PHARMACOLOGY MATTERS

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

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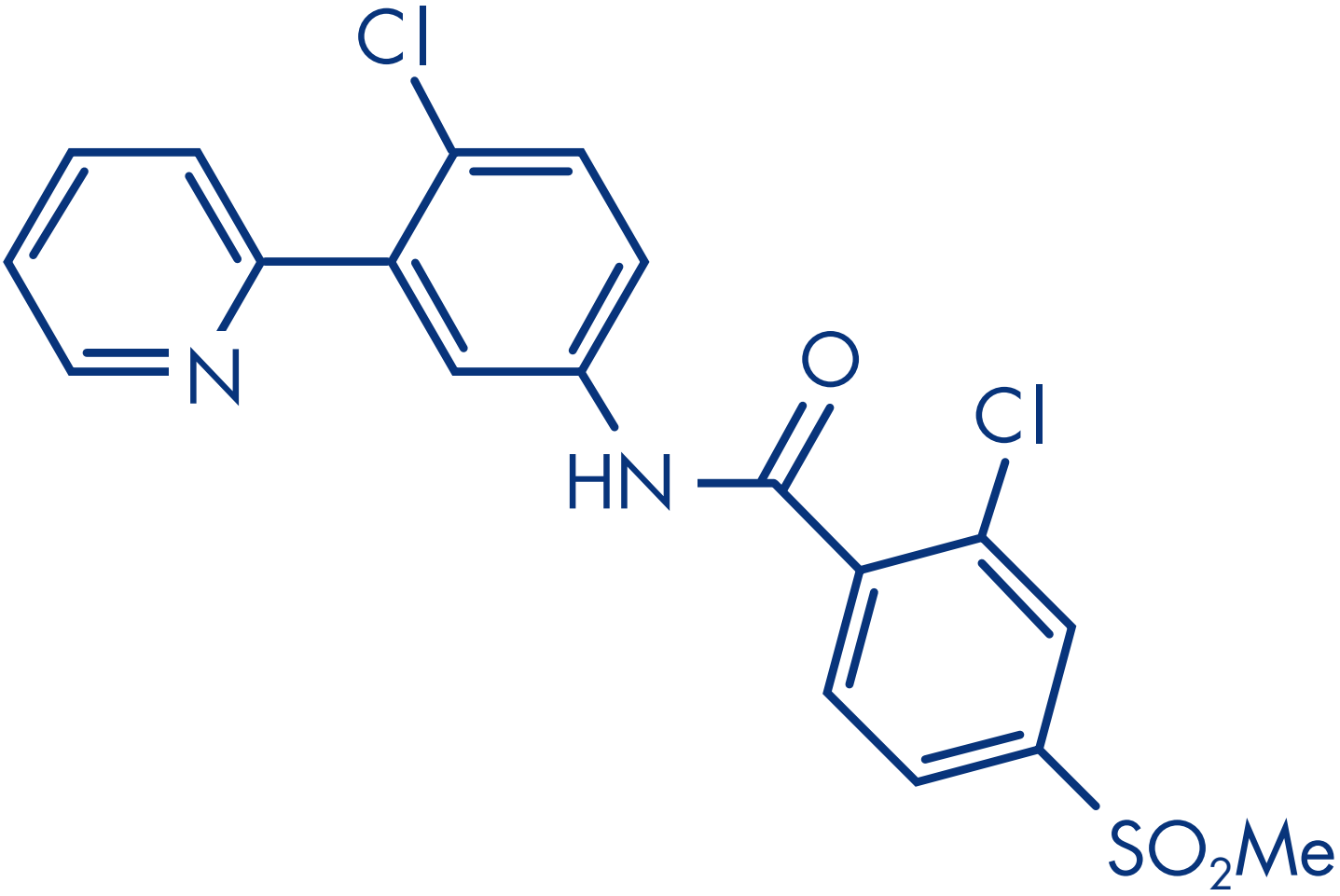


Vismodegib | Honorary fellowships | Stem cell therapy | Drugs for pain relief

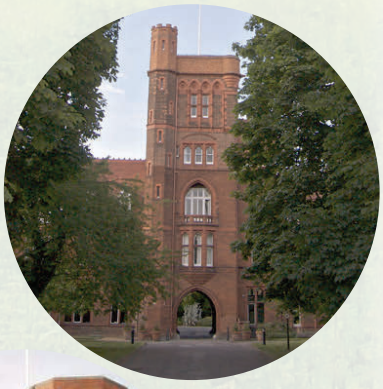
Celebrating 40 years of promoting clinical and behavioural neuroscience

2014 Summer Meeting

Robinson College and West Road Concert Hall, Cambridge

Sunday 20th to Wednesday 23rd July 2014

Highlights



2014 Guest Lecture to be presented by David Nutt, followed by a plenary mental health session 'Is psychiatric diagnosis relevant to psychopharmacological treatment?'

9 invited symposia covering cutting edge psychiatric neuroscience and psychopharmacology:

Monday 21st July – Psycho-immunology; Predictors of clinical response in depression; ADHD and obesity: Overlapping neurobiology and development of pharmacological treatments

Tuesday 22nd July – Cannabinoids in psychiatry: current understanding and future treatments; Chickens and Eggs: Separating Cause and Effect in Drug Addiction; Genetic pathways in Psychosis: the road to new treatments?

Wednesday 23rd July – The adolescent brain – A key stage in the development of psychiatric disorders?; Tobacco addiction in schizophrenia: a translational investigation; Dopamine, impulse control disorders and Parkinson's disease

PLUS 2 dedicated Poster Sessions, Satellite Symposia and BAP Special Sessions

Joint BAP/RCPsych Workshop for Clinical Trainees

Conference Dinner at Girton College including presentation of the 2014 Prizes and Awards

For full details of the meeting go to www.bap.org.uk/summermeeting2014

Editorial

Graeme Henderson
Guest Editor
Pharmacology Matters

I feel rather a fraud writing this editorial for *Pharmacology Matters* as I have made very little contribution to it. Unfortunately due to work pressures Tim Atkinson has had to resign as Editor-in-Chief of *Pharmacology Matters*. On behalf of the Society I would like to take this opportunity to thank Tim for all the hard work he has put in during his period in office. We have not yet made an appointment to replace Tim and so this issue has been assembled by the ever-dependable Hazel O'Mullan at the Schild Plot.

Younger members of the Society may take *Pharmacology Matters* for granted and think it was always so. But other readers, who have been members of the Society for as long as (or longer) myself, will recall days when there was no such interesting and informative publication. We have progressed through the BPS Bulletin and then pA2 to where we are now. The recent Membership Survey *(bit.ly/1nfYGHl)* indicated that *Pharmacology Matters* is well regarded by BPS members. However, there is always room for improvement and, in collaboration with the editorial board and the Publications Committee, we have been giving some thought to ways in which *Pharmacology Matters* could be improved even further. I would welcome any ideas that readers may have (email to *hom@bps.ac.uk*). It will be an interesting and exciting role for whomever is appointed as the new Editor-in-Chief of *Pharmacology Matters*.

As usual there is something for almost everyone in this issue. Exciting new developments in the treatment of CNS disorders are described in two articles that cover stem cell therapy in stroke and drugs for pain relief. The complex process of drug development is covered in an article on the ground breaking drug, vismodegib. This was the first drug targeting the Hedgehog signalling pathwayto be approved. Finally, Chloe Rose's interviews Barbara McQuade of GSK in the latest of our women in pharmacology role models series.

Finally, congratulations are due to Hazel O'Mullan. She and her partner have recently been coping with the inevitable lack of sleep that has come with the arrival of their new baby, Hugh.

Contents

Cover credit: iStock

Your BPS

Jonathan Brüün
BPS Chief Executive

BPS is keen to do all it can to better represent and serve its members, and to take decisions more quickly and efficiently than it does at present. The 2013 Your BPS Member Engagement Survey [bit.ly/1nfYGHl] produced some interesting feedback:

- Members rated BPS highly across its many activities, and in comparison with other organizations.
- However, there were areas for improvement in response to some of our member feedback: 72% of the members who took part in our survey agreed that 'BPS is open and transparent' while 67% indicated that 'BPS responds to the needs of its members'.
- Members who rate BPS most highly identify the Society as one that is 'forward-thinking' and 'efficient' – and it was felt more could be done to fulfil these characteristics
- Almost half (49%) of members would prefer to give their views through a group or committee – with 22% of members having joined a BPS committee in the last 10 years

It had long been an objective of BPS Council to renew its governance structures. Having this new and informative feedback, however, really focused minds on the need to address transparency issues, to reinvigorate our committees, and to ensure they are representative and forward thinking. In response BPS Council commissioned a report from an external consultant, Sue Thorn, on the Society's existing governance structures.

BPS has benefited from Sue's 35 years of experience in charity governance and strategy (she has previously been Chair of the international Association of Learned and Professional Society Publishers, and Chief Executive of the UK Society for Endocrinology). She has been widely recognized for her contributions to other Learned Societies, for which she was awarded a Fellowship from Society of Biology in 2009 and an Honorary Membership from the Society for Endocrinology in 2010. She is also a member of the Biochemical Society and a Fellow of the Institute of Association Management.

BPS existing governance structures is under review

In her report, among other findings, Sue noted that BPS currently has no fewer than 27 separate committees, some with terms of reference that are no longer relevant, and others that rarely, if ever, meet. In response, a Governance Review group has been convened; comprising members that will develop initial recommendations in a number of areas, including a streamlined committee structure and new roles for Council/Executive Committee.

At the time of writing, this phase of work is nearing completion and Humphrey Rang, as BPS President, will soon be writing to members to share some initial recommendations and seek comments, in order that the final proposals taken to the membership at the BPS Annual General Meeting in December.

Member responses to the 2013 survey have proven to be invaluable to the Society and shaped its activities, and I hope this participation will continue for the 2014 Governance Review.

Another important development that I'm pleased to be able to update you on is the BPS bid to host the 19th World Congress of Basic and Clinical Pharmacology in 2022. In the last issue, David Webb (then Vice President – Meetings, now President-Elect) confirmed that the bid to host the congress in Glasgow had been shortlisted and will be presented to the IUPHAR General Assembly during the 2014 World Congress in Cape Town in July.

WCP 2022
19th WORLD CONGRESS OF BASIC & CLINICAL PHARMACOLOGY
Glasgow, Scotland

Since the last issue, the BPS bid has been significantly strengthened with the addition of two official patrons representing basic and clinical pharmacology, Professor Sir Salvador Moncada and Professor Sir Michael Rawlins, as well as an Honorary President for the meeting, Professor Humphrey Rang. I would like to thank them for their support as well as emphasising my appreciation for everyone who has continued to contribute to the bid – from its original conception through to preparing for the final presentation in July.

