why did you choose to study pharmacology at university?

Well initially I didn't – initially I was doing a biochemistry degree. One of the things that attracted me to do biochemistry at Strathclyde University was an option to split into joint honours. At the end of my second year (4 year course) I opted to do a joint honours in pharmacology. The main reason is I have always been intrigued around how drugs work and in particular how drugs work in the brain - which is where I spent a lot of my focus. It's just that curiosity; and although I'm a joint biochemist/pharmacologist, I consider myself a pharmacologist.

2. What made you decide to specialize in neuropharmacology?

Neuropharmacology – well one of the things is that the brain has always intrigued me, and still does, and I think the reason that science around the brain intrigues me is because there are no absolute answers. So it's much more like an art compared to many other fields of science. It's the combination of the theory with the unknown. I think it is really testing our ability as scientists, to accept that there are some things we probably never will fully understand and that's actually ok.

3. Why did you decide to continue at Strathclyde?

I applied for a lot of PhDs when I finished my first degree, but the one at Strathclyde with Judy Pratt interested me most for a couple of reasons. First of all, it was very specific around 5HT3 receptors which had recently been identified. There was a lot of interest in the potential psychopharmacological effects of this receptor and the PhD project was completely focused on this area. It was something new and there was also a lot of interest from industry. The PhD placement at Strathclyde University was sponsored by Glaxo who had a huge interest in 5HT3 receptors. It was a very deliberate decision; it wasn't a case of by default I rolled into it. I had a place at Park Davis/Cambridge for a much more theoretical project, whereas this I felt that the one I chose had a very practical application, as science was moving forward in relation to medicines.

4. What was your PhD project on and which aspects did you most enjoy?

My PhD was largely split into two main components; one was on behavioural pharmacology and one was on neuroimaging. Using these techniques, the project focused on identifying if there was a link with 5HT3 receptors in anxiety states and addiction. I did quite a lot of work with nicotine to identify if some aspects of nicotine-induced addiction could be modified with 5HT3 receptors: the rationale being that as a presynaptic receptor, blockade of the 5HT3 receptor could have a modulating role on other neurotransmitters including dopamine.

On the neuroimaging side, I did a lot of work on a technique called 2-deoxyglucose, where radioactive 2-deoxyglucose was injected as a marker to trace areas of increased neuronal activity in the brain. I think that on balance it was the behavioural side that I preferred, again maybe because it tapped in more with the art of science. But the two approaches did tie quite nicely together, and there were some interesting conclusions from the project.

5. Why did you enter the pharmaceutical industry and choose to work for GSK?

I was pretty certain even when I finished my first degree that my inspiration was to work in the pharmaceutical industry because I had a real passion for understanding how drugs worked. I felt that working in the industry would give me the opportunity to be involved in the research, and the development of new drugs. I could've gone straight to industry after having done my first degree; but I opted to stay on in academia and do the PhD, really because I wanted to deepen my experimental skills and knowledge of a stand-alone research project. I opted to do a PhD that was sponsored by Glaxo; as a consequence of that I spent about six months working at the research labs in Ware. It was a very good connection, and later when there was an opportunity to join their organization, I took it, and the rest is history.

6. Would you recommend doing a PhD to someone who wishes to enter industry?

I don't think it's a simple answer. It depends, and it has to be on a case by case basis where the individual needs to look to themselves and decide what it is that really interests them and fires them up. I don't ever think it's time wasted doing a PhD; you learn about how to work with data, you learn how to interpret data, you learn about the ambiguity of the data but yet the logic of data. And the way you learn is through experience.

7. What is your current position at GSK and what does the role involve?

I left working in basic research about 17 years ago and for me moving into late stage drug development was the best thing I ever did. Since then I've been working to develop potential new medicines in the clinical stages of drug development. Most recently I've had a great opportunity to be involved in leading a cross-functional team to bring a new medicine to market. Thinking back to what my objective was for coming into industry, I consider myself one of the privileged few who has actually seen that all the way through and done what I came here to do. I say privileged few because the majority of potential new medicines don't progress into clinical trials, far less all the way to regulatory approval.

The drug I was working on was a new treatment for epilepsy. Most anti-convulsive drugs work through sodium channels and GABAergic mechanisms and this was a potassium channel opener.