Finally, I, along with the team at head office, have been delighted to welcome Chinara Rustamova to the BPS. Chinara joined us in January as Executive Assistant, having held similar positions at The Challenge Network and UNICEF, and will support the work of BPS President, President-Elect and myself as CEO along with many of our core committees. Welcome Chinara!

I hope you enjoy this edition of *Pharmacology Matters*.

Vismodegib, a hedgehog pathway inhibitor: a breakthrough targeted therapy for advanced basal cell skin cancer

Richard A. Graham
Genentech, Inc.

Jeannie Hou
Genentech, Inc.

Richard Graham received his Bachelor's and Master's degree in Biochemistry from Iowa State University and his Doctorate of Philosophy degree in Pharmaceutical Sciences from the University of North Carolina (UNC) at Chapel Hill. While working in the pharmaceutical industry for more than 10 years (GlaxoSmithKline and Genentech), Dr Graham has represented discovery and development teams across multiple therapeutic areas, including infectious disease, metabolic disease, neuroscience, ophthalmology, immunology, and oncology. Dr Graham is an adjunct faculty member at the UNC, Eshelman School of Pharmacy. In this capacity he teaches students various aspects of drug development with an emphasis on drug metabolism and clinical pharmacology. Additionally, he serves as a graduate student dissertation committee member. In his role at Genentech, Dr Graham has responsibility for the clinical pharmacology strategy for biologics and small molecules to ensure that appropriate dose, route, and regimen decisions are made using state of the art practices.

Jeannie Hou received her Bachelor degree and Medical degree for the Northwestern University and later completed her postgraduate residency training in internal medicine at the Weill Cornel Medical Center and Memorial Sloan Kettering Cancer Center in New York City. She subsequently completed her Medical Oncology fellowship at the National Cancer Institute where she also conducted research on the ex-vivo expansion of T-lymphocytes to treat graft-versus-host disease. Dr Hou began her career in the pharmaceutical industry over 10 years ago at AstraZeneca as the Director of Clinical Research and clinical lead, responsible for the design of a phase III clinical trial that led to the FDA approval of Caprelsa for the treatment of medullary thyroid cancer. She then moved to Shanghai where she led a team to develop oncology medicines for regulatory approval in China. Dr Hou joined Genentech in 2010 where she served the medical lead for the phase 3 development of Zelboraf for the treatment of metastatic melanoma. She is currently a Senior Medical Director and oversees global clinical development of vismodegib, a treatment for metastatic basal cell carcinoma.

In 1971, an epidemic of cyclopia in lambs was traced to pregnant ewes ingesting the California corn lily. The responsible compounds were identified (cyclopamine and jervine) and their teratogenic effects are due to specific inhibition of Hedgehog (Hh) signaling by binding to Smoothened (SMO). This established that SMO could be inhibited pharmacologically as a prospective target to treat Hh-related cancers, such as basal cell carcinoma (BCC).

The Hh pathway plays a critical role in embryonic development, but its activity is reduced or absent in adult organisms. The Hh proteins are secreted extracellular proteins. In adults, Patched (PTCH), a cell membrane protein, suppresses SMO and inhibits signaling through the Hh pathway. Hh binding to PTCH releases the inhibition of SMO and leads to activation of downstream transcription factors such as

BPS President Professor Phil Routledge presented the Drug Discovery of the Year Award at the Annual Dinner and Prize Giving in 2012

GLI1. Activation of the Hh pathway is important in the development of BCC, both the inherited form (Gorlin syndrome) and the common sporadic form.

Vismodegib, a SMO inhibitor, entered clinical trials in 2007. The Phase 1 study enrolled 33 patients with advanced BCC and the overall response rate was 50% in metastatic BCC patients and 60% in locally advanced BCC patients; this promising result led to the initiation of the pivotal Phase 2 study. The pivotal study enrolled 104 patients with either locally advanced or metastatic disease. The objective response rates by independent review, the primary endpoint, were 30% (95% CI, 16 to 48; P=0.001) in 33 patients with metastatic BCC and 43% (95% CI, 31 to 56; P<0.001) in 63 patients with locally advanced BCC. The median duration of response was 7.6 months. With additional two years of follow-up after the primary analysis, duration of response for those patients with objective response by investigator assessment increased from 9.2 months and 11 months in the locally advanced and metastatic BCC cohorts to 26.2 months and 14.8 months, respectively. Because durable response in malignancies with predominate skin involvement is clinically meaningful, these results led to approval of vismodegib for the treatment of locally advanced and metastatic BCC in 38 countries globally. Vismodegib was approved by the US FDA in January 2012 and by the European Medicines Agency in July 2013. Although the majority of BCCs are treated surgically, vismodegib is an important breakthrough for patients who had no other therapeutic option previously.

On 20 December 2012, vismodegib was named Drug Discovery of the year by the British Pharmacological Society. The award celebrates the importance of pharmacology in the development of new medicines and was awarded for the detailed pharmacokinetic/pharmacodynamic analysis that was completed during the drug development process. To optimize the dose of

vismodegib, the development team utilized results from detailed experiments in preclinical models and humans, relying on a balance of understanding the pharmacokinetic mechanisms and basic pharmacology of vismodegib.

Target efficacious exposures of vismodegib were predicted using a mathematical model, which integrated data from preclinical pharmacokinetic, pharmacodynamic, and efficacy experiments. The analysis showed that there was a very steep exposure-response relationship for PK and efficacy, analogous to an "all-or-none" response. These preclinical observations suggested that there was likely a threshold plasma concentration of vismodegib, which needed to be maintained to lead to drug effect in the clinical setting; if concentrations were to drop below the threshold, efficacy would be significantly impacted. The careful analysis and understanding of the preclinical pharmacology provided a clear target threshold concentration for clinical dose optimization.

The clinical pharmacokinetics of vismodegib is atypical and governed by two separate, non-linear processes: solubility limited absorption and saturable protein binding. A series of clinical pharmacokinetic studies were conducted to elucidate the mechanisms of PK nonlinearity for vismodegib. Two of the key studies were (1) intravenous administration of a radiolabeled tracer dose of vismodegib and (2) administration of vismodegib with alternate dosing schedules relative to once per day. The first of these clinical PK studies led to a mechanistic understanding for the observation that the unbound fraction of vismodegib changes in a concentration dependent manner due to saturation of protein binding (i.e., with continuous daily dosing). In the second study, alternate dosing schedules of vismodegib were investigated, and it become clear that unbound (but not total) concentrations of vismodegib decreased markedly with either three times per week or once per week dosing.

Considering the results from the dose scheduling and preclinical pharmacology studies, the vismodegib development team concluded that patients receiving vismodegib on an alternate schedule to daily dosing would be at risk of not achieving efficacious unbound plasma concentrations. Whilst the PK challenges faced with vismodegib were significant, overcoming these challenges was paramount for administration of the right drug, for the right patient, at the right dose.

Receiving the Drug Discovery of the year award from the British Pharmacological Society was extremely meaningful to the vismodegib development team. In December 2012, the team was in the midst of complex global health authority interactions and seeking approval for the use of vismodegib in patients with advanced basal cell carcinoma. During these challenging times, teams can often lose sight of the significant accomplishments that were made. Upon notification that the vismodegib development team had been selected to receive the BPS Drug Discovery of the Year Award, there was recognition of accomplishment that provided important motivation to the team. We're hopeful that this award will continue to recognize, motivate, and inspire scientists who work in industry for their significant accomplishments toward the development of new medicines.

Vismodegib, a new targeted therapy, provides an option for patients with metastatic basal cell carcinoma, or with locally advanced basal cell carcinoma that is inappropriate for surgery or radiation. To date, vismodegib has been approved as a treatment for advanced basal cell carcinoma in 38 countries worldwide and submitted for regulatory approval in more countries globally. Trials are ongoing in other forms of BCC and in disease areas where hedgehog signaling pathway may be important such as acute myeloid leukemia and idiopathic pulmonary fibrosis. Targeted therapy is at the forefront of research in cancer and in dermatologic diseases with significant unmet medical need.

When Henderson met Hammond

Graeme Henderson
BPS Vice President - Publications

A blast from the past recently launched our former President Graeme Henderson into the media spotlight, an experience he survived but is unlikely to repeat.

In mid-January this year I received an email from the producer of Dr Phil Hammond's BBC Radio Bristol's Saturday morning show asking me if I would agree to be interviewed on the topic of pharmaceutical companies suppressing negative clinical trial data. I declined saying that this was not an area I knew much about and suggested that they contact Phil Routledge. In what was intended as a humorous aside I pointed out that I had taught Phil Hammond pharmacology at Girton College, Cambridge in 1993 and that he had never listened to me much then so I was surprised that he wanted to interview me now! This obviously struck the right note as Phil's immediate response was to ask me to come on his show and be interviewed for an hour about my life and my research. I would also be allowed to choose two pieces of music to be played and discuss who I would invite to an imaginary dinner party.

Phil Hammond combines work as a GP in Somerset with stand-up comedy, journalism (he has been Private Eye's 'medical correspondent' for many years) and hosting a medically orientated chat and music show.

So, I went through my CD collection and managed to reduce the possibles down to five artists and 30 tracks. Katharine Richardson at the Schild Plot helpfully suggested 'Drugs don't work' by the Verve. I liked the title but had no idea who the Verve were! Finally I decided on 'Waterlily' by Karine Polwart and 'All the way with you' by John Prine (if you have never heard either then you can check them out on YouTube).

On the day before the show the producer emailed to say that it was a 'popular music' show and that they did not have my choices on their play list. That was a bummer as I had thought up clever, amusing anecdotes about both. They also rejected my next choice, 'May you never' by John Martyn (aka Ian McGeechie as he was known at school) even though it has 1.5M hits on YouTube. So I was reduced to a single choice of 'Sailing' by Rod Stewart and the producer chose all the other music. My colleague at Bristol, Eamonn Kelly, guessed that I had little choice in the music as he doubted that I was ever a fan of Fat Larry's Band.

The dinner guests were chosen over two or three evenings with my wife, Julie, and our dog in front of a log fire in the village pub. There had to be a sporting hero and in the end, because it was Radio Bristol, I chose Joe Jordan whom I had seen score the winning goal for Scotland against Czechoslovakia that took Scotland to the 1974 World Cup in Germany. He went on to manage Bristol City and is now at QPR with Harry Redknapp. My literary figure was Ian Rankin, author of the Rebus novels. My choice of scientist was Charles Darwin, mainly so that I could recycle an old story about Darwin having started to study medicine at Edinburgh University but giving up because the pharmacology lecturer was boring, pompous and stupid – hope things are better in Edinburgh nowadays! For my final choice I realized that I had to adhere to the BPS directive that there should be at least 25% female representation and so I, or rather my wife, chose Dolly Parton. I think Julie wanted to ensure that I did not come over as some boring old stuffed shirt professor.

I have never been so nervous about anything before, largely I think because the show goes out live and I was terrified of saying something stupid or just drying up. Had I realized that Phil Hammond was not Jeremy Paxman or John Humphrys and that it would be a friendly chat rather than an inquisition then perhaps I could have managed some sleep on the nights before the show. I did manage to squeeze in a mention of the DrugScience website and of the BPS Younger members initiative to support young African scientists to attend the IUPHAR Congress this summer in South Africa. I presented Phil with an 'I Love Pharmacology' tee shirt that he wore throughout the show.

Country legend Dolly Parton would be on Graeme's guest list

Phil Hammond loves pharmacology

Think in future I'll stick with the day job though. Opening an editor's report on a paper you have submitted, or the decision email on a grant you have submitted is a lot less stressful.

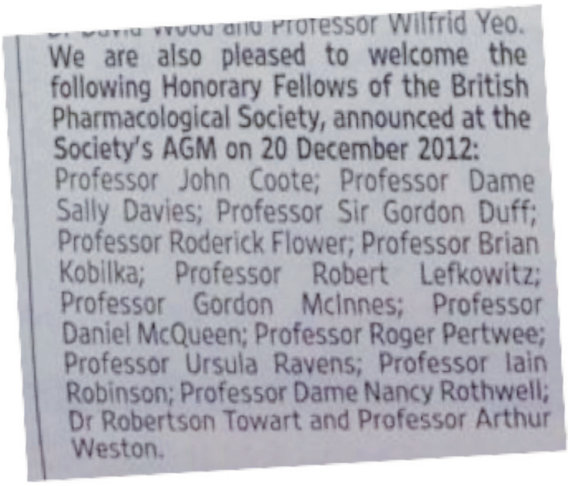
BPS Honorary Fellowships: an appeal for nominations

Humphrey Rang
BPS President

BPS offers a variety of prizes, awards and medals that recognize the contributions of members throughout the different phases of their careers in all branches of pharmacology.

The highest honour bestowed by the Society is Honorary Fellowship, which is awarded to senior BPS members (or exceptionally to non-members) distinguished for their sustained leadership role in pharmacology. Through this, BPS recognizes outstanding achievements in research or teaching, effective promotion of the discipline, or a record of long and valuable service to the Society.

The award has evolved from the category Honorary Membership, which was created in 1932. The first two honorary members were JJ Abel of Baltimore (founder of the first pharmacology department in USA) and HH Meyer of Vienna (famous for the Overton-Meyer theory of narcosis). Nowadays, Honorary Fellows are entitled to use HonFBPharmacolS after their name, receive free membership of the Society (with all the benefits of Membership) and are invited to the BPS Annual Dinner to receive a certificate in the year in which they become an Honorary Fellow. Currently 88 out of 3,460 BPS members are Honorary Fellows, each year's intake being officially announced in the *Times* newspaper in early January (see photo):



and Professor Wilfrid Yeo.
We are also pleased to welcome the following Honorary Fellows of the British Pharmacological Society, announced at the Society's AGM on 20 December 2012:
Professor John Coote; Professor Dame Sally Davies; Professor Sir Gordon Duff; Professor Roderick Flower; Professor Brian Kobilka; Professor Robert Lefkowitz; Professor Gordon McInnes; Professor Daniel McQueen; Professor Roger Pertwee; Professor Ursula Ravens; Professor Iain Robinson; Professor Dame Nancy Rothwell; Dr Robertson Towart and Professor Arthur Weston.

For me, the award of Honorary Fellowship was unexpected and much appreciated, as recognition of a long career in pharmacology, which included a few successes that came amid many years of unremitting slog – a pretty typical career in fact. A major highlight for me has been the success of the student textbook that Maureen Dale and I wrote in the mid-80s. The book quickly took on a life of its own (as well as taking over much of mine and those of the excellent co-authors of subsequent editions), and it pleases me hugely that it has helped to open the eyes of many students to the fascination of pharmacology. That this and other contributions to the discipline and to the society are seen by my peers as worthy of the award of an Honorary Fellowship means a lot to me.

Other recently-elected Honorary Fellows express similar thoughts:

Professor Rod Flower
HonFBPharmacolS since 2012

The influence of the learned societies on the scientific culture of the UK is difficult to overestimate. In an academic environment too often dominated by concerns about targets and output markers, these organizations alone seem to have preserved the tradition that the core business of science is, first and foremost, the acquisition of new knowledge for its own sake. I have been a member of the BPS since I was a postgraduate student and it has been enormously important to me both professionally and personally. I felt very proud to be elected as an Honorary Fellow.

Professor Dame Nancy Rothwell
HonFBPharmacolS since 2012

I was very presently surprised to be offered Honorary Fellowship – I have been a member for many years. It is also a great honour to join so many eminent scientists who are honorary fellows.

BPS Council believes that we may be overlooking excellent candidates for Honorary Fellowship, and is seeking to improve the process for identifying eligible individuals. To this end, a Nominations Group has been established, to support Honorary Fellowship elections. The Nominations Group, which I now chair as BPS President, is responsible for encouraging and evaluating nominations for Honorary Fellowship submitted by BPS members. There is no fixed quota, but we are aiming to elect about 10 Honorary Fellows each year.

But the Nominations Group cannot do this without the support of the BPS membership! BPS Members, Fellows & Honorary Fellows (including Retired Members & Fellows) and I appeal to all to nominate candidates for Honorary Fellowship. The group will rely upon these nominations to ensure that eligible individuals aren't overlooked and that excellence in all aspects of pharmacology is represented in this, the highest echelon of the Society.

A list of existing Honorary Fellows, and a nomination form are available online (*bit.ly/1fPTPIR*). Nominations must be submitted before the deadline of **1 July** to Paul Tizard (*paul.tizard@bps.ac.uk*), Membership & Awards Officer.

Young Pharmacologists: an update

Maria Fernandes
Editor, *Pharmacology Matters*

Maria is finishing her PhD at the Institute of Pharmaceutical Science, King's College London. She has a great interest in public engagement and outreach. She currently sits on the BPS Outreach, Young Pharmacologists and AWIP committees.

Before I start updating on everything that the Young Pharmacologists Committee has been up to recently, I'd like to take this opportunity to thank Hannah Watson for reporting on our activities up until this issue. Thank you Hannah, we wish you all the best for the future!

2013 was a great year for the Young Pharmacologists committee (if we do say so ourselves). We made fantastic progress in fundraising for *17th World Congress of Basic and Chemical Pharmacology* bursaries for African scientists – our final total is a whopping £17,118.55 (let's not forget the 55p). We're massively grateful to everyone who bought 'I heart pharmacology' merchandise and donated via other means. We are hoping to continue our fundraising in the future – we'll let you know more in future updates.

In 2013 we also contributed to discussions shaping the Society's five-year publication strategy, reached over 5,000 views of our How Do Drugs Work videos (at the time of writing) and took our *Stem Cells – Pharmacology and Therapeutics* symposium international to *Experimental Biology 2013*.

Pharmacology 2013

We had a fabulous time at our second Welcome Reception at The Library, SixtyOne Whitehall! The incredibly talented Daryl Kellie once again provided the musical entertainment, with a guest spot from Tom Nicholls on ukulele. It was fantastic to see so many delegates and exhibitors in attendance, and so many merry conversations going on around the room, facilitated by the wonderful staff at 61 Whitehall. We have some very exciting plans for next year's Welcome Reception, which I'll come back to in just a moment.

Our organized symposium on *Pharmacology and OMICS technology* was a great success and proved to be a platform for some fascinating and intense scientific discussion at the cutting edge of pharmacology and research. We'd like to thank all of the speakers and BPS staff for making our 4th successive symposium such a success.

How Do Drugs Work? Videos

You may have seen our 'How do drugs work?' videos on YouTube (*www.youtube.com/user/BritPharmSoc*). These videos were made to help describe how the most widely used medicines in the UK work. We've already had several videos from painkillers to proton-pump inhibitors and we're looking for more! If you'd like to get involved and have an idea for a medicine that you could explain to the general public, please contact Hazel O'Mullan (*hom@bps.ac.uk*).

Welcome Reception 2014: The Teaching Awards

In recognition of the exceptional pharmacology teaching going on at UK universities, you will have seen that we are launching our very first Pharmacology Teaching Awards at *Pharmacology 2014*. We are excited to hear from undergraduate and taught postgraduate students about the best teachers of pharmacology in the UK. We're looking forward to welcoming the nominees to the Welcome Reception at *Pharmacology 2014* and deciding who will receive the student choice award for best pharmacology teacher!

A great time was had by all at the Welcome Reception

Tom Nicholls and Daryl Kellie provided entertainment at the Welcome Reception

Open your Is and you won't fall off the bicycle

Steven Tucker
Editor, *Pharmacology Matters*

Steven graduated from the University of Aberdeen with a first class honours degree in Biomedical Sciences (Pharmacology) in 2000, winning both the class prize and the University Quincentenary Award. He then did his PhD studies in the laboratory of Dr Dave MacEwan in the Department of Biomedical Sciences at the University of Aberdeen. Steven then embarked on a three year post-doctoral research project in the laboratory of Dr Matt Wright, also at the University of Aberdeen.