8. How did you reach your current position at GSK?

I have had a number of varied and different roles at GSK. For the first five years I was a research neuropharmacologist I then had an opportunity to move into clinical development, where I was still able to use my scientific and analytical training, particularly in experimental design. I loved the work and the challenges it brought, and just by coincidence one of the drugs I was working on was the same 5HT3 receptor antagonist that I did my PhD on. The role was very diverse and offered a great opportunity to learn a lot of the fundamentals of drug development: setting up clinical trials, writing protocols, working with hospitals and developing regulatory submissions. My next role was within project management. I made that change because I wanted to learn about other aspects of drug development. While I had worked in both pharmacology research and clinical development, there are many other specialist roles that need to come together to develop a new medicine. In the project manager role, I was able to start working with drug development teams, which are comprised of people from all of the specialist areas that are required to develop a new medicine. More specifically my role was to develop project plans and to work with teams to figure out what data we had to generate and then to be involved in reviewing results. These might indicate that we would move the potential new medicine forward. More commonly the data would show that there was either no beneficial effect of the drug or that there were safety concerns – and both would cause us to stop development. I then moved into a role where I lead these cross-functional teams to devise and drive the strategy for a new medicine; and I primarily worked on two drugs for the treatment of epilepsy: first Lamictal and then in 2008 I started work on Trobalt the latter being the work that I described above.

9. How have you maintained your work/life balance at GSK?

There have been many occasions when work does not stop on a Friday evening, and this was particularly the case when I was working on the regulatory submission work for Trobalt. The challenge of bringing a new medicine to patients cannot be contained within a standard 5 day working week! Flexibility is a key part of this work – some days you need to be working until 9pm in the evening. Other days you can stop at 4pm.

But it's also important that I have interests and goals outside of work. This year I plan to start playing the piano!

10. So you mentioned setting yourself goals is there particular things you do to relax?

I've trained as a garden designer, and occasionally I give the other side of my brain – the artistic half – time to play. When I work on a garden design I can't think about anything GSK or drugs or data. And I love to cook.

11. Has there been anyone in pharmacology who has been your inspiration?

I had a chemistry teacher at school that initially got me interested in science. I was one of those irritating students who always had a 'so what' question. But he always took the time and encouraged me to keep asking questions and to go and find the answers. This shows how important teachers can be when you're young and just developing an awareness of science.

12. Are there any female role models who have inspired you?

Once you start to overlay, differentiate male/female it just reinforces that there is a difference, when there is no difference.

13. Do you have particular advice for women in industry?

I've got advice for anyone in industry: just make the most of every opportunity you can whether you are male or female. At GSK I have never been made to feel disadvantaged for any opportunity because I'm female rather than male. I think the more you think about it, the more psychological barriers you put in your way. My recommendation is: know where you want to go, go for it and don't stop and think things aren't open to you simply because you're a woman.

14. If you could have invented any drug what would it be?

It would have been lovely to have been associated with penicillin because it represented an enormous change in the way patients were treated. Even today people aspire to be involved in developing a medicine that makes a step change in how patients are treated. It must be wonderful to be associated with the oncology medicines that are being developed today, knowing that you're developing something that makes such a difference to patients. GSK have developed BRAP and MEK inhibitors for melanoma. Previously there has been nothing on the market for these patients; now they've got not one, but two potential medicines that will change the way patients are treated for this disease. I'd always like to be involved with medicine that makes that change to people's lives.

To read about other female pharmacology role models, including the winners of our Astra-Zeneca Women in Pharmacology prize, please visit the Women in Pharmacology pages of the BPS website (www.bps.ac.uk). Perhaps you would like to write about someone who inspires you? If so please contact Hazel:

hom@bps.ac.uk

BRITISH PHARMACOLOGICAL SOCIETY

Coin Street, London
12 September 2013

Pharmacokinetics & Pharmacodynamics

PK

PD

PD

PK

Speakers

Piet van der Graaf, LACDR
Colin Howes, AstraZeneca
Phil Jeffrey, GlaxSmithKline
Neil Upton, Transpharmation

e-mail: meetings@bps.ac.uk
visit: www.bps.ac.uk/meetings
call: +44 (0) 207 239 0170