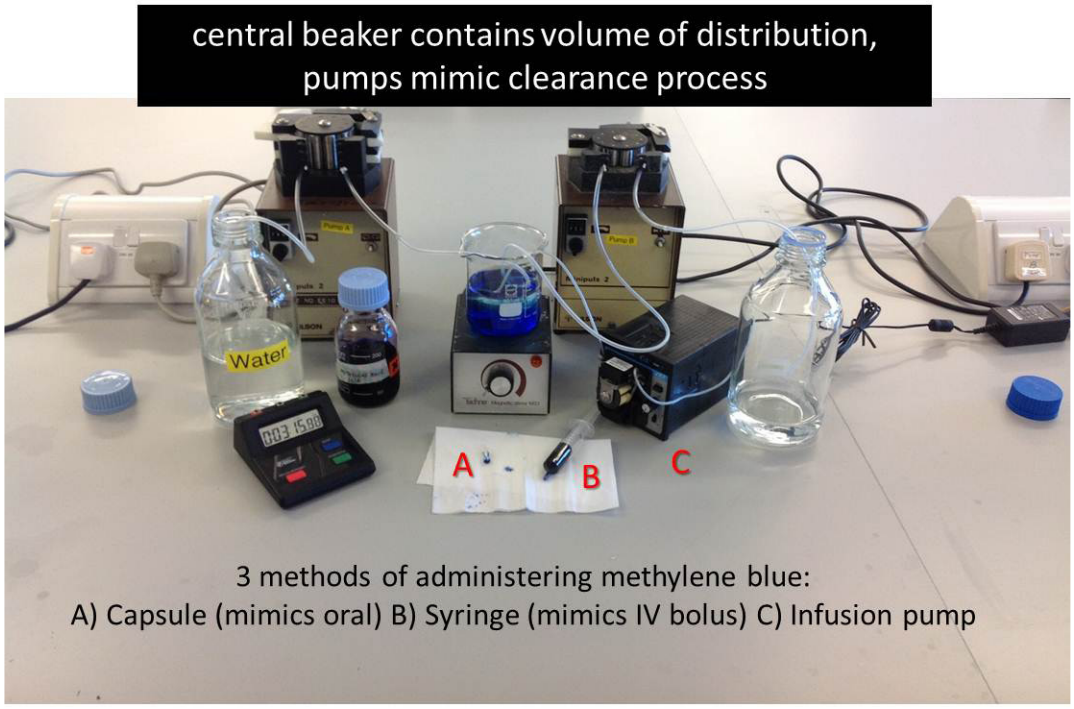
In 2005 Steven moved to the University of Edinburgh and worked in a more clinical setting, studying new antibody-targeted therapies in the treatment of acute myeloid leukemia at the Western General Hospital. He returned to the University of Aberdeen around a year later and joined the laboratory of Dr Derryck Shewan as a post-doctoral research fellow, where he developed a state-of-the-art imaging system for studying signalling within neuronal growth cones. In 2008, he became a Teaching Fellow in the School of Medical Sciences, where his main duty was provision of undergraduate and post-graduate teaching. Steven continued to actively research with Dr Derryck Shewan and other collaborators. Steven is currently a senior teaching fellow developing his own pedagogical research into innovative ways to deliver practical skills, and he is studying the role of cAMP in cancer cell proliferation and migration.

Outside academia, Steven has a keen interest in music and play drums, bass guitar and keyboard. He also loves sport including football (and his beloved Aberdeen football club), cricket, tennis, American football, cycling and golf.

It all began in the summer of 1983. As a headstrong, bossy and mildly spoilt five-year-old child, I was determined that I would go for a long, exploratory ride around the village on my bicycle. However, the rate limiting factor was my friend Gregor! I couldn't understand or comprehend why he couldn't ride his bike unaided; he was older than me after all! I recall a sense of frustrated incredulity at his lack of competence; "You just do this," I had uttered on several occasions demonstrating my skills at pedalling, steering and maintaining an upright status throughout. This early, petulant copycat teaching methodology crashed several times like Gregor had, and a realization dawned on us both that "If at first you don't succeed, try and try the same thing again" was not going to bring success in a teaching context.

Not to be defeated by my wobbly friend, I eventually rode alongside him as a makeshift stabiliser (a suggestion from my older brother) until he had sufficient confidence (and speed) to continue unaided. Success at last, and an early indication of the importance of determination and support, both of which are cornerstones of my approach to student learning some 30 years later. This early, formative experience of teaching evidences that professional development begins long before we become professionals and that as human beings many of our early childhood experiences involve the development of our capacity for making what we hold implicit, less tacit.

Figure 1



The apparatus used to model pharmacokinetic processes in class practicals. This has created a novel, interactive and innovative way of teaching the subject and allowing students to bring the numbers to life.

Fast forward 30 years and currently my typical academic year involves over 260 timetabled contact teaching hours across Medical Science disciplines and it is a great privilege to interact with an increasingly diverse range of students across many of the same courses I studied as part of my Biomedical Sciences (Pharmacology) degree at the University of Aberdeen. Interestingly, many of my experiences as an undergraduate still strongly shape my current teaching practice, in the same way that my early experiences with Gregor are a primitive representation of my commitment to passing on my acquired knowledge and expertise at all costs!

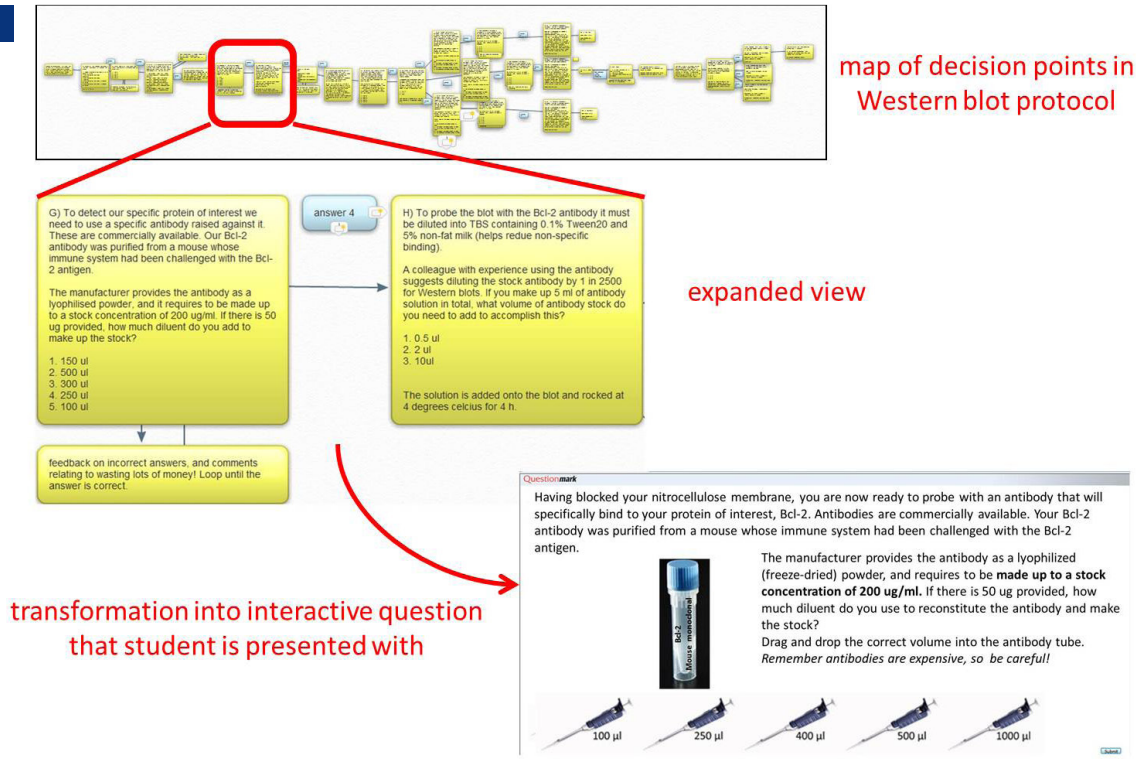
One aspect of my own undergraduate degree programme that I recall as particularly grim was pharmacokinetics. This was taught "live" on a rapidly scrolling roll of acetate; a millions miles from the benchtop or bedside where these numbers were important. As a result of this didactic and dry approach, and my own inability to see through the Maths and link the numbers to something real and pharmacologically relevant, it is fair to say I wasn't very good at pharmacokinetics! Recalling conversations among my peers at that time, it was clear I wasn't alone, and we were united by our inability to see the pharmacological wood for the pharmacokinetic trees. In the years that followed, I heard from various sources across the different Institutions I worked at and visited, that this wasn't a problem specific to Aberdeen. Instead, it was a problem inherent to the subject and the archaic approaches to its teaching and learning.

It has become a personal obsession of mine to transform pharmacokinetic teaching into something modern, relevant, enjoyable and, most importantly, understandable. In doing so, I have developed new approaches and strategies for teaching this subject area according to "the Three I's": imagination, innovation and interactivity. Indeed, these are central drivers of many of my teaching approaches and show how far formative experiences have honed my approach from the "try anything that comes to mind" approach of my five-year-old self.

- **Imagination** is required in order to present material in an interesting and enlightening way, but also to help bring concepts to life with novelty and purpose. The imagination also relates to the student though their capacity to imagine taught concepts independently and on their own terms.
- **Innovation** relates to the use of novel strategies and technologies to enhance teaching and learning. In the futuristic age in which we live, there is a vast array of resources available to us, and we have a collective responsibility to move with the times by utilizing such tools to help transform teaching practice into the modern world.
- Finally, **interactivity** is a critical component, as it drives experiential learning. This means students learn from experiences and feedback, and gradually assimilate knowledge and skills, much in the way Gregor did on his bicycle. Aside from this, interactivity is central to engaging the student and putting them in the driving saddle of their own learning journey.

Examples of my utilization of "the Three Is" in my approaches to teaching pharmacokinetics has involved development of a series of practicals using a simple and adaptable model system (figure 1) supported by a BPS teaching grant. The model system has a central beaker containing water representing the volume of distribution into which methylene blue is delivered, with the two pumps mimicking clearance by removing the methylene blue containing water from the beaker at the same rate as this is replaced with fresh, clean water. Methylene blue quantification is simple using a spectrophotometer, and thus students plot concentration time graphs illustrating progressive removal of the drug (methylene blue) following administration of the dose, using these for derivation of pharmacokinetic values. Simple alteration of dose added, volume of distribution or clearance in the model system allows students to experiment within structured classes and determine the effects of varying these specific pharmacokinetic parameters. Furthermore, they can generate, analyse and calculate

Figure 2



The transformation from decision point plan into the online interactive Western blot "pseudo-practica'"

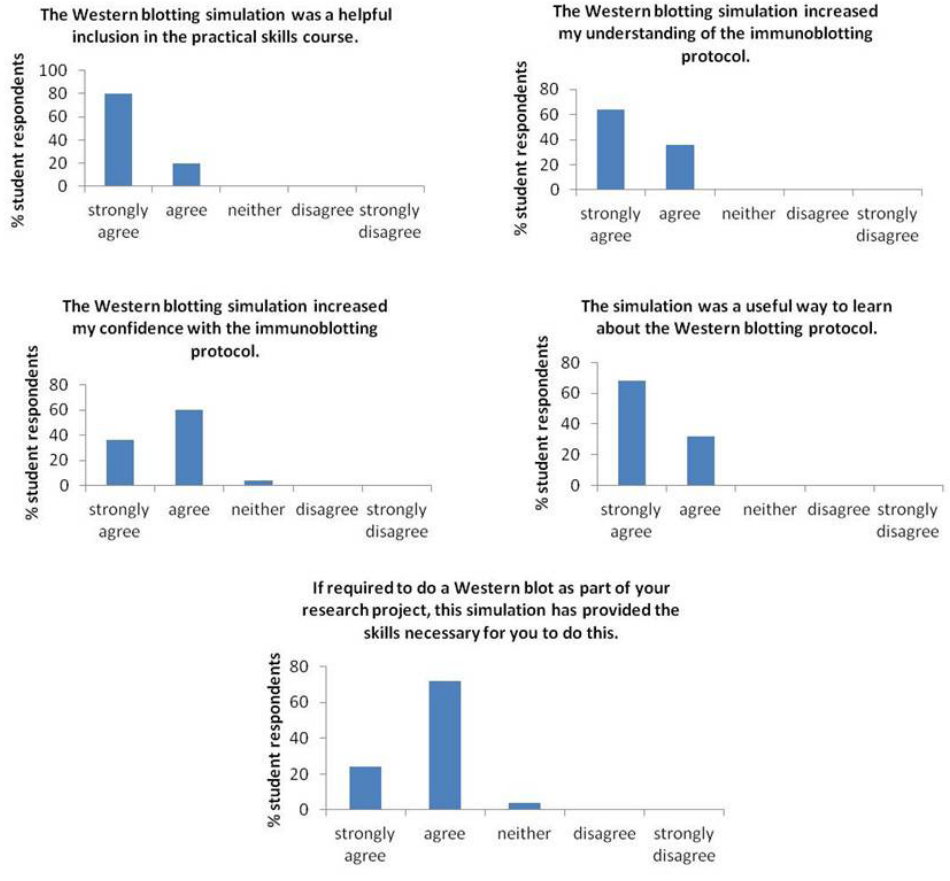
their own data pertaining to IV bolus administration, single oral dose administration, repeated oral doses or IV infusion, as I have also developed ways of modelling these routes of administration (A, B and C in the figure). Effectively, this novel and highly accurate approach brings the numbers to life and lets students see directly the relevance of the concepts to drugs in the body. These practicals provide application of materials closely aligned to the lectures and have significantly benefitted the pharmacokinetics element of the programme by adding an entirely new dimension to student understanding. It is clear the level of imagination, innovation and interactivity inherent in this strategy helps it achieve this key objective.

Aside from pharmacokinetics, I have also recently completed a project that involved design, development and implementation of an interactive Western blot simulation within our undergraduate and postgraduate curriculum. Western blotting is a central technique across the life sciences and I felt this could be a useful training and skill development tool, with the cost, time and complexity issues surrounding running an actual practical necessitating development of this "pseudo-practical" as the next best thing. In reality, a Western blotting practical would take 2–3 days of timetabled classes and would cost hundreds of pounds per run. The "pseudo-practical" is cost and risk-free, taking around 90 minutes to complete and developing knowledge, understanding and applied experience of key decision points in the protocol. The initial step in its inception involved mapping the protocol as a series of decisions (shown as a structured flow chart at the top of figure 2, zoomed out to show the number of decisions in the lengthy procedure). Each stage involves a decision relating to the protocol and consequences in the form of feedback (see zoomed in panel as an example). An online and simple flowchart tool was used for this process (bubbl.us). I then built these into an online quiz where decisions at each experimental stage are followed by feedback, which reinforces a correct answer or constructively criticises an incorrect answer providing explanation about why the answer was wrong. In the event of an incorrect answer, the student is returned to the question to try again armed with the helpful feedback. This was done using Questionmark Perception assessment authoring software, which is intuitive and simple to use, with a huge amount of in-built flexibility. This imaginative structure and design provides an innovative opportunity for students to interact with the protocol, enhance their understanding and skills associated with the technique and drive their own learning through the decisions they make. This format is broadly applicable to other central techniques and provides a useful, flexible and well received teaching instrument. Figure 3 displays feedback gathered from an MSc class (~50 students) and suggests this instrument is effective and enjoyable for students and helps develop understanding and confidence with the protocol. Furthermore, students felt that the exercise would form an ideal training exercise prior to actually performing a Western blot in the laboratory. Further analysis through the Questionmark software will allow targeting of specific help at points where students consistently struggle and require many turns of the feedback loop to progress.

As demonstrated above, teaching is a lifelong and personal journey, however it need not be travelled in isolation, and indeed collaboration, discussion and practice sharing creates fourth and fifth Is: integration of ideas. In this context, best practice is sharing practice, and by combining our strategies there is benefit for all the stakeholders associated with higher education. Just as teaching is lifelong, so is learning and we can learn so much from each other, as is evidenced by my brother's role in my opening story. Today's lesson is simple, let us all open our Is.

Pharmacology Matters would like to encourage the sharing of best teaching practice by including relevant articles as a regular feature, so please send in any articles describing your approaches to pharmacology teaching to Hazel O'Mullan (*hom@bps.ac.uk*).

Figure 3



BPS Meetings: an update

Barbara McDermott
Vice President – Meetings

Karen Schlaegel
Head of Meetings and Events

It is a new term for the BPS Meetings Committee and Barbara McDermott took up the Chair at the beginning of January. We have just recently held the first committee meeting of 2014 and, among a packed agenda, we had the opportunity to reflect upon 2013. The year ended on a high with the rebranded annual flagship meeting, *Pharmacology 2013*, held 17–19 December in London.

Pharmacology 2013

The success of this meeting was a huge tribute to the scientific leadership provided over the past two years by David Webb along with the committee members, and all-important details were so reliably put in place by BPS office staff, led by Karen Schlaegel.

As the meeting had been fully booked for the two previous years, we secured a larger and a better configured space at the Queen Elizabeth II Conference Centre and so were able to welcome more participants, display more posters and accommodate more exhibitors.

Feedback from participants during and after the meeting continues to be highly positive. Compared with the 2012 meeting, we saw even greater increases in participants' satisfaction with the programme (81% vs. 89%) and speakers (92% vs. 97%). We were able to attract more sponsorship too, and would like to especially thank the scientific organizers of the nine symposia for their invaluable support with this.

Moving the AGM from Thursday afternoon to Wednesday lunchtime also worked very well and we were pleased that the AGM attracted a record number of attendees. Introducing a lunch break – albeit a short one – also seemed to meet with approval. Last but not least, good attendance on the final day for the plenary lecture and the final poster session brought the meeting to a fine conclusion.

The BPS Meetings Committee has considered the constructive comments about how certain aspects of the meeting could be further improved and this has led to a number of changes that will be put in place in time for *Pharmacology 2014*.

Pharmacology 2014

We have received almost twice as many symposia proposals for *Pharmacology 2014* than for last year's meeting – further proof that our annual meeting is growing and establishing itself as a meeting not to be missed. In order to include as many of these high quality sessions, four instead of three symposia will be run in parallel. This means that there will now be twelve symposia taking place throughout the three days, allowing participants to keep up-to-date across an even bigger range of topics.

Thinking around how to create a positive initial experience of presenting for early career investigators, we have decided to ask all symposia organizers to incorporate two oral presentations chosen from the abstract submissions. Thus these presenters should reach a wider audience. The dedicated oral sessions held in the afternoons will also be shortened and we plan to create a significant number of themed sessions. All poster sessions will be extended to 1.5 hours and we are planning to introduce guided poster tours, ensuring that all authors have the opportunity to present their work to as large an audience as possible.

5th Focused Meeting on Cell Signalling, 28–29 April 2014

The fifth in this successful series of meetings has already attracted a number of exhibitors and sponsors and we are very grateful for the support from Abcam, Cisbio, DiscoverX, LabLogic, Novus Biologicals, R&D Systems and RenaSci. At the time of writing, abstract submissions and registrations are promising and we are looking forward to another successful meeting held at the University of Leicester.

8th Congress of the Hellenic Society for Basic and Clinical Pharmacology, 23–25 May 2014

BPS will have a session on education as well as an exhibition stand at the annual meeting of the Greek Society which will be held in Athens. We are delighted that Steve Alexander, Rod Flower, Ian McFadzean, and Jess Strangward will be representing BPS at this meeting.

17th IUPHAR World Congress of Basic and Clinical Pharmacology 2014, 13–18 July 2014

BPS is a Gold Sponsor of the congress and we are supporting three symposia and four plenary speakers. In addition bursaries have been awarded to BPS members who are presenting at the meeting.

As previously mentioned BPS will also be presenting its bid to host IUPHAR 2022 in Glasgow. We would like to thank everyone who has supported the bid so far.

James Black Meeting – Inspired Biologics 2014, 18–19 September

The meeting, which is a follow up of the Biologics meeting held in 2011, will again take place at Murray Edwards College in Cambridge and will focus on respiratory pharmacology. The BPS Industry Committee is collaborating with the BioIndustry Association and will host a networking event on the evening of the first conference day. All delegates will be invited but it will also be open to a wider (industry) audience.

The next Meetings Committee will take place in June, where we will look ahead to 2015 and 2016. If you have any ideas for meetings, please do not hesitate to get in touch (*ks@bps.ac.uk*)!

We hope to see you at one of our meetings!

Barbara and Karen

Stem Cell Therapy: the 'miracle cure' for stroke?

Felicity N. E. Gavins
Editor, *Pharmacology Matters*

Felicity's research crosses the boundaries between integrative physiology and pharmacology and uses multidisciplinary approaches to advance understanding of the vascular physiology and pathophysiology of inflammatory and related disorders, at the molecular, cellular, tissue and whole organism levels. In particular she focuses on the microcirculation, studying leukocyte trafficking and endothelial dysfunction in both the brain and the periphery, using a variety of imaging techniques, including: confocal intravital microscopy; magnetic resonance imaging (MRI); positron emission tomography (PET) and single photon emission tomography (SPECT).

Stroke and global health in the 21st century

Are you healthy? On the face of it, this may appear to be a very simple question to answer, however it becomes more confounding when one ponders the exact definition of health. As a biomedical scientist, I could define health as "an absence of disease as the body maintains homeostasis". The World Health Organization (WHO) extends this definition to "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity".

In 2011, the census asked UK households this very question: "are you healthy?" Approximately 9% of the UK said that they were not in good health. Even more interesting were the large regional differences in response across the UK: just 4% of the population in one of the most affluent areas conceded that they were not in good health, which increased to 18% in one of the most deprived areas. There are many theories for these differences, which are beyond the scope of this article, but what remains constant, irrelevant of the socioeconomic situation, is the continuing epidemic of cardiovascular disease (CVD) across the UK and worldwide. The widespread occurrence and silent progression of atherosclerosis as well as high blood pressure (the highest risk factors for heart disease and stroke, see Table 1) has created a CVD burden that is massive in terms of death, disability, and social and economic costs.

This article will focus on one aspect of CVD: stroke. Circa 400 BC, Hippocrates used the term "apoplexy" to describe very acute nontraumatic brain injuries (1), and one of the very first uses of the word "stroke" dates back to 1689 by William Cole in *A Physico-Medical Essay Concerning the Late Frequencies of Apoplexie* (2). In the 1950s, doctors decided that the term "stroke" should not cover temporary (short-term) vascular-related episodes of brain dysfunction, and so, "transient ischemic attack" came into use. As of 1970, the WHO has defined stroke as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin." (3)

Stroke is the third leading cause of death in the UK, behind heart disease and cancer, claiming 15 million lives worldwide each year. In the UK alone, someone has a stroke every five minutes and almost 50% either die or are disabled at six months (4). In 2005, an estimated 16 million first-time strokes and 5.7 million deaths occurred, and these numbers are expected to increase to 23 million first-time strokes and 7.8 million deaths in 2030 (5).

The main burden of this disease is survival with disability, dementia, depression, epilepsy, falls and other complications (6). Post stroke, approximately a third of patients have dysphasia (loss of speech), with 50% of patients losing the ability to swallow on admission to hospital (7).

5.5% of the total UK expenditure on health care – £4 billion – is spent on stroke, with cumulative costs (which include "indirect" care: specialist care and income support) thought to be close to £9 billion. With the burden of stroke predicted to increase due to the number of elderly people living longer, this indicates a further increase in expenditure to an already stretched budget (8).

Table 1

Common risk factors for stroke

Modifiable risk factors	Diet
	Obesity
	Increased cholesterol
	Lack of exercise
	Alcohol
	Hypertension
	Smoking
	Diabetes
	Atrial fibrillation
	History of trans ischaemic attacks
	Sleep apnoea
Non-modifiable risk factors	Increasing age
	Gender
	Ethnicity

Types of stroke

The brain constitutes 2% of the total body weight in adult humans, yet receives 15–20% of the body's blood supply, rendering brain cells extremely vulnerable to fluctuations in blood flow. There are two main types of stroke: ischaemic and haemorrhagic. The vast majority (85%) are ischaemic in origin (although interestingly, in 2010, most of the global burden of stroke was due to haemorrhagic, not ischaemic, stroke (9)) and are characterized by an obstruction of a vessel, preventing or reducing blood flow to the brain (10). The obstructions are most often caused by a thrombus or embolus from the heart, myocardial infarction, or trauma.

Treatment for stroke

Despite numerous studies on neuroprotective agents, the only FDA approved treatment for ischaemic stroke is the removal of the thrombus/embolus either pharmacologically by thrombolysis with intravenous administration of recombinant tissue plasminogen activator (tPA), or mechanically with a retriever (11). tPA has a very short time window for therapeutic intervention (4–6 hours),

which therefore limits its use to a small minority (2–4%) of patients (12). Additionally, approximately half of the patients who receive tPA for acute ischaemic stroke and survive to day 90 have a significant long-term disability. (Of interest, there are currently five randomized trials taking place worldwide to evaluate the safety and effectiveness of acute intra-arterial clot-retrieval interventions. The results of the available data to date show that the clot-retrieval interventions failed to improve stroke-related disability.)

Poor outcomes following treatment highlight the complexity of the brain, the difficulty in applying timely recanalization, the extreme sensitivity of neurons to ischaemia, and the disabling nature of the deficits obtained from stroke (13). Despite this the "injured brain may be primed for potentiation of neurorestorative processes" (14), because when the brain has been injured by a stroke, it displays a gene and protein expression profile very similar to that of the developing brain during embryogenesis (15).

Are cell-based therapies the answer?

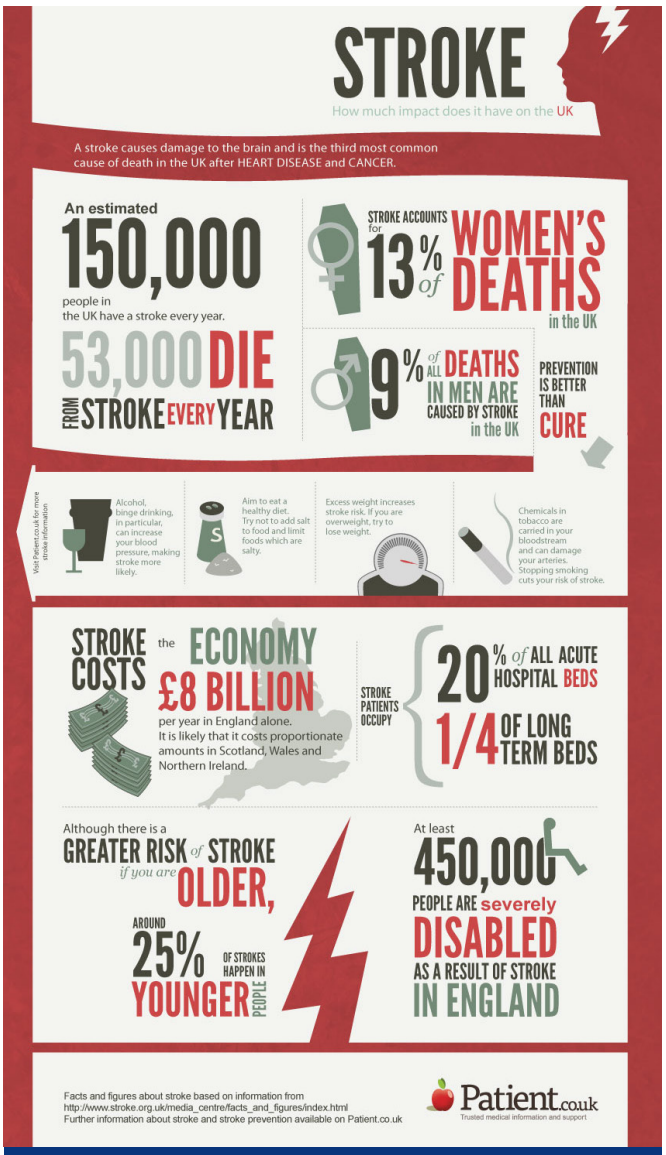
The potential for small molecules and other strategies to enhance the recovery process post-stroke are being explored, but cell based therapies are emerging as one of the greatest hopes for possible therapeutic strategies for enhancing tissue repair and neurologic recovery in ischaemic stroke (16,17). This is certainly reflected in the amount of funding available for stem cell therapy, which reached over £72–88 million in 2011, and continues to rise. The objective of these therapies is to seek to enhance regenerative mechanisms such as angiogenesis, neurogenesis, and synaptogenesis in ischemic stroke.

The cell types used can be categorized into embryonic (considered the "gold standard" of stem cells, but are controversial due to their origin), fetal, adult and nonhuman stem cells (18). Advances in stem cell biology have now made it possible to manufacture many of the purified cell types from different tissues, paving the way for the application of allogeneic, off-the-shelf products that may not require concomitant immunosuppressive drugs (19).

Recent studies have indicated that stem cell based therapies enhance functional recovery at least partially via their ability to secrete neurotrophic factors and immunomodulation (20, 21). There is much discussion and debate with respect to the underlying beneficial mechanisms of stem cell based therapy, including aspects of proliferation, migration, differentiation and apoptosis. What makes stem cell therapy an attractive therapeutic opportunity for stroke? Many reasons, but the greatest being their positive effect in cardiology and a greater therapeutic window for administration over tPA. However, despite their promise, there are a number of issues with stem cell based therapies for enhancing neurologic recovery in ischaemic stroke, such as best cell source (e.g. adipose, human fetal/embryonic tissue, bone marrow, peripheral, umbilical cord), timing of cell therapy (Figure 1), dose and route of administration (e.g. intracerebral, intra-arterial, intraventricular).

Currently, there are 25 completed (unpublished) or ongoing registered clinical trials, according to the National Institutes of Health clinical trial registry (*www.clinicaltrials.gov*). Most (16 studies started in 2011 and 2012) are being conducted in the United States or China. A variety of routes of administration have been chosen e.g. 13 trails have chosen intravenous administration alone, seven trials intracerebral alone, three trails intrathecal alone and the rest a combination of different routes (For a review of clinical trials with stem cell based therapies see reference 22).

Pilot Investigation of Stem Cells in Stroke (PISCES), one of the first ever trials to test the safety of stem cells as a treatment for



Stroke is the third leading cause of death in the UK

stroke, is due to draw to a close this year. This is a phase 1 clinical trial involving the injection of fetal stem cells into infarcted brain regions of 12 patients, 6–24 months after ischaemic stroke. Although primarily concerned with assessing the safety of ReNeuron's ReN001 neural stem cell line for clinical use, the trial is based on accumulated evidence. Last year, investigators reported at the *22nd European Stroke Conference* in London, that the first nine patients on the PISCES trial show "no cell-related or immunological" adverse side effects, and most patients have shown modest improvements. Encouraged by these results, the team has now submitted an application to the UK regulatory authority to commence a multi-site Phase II clinical trial to examine the efficacy of their ReN001 stem cell therapy in patients disabled by ischaemic stroke.

A major concern with stem cell based therapies is the possible complication of spontaneous tumor formation. Whilst autologous stem cells isolated from bone marrow have a safety 'halo' because of decades of safe experiences in bone marrow transplantation, pluripotent cells often forms teratomas (24). Therefore it is most important to monitor stem cell transplants over a period of time. Imaging offers the potential to follow the fate of the stem cells. From a clinical perspective, the development of multimodal, non-invasive and sensitive imaging techniques in order to track stem cell migration and/or differentiation would be invaluable.

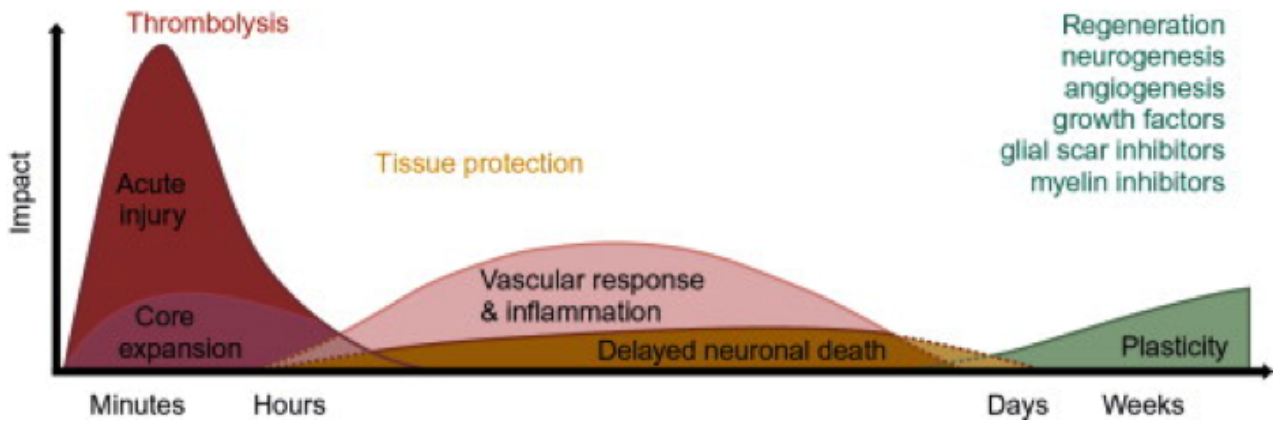
My group, and others, are employing and developing multimodal, non-invasive and sensitive imaging techniques in order to track the fate of stem cells *in vivo*, in particular to monitor their survival, migration, and proliferation. We are using positron emission tomography (PET), magnetic resonance imaging (MRI), and optical imaging - both alone and in some cases as a multimodal approach - for tracking *in vivo* stem cell transplantation in stroke. There are advantages and disadvantages to all imaging techniques that are currently used, for example, although PET has low spatial resolution compared to MRI, it offers higher sensitivity, which allows the detection of cellular events at a smaller scale. Multimodal approaches offer the capability of integrating modality-specific strengths. The ultimate goal is to identify the best source, dose, route and time of administration of stem cells and subsequently to be able to track cells in the clinic.

Much regenerative medicine research to date has focused on evaluating and developing the potential of neural stem cells in cerebral ischaemic repair, with the rationale that these cells stimulate electrical impulses in the brain, and will help to restore tissue that has been damaged by oxygen deprivation. Improvements in neurologic function in rats post stem cell transplantation are poorly understood, although the release of trophic factors by transplanted cells are thought to enhance existing host cell connections by facilitating synaptic activity and axonal regeneration (25).

Recently the field has moved on to the role astrocytes may play in fighting against stroke, evoking the thought that isolating characterized unique glial cell types could have tremendous implications for possible therapeutic interventions following CNS damage (26).

We and others are extremely interested in haematopoietic stem or progenitor cells (HSCs), as they have been shown to mobilize to the peripheral circulation from bone marrow in response to stroke (27). Furthermore, higher concentrations of serum HSCs correlate with improved neurologic function following stroke (28, 29) and smaller infarct size (30). It may be that bone marrow does indeed participate in brain repair by mobilizing and releasing stem cells, but this will need further study.

Figure 1. Potential windows for cell therapy interventions in stroke. Taken from reference 22.



Exogenous administration of HSCs in mice with cerebral ischaemic injury has shown their potential in reducing stroke injury and facilitating recovery (31). Injured tissues release growth factors that signal for HSC mobilization from the bone marrow into the circulation, where they can differentiate into a variety of different cells. It has been found in vivo that further stimulation by the administration of growth factors such as granulocyte-colony stimulating factor (G-CSF) can enhance this mobilization (32, 33). Sadly, these pre-clinical findings have not been translated to the clinic, with the results of the phase II AXIS-2 trial (comparing Filgrastim - a G-CSF analog used to stimulate the proliferation and differentiation of granulocytes - to placebo in a randomized trial of over 300 patients), failing to show effect for treatment with G-CSF (34).

Summary

Overall, there is growing evidence that stem cell based therapies, through their trophic and multipotent properties, may hold great potential improving the outcome after stroke. However, they can only be taken and used in the clinic if safety and beneficial effect of the transplanted cells can be assured. Over the coming years, the results from stem cell research and the findings from phase III trials in humans will provide us with a greater understanding of how best to treat stroke, and whether stem cells really are a 'miracle cure' for stroke.

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Evidence-based drugs for pain relief

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University of Cambridge

Christopher Tsantoulas received his BSc in Biology from University of Athens in 2003. Following a Master's in Molecular Medicine at University College London, he was awarded a PhD studentship in Neuroscience from King's College London. He completed his thesis on "The Role of Potassium Channels in Neuropathic Pain" in 2010, after which he undertook an industrial post-doctoral position at Pfizer developing a novel microfluidic platform for pain studies. He is currently a post-doctoral research associate in the Department of Pharmacology, University of Cambridge working on ion channels and peripheral pain modulation.

Chronic pain affects one in five people worldwide, with the incidence rate rising in line with the ageing population.[1] It can be caused by diverse aetiologies encompassing nerve trauma (avulsion injuries, amputations), metabolic diseases (diabetic neuropathy), viral infection (post-herpetic neuralgia, HIV-associated neuropathy), chronic inflammation (arthritis), malignancies, rare genetic disorders, as well as more common conditions (low back pain, migraine). The incapacitating symptoms associated with these states, namely spontaneous pain and hypersensitivity to stimulation represent a huge burden for patients. Additionally, chronic pain management inflicts vast economic costs with the global pain management market estimated to hit $60 billion by 2015.

This type of pain often arises as a result of direct lesions in the nervous system, in which case it is called neuropathic. Neuropathic pain is particularly refractory to treatment, with less than half patients reporting satisfactory (>50% improvement) relief. Current therapies (e.g. narcotics, anti-convulsants and anti-depressants) cause dose-limiting side-effects, including sedation, nausea, tremors, bradycardia or sensory disturbance due to the non-selective activity across the nervous system, muscles and heart. Therefore, identifying a molecular target that governs behaviour of pain-sensing neurons but is not essential for cardiac, brain or other functions has been the holy grail of pain research.

Pain detection relies on the function of pseudo-unipolar sensory neurons called nociceptors, which innervate the skin, internal organs and muscles. The cell bodies of these neurons reside paraspinally in the dorsal root ganglion, while central axons connect them to the spinal cord. Painful stimuli acting on peripheral nerve terminals activate specialized receptors, causing membrane depolarisation and action potential (AP) generation. This pain signal is then transmitted towards the spinal cord and eventually the brain where it is consciously perceived. It is widely believed that neuropathic pain is the result of a hyperexcitable peripheral nervous system (PNS). We also know that neuronal excitability is crucially dependent on the activity of ion channels controlling AP conduction. However, there are more than 400 different ion channels in humans and many are also mediators of essential physiological functions like cardiac pacemaking. So despite the powerful rationale, pain scientists had no real lead to follow.

This was until the discovery of rare individuals with congenital indifference to pain (CIP).[2] These people feature painless bone fractures, burns, tooth extractions and childbirth but appear normal in all other cognitive and sensory aspects. Genetic analysis of their DNA traced the peculiar phenotype to a single mutation that renders the SCN9A gene inactive. This gene encodes the sodium channel Nav1.7 and further studies also implicated increased Nav1.7 activity in extreme pain phenotypes. Thus, gain-of-function Nav1.7 mutations found in inherited erythermalgia are responsible for excruciating pain in the extremities, typically induced by mild warmth, exercise and/or humidity. Similarly, paroxysmal episodic pain disorder (PEPD), a condition where mechanical stimulation on the lower body triggers severe rectal pain attacks, has also been genetically linked to enhanced Nav1.7 function.

A large body of additional research since has established a dominant role for Nav1.7 in pain signalling. We now know that Nav1.7 is enriched in peripheral sensory neurons and its expression is upregulated in some chronic pain conditions. Nav1.7 is a low-threshold channel, meaning that it can be activated by small depolarisations due to modest stimuli. Opening of Nav1.7 facilitates Na^+ influx, which further depolarises the cell membrane. Because this contribution drives the membrane potential towards the threshold for AP firing, Nav1.7 function sets the gain of peripheral excitability, and therefore constitutes a gatekeeper of pain. Indeed, results from transgenic mice demonstrate a clear involvement in nociceptive neuron firing and pain behaviour; most notably, Nav1.7 ablation in both sensory and sympathetic neurons abolishes all pain sensations and recapitulates the pain-free phenotype seen in CIP individuals.[3]

The converging evidence strongly suggests that Nav1.7 is an attractive candidate for novel pain pharmacotherapies. Realizing the therapeutic opportunities, a number of pharmaceutical companies have launched programmes to develop Nav1.7 blocking molecules and several of these putative analgesics are currently in clinical trials for a variety of pain pathologies. The Cambridge UK-based pharmaceuticals company Convergence is assaying efficacy of its CNV1014802 compound in trigeminal neuralgia (TN), a rare pain syndrome linked to hyperexcitability of the trigeminal nerve, which provides sensation to the face. TN symptoms include excruciating pain episodes, occurring spontaneously or provoked by light touch at facial trigger points. Although the drug is still in Phase II evaluation, a provisional analysis reported that 70% of patients exhibited satisfactory analgesia with good tolerability. Encouraged by the favourable pharmacokinetic profile, the company has also launched a Phase II trial in lumbosacral radiculopathy (LSR), a neuropathic pain state caused by nerve root compression in the spine.

Xenon, a Canadian biotech focusing on rare genetic diseases, carried out an exploratory study with its Nav1.7 inhibitor XEN402 which indicated that the compound can significantly attenuate evoked pain in four SCN9A mutation-proven patients with inherited erythermalgia[4], XEN402 was also effective in inflammatory dental pain, where it increased the proportion of

patients with clinically meaningful pain score reductions compared to placebo. Following these promising results, an ointment formulation of the same compound was assessed in post-herpetic neuralgia (PHN), a pain syndrome caused by reactivation of the shingles virus in the nervous system. Local XEN402 application for three weeks provided substantial (>50%) pain relief, and also improved sleep and other co-morbidities. In contrast to other systemic therapies for PHN, adverse side-effects like dizziness and drowsiness were absent. Put together, these preliminary data suggest that XEN402 holds promise for suppressing multiple painful conditions of either inflammatory or neuropathic nature.

Finally, Pfizer has recently completed Phase II studies on the efficacy of its own PF-05089771 in patients with erythermalgia or post-operative dental pain, however no results have been released in the public domain yet.

What is the outlook on Nav1.7 drug development? The fact that Nav1.7 is enriched in the periphery creates exciting optimism for a superior therapeutic index, devoid of unwanted CNS side-effects. A key factor will be the ability to specifically inhibit Nav1.7, without off-target effects on other Nav isoforms with chief physiological functions. For instance, Nav1.4, Nav1.5, Nav1.6 regulate excitability in muscle, heart and nodes of Ranvier, respectively. Such non-specific blockage of other channels can cause unwanted side-effects which limit the therapeutic window and curtail analgesic efficacy. Although all aforementioned inhibitors in clinical trials are not entirely selective, they show much higher affinity for Nav1.7 over other isoforms; this suggests that adequate pain relief may be achieved with good tolerability. Another area of concern is the impact of Nav1.7 blockage in other types of sensory neurons; Nav1.7 is found in olfactory neurons and both CIP individuals and knock-out mice exhibit anosmia.

Are entirely selective Nav1.7 inhibitors a realistic possibility? It appears the answer is yes, and nature got there some million years ago. By examining the panoply of venoms used by scorpions, tarantulas and centipedes, scientists have uncovered potent Nav1.7 blockers which can neutralise the prey's pain system by inducing powerful analgesia.[5] Even more striking was the fact that the selectivity of these peptides far surpasses that of small molecule Nav1.7 inhibitors currently in development. It is plausible that extensive interactions of these large natural peptides on multiple sites of the Nav1.7 protein are critical for their superior blocking specificity. Therefore, unlocking the molecular architecture of natural peptides may further improve medicinal chemistry.

Although the pivotal role of Nav1.7 in regulating neuronal excitability is evident, it is still unclear whether this is reliant on a particular subcellular localization. Nav1.7 is expressed along the entire sensory neuron trajectory, from peripheral terminals and axonal segments to cell body and central arborisations in the spinal cord. Identifying the exact site of action will instruct future drug design and treatment options. For instance, a critical function in central processes would require systemic administration of compounds capable of crossing the blood-brain barrier. Nevertheless, the apparent efficacy of topical XEN402 suggest that at least some blocking is conferred at peripheral terminals and can be exploited with local administration regimes.

The discovery of on-demand anaesthesia and analgesia in the 1800s revolutionized medical treatment and pain management. However, over a century has passed without any major breakthrough and clinical control of chronic pain states in particular remains a greatly unmet need. The development of Nav1.7 targeting compounds is an exciting chapter in evidence-based medicine that may become a long sought success story in translational pain research.

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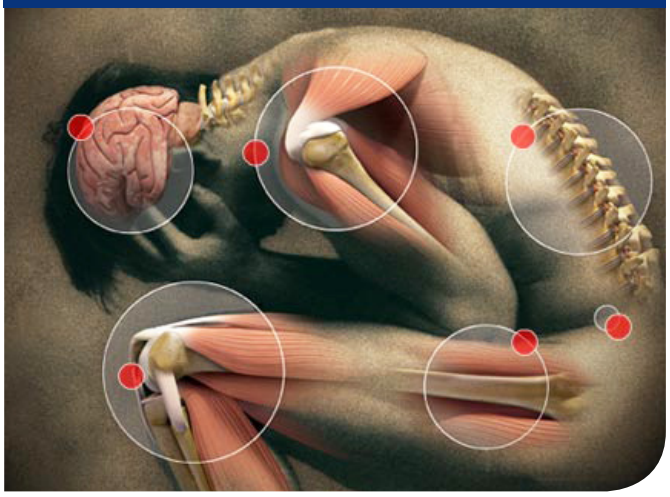
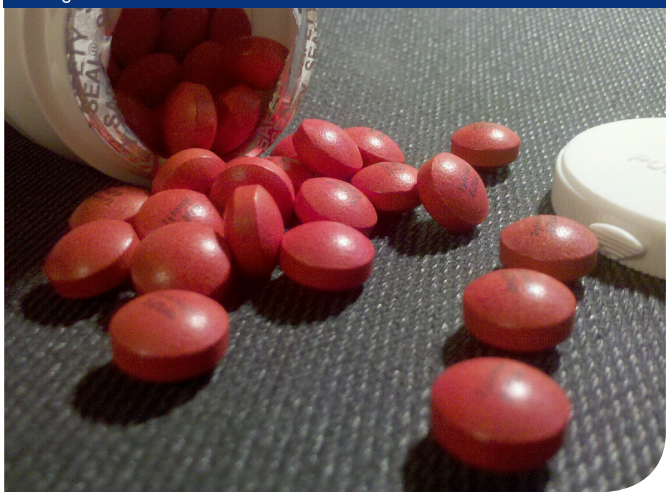
Chronic pain affects one in five people worldwide



Discovery of anaestesi and analgesia in the 1800s revolutionized pain management



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Women in Pharmacology: Role models

Chloe Rose
GlaxoSmithKline

Barbara McQuade (VP Medicines Development Leader, GlaxoSmithKline) was interviewed by Chloe Rose, currently an undergraduate Pharmacology student doing an industrial placement as a clinical research scientist with GSK.

Why did you decide to study science at University?

I liked science at school and whilst there I studied Physics and Chemistry but not Biology because it wasn't taught at my school at the time. I just enjoyed science, but I could have easily gone on to study languages because I enjoyed those too. I did my Highers in Scotland where you can usually study more subjects than for A-levels. I chose French and English as well as Physics, Chemistry and Geography. I then went off to university and decided to include biology in the mix of subjects I studied in the first year as it was new to me. I really enjoyed Biology and so then chose to specialize in biological applications of Chemistry and ended up with a first class degree in Biochemistry from the University of Glasgow.

What did you do your PhD project on? Which aspects did you most enjoy?

I joined Glaxo based in Greenford in the outskirts of London when I finished university and whilst there I studied for a masters degree in Pharmacological Biochemistry, which was a part-time course. I was fortunate enough to be sponsored by Glaxo to work on a PhD project looking at aspects of the enzymes in the biological production of penicillin. One of the many opportunities I had during my PhD studies was to work with colleagues in the manufacturing pilot plant for antibiotic improvement programmes in Ulveston.

During this time, I also enjoyed external collaborations with academics; it was a really nice balance of working in the industry and also working with people outside of my day to day environment. I really enjoyed writing up my thesis and I think that goes back to my love of languages.

What have been your previous roles at GSK?

So I've done a lot of different things. I always had an interest in clinical research and that's the real reason I joined the pharmaceutical industry. After my PhD which was very biochemical in its basis, I had an opportunity to move to clinical research to work on ondansetron a newly discovered medicine which later became marketed as Zofran, the anti-emetic for patients with chemotherapy and radiotherapy-induced emesis and for patients with post operative nausea and vomiting. This was a really exciting and satisfying experience and I felt that the work I did was worthwhile and of true benefit to patients. Then I did something that felt quite radical at the time and moved to a strategy role, which was in early discovery science in the respiratory area. It was very different but had a lot of links with what I'd done before, e.g. with my Masters degree thesis on allergy. After a short while in this role I was able to bring together the threads from my early discovery science experience and my clinical research experience in a role leading the development of

Barbara McQuade and Chloe Rose

medicines from discovery through development and to first launches. I've been working in the respiratory area now for 12 years and can honestly say that I love my role.

Why did you join the pharmaceutical industry?

I joined because I wanted to do something useful for mankind, to link my biology and biochemistry with something that would make a difference. Glaxo was a relatively small company at the time and published lots around basic research in medicine development that interested me. Also they were based in London and I wanted to come to London.

Would you recommend a PhD for someone wishing to enter the industry?

I think that's an interesting question. It depends on what people's aspirations are and what they want to do. I think for any career in basic research I would recommend it. For people more interested in other aspects of medicine development or commercial areas then I'd suggest doing something else. Particularly for careers in commercial areas then I would consider an MBA. It depends on what people want to do, I don't think it's necessary for everyone but for people who are academically interested it's a good thing to do.

What does your role as medicine development leader involve?

I've held this role on a number of projects and it varies depending on the challenges and opportunities that any particular project brings. I'm currently working on fluticasone furoate and vilanterol trifenatate (Relvar/Breo), which we submitted to regulators for license approval so my job currently involves making sure we work with the regulators with the aim of gaining approval for the medicine. I also work closely with my commercial colleagues to help make this medicine available to the appropriate group of patients by providing the supportive evidence that is needed. I work with a relatively small group of people who are specialists in their areas and they all have teams themselves. As examples, I have a project physician leader who runs a large clinical team, and a global regulatory leader who runs the global regulatory network. I love projects that have passed their proof of concept stage and are in Phase IIb or Phase III when we are still designing clinical studies. Having said that many interesting studies are conducted in Phase IIIb and even when we have a license to market. These phases of studying medicines can be really exciting too. I am fortunate to have a very varied and interesting job and get to work with lots of talented people in lots of different areas.

What has been your favourite project?

My favourite project was our Zofran project which I worked on when I was in clinical research. It was so obvious it was making a difference to patients and, I really loved it. One of the opportunities I had then was to run the paediatric programme and working with the paediatricians was fantastic.

How do you maintain your work/life balance?

I think I've been good at that; I have two children and a husband. We were lucky to have a nanny when the children were young; but I always made sure I was home – certainly at weekends and most evenings and that's something I've always maintained to be important. I've got lots of interests outside of work and lots of friends. I make sure that we have that kind of balance and I've always been interested in interior design, decorating and garden design. I do that as well as lots of sports: cycling, swimming, skiing and doing things with the family. I've been lucky; I have a very supportive husband, he is a scientist too so we've always had that in common. We met at University and came to London together.

Who has been an inspiration person during your career?

The person who made the biggest impression on me by setting an example of what a good balanced all round project leader was the Head of Toxicology at GlaxoWellcome. He was a great mentor to me.

If you could have invented any drug what would it be and why?

If I had been of a different generation, I think penicillin was a real turning point. Just making that connection between what was seen in a Petri dish and what made a huge difference to mankind. I'd love to make that kind of a leap in science that ends up in medicine or a series of medicines that change the way we treat diseases. A great aspiration; but unlikely to be realised at a personal level. However I hope we will see that kind of revolution again at some point.

BPS journals: Editors' picks

Selected by *BJCP* Guest Editor Andrea Malizian
Volume 77 issue 2

Drugs for addiction: a therapeutic area in need of a 'shot in the arm'

February's issue is dedicated to the clinical pharmacology of treating or preventing addictions with a foray on using drugs of addiction as therapeutic agents. The accompanying editorial puts the problem in context and guides readers to what is available in the issue. It is often said that the effects of pharmacological treatments of addictions is modest, however it is also true to say that funding and therefore effort in discovery and development has been extremely limited compared with the size of the problem.

While all the articles are thought provoking for specialists and interested parties there are four that are thought provoking for generalists as they focus on concepts that can change attitudes. The first is a review on pharmacological treatments for pathological gambling that sets the scene for understanding how therapeutics can be used to moderate a condition that could still be seen as a behaviour with disastrous consequences. Furthermore, as data is accumulated from patients with Parkinson's disease that develop this affliction with pharmacological or neurosurgical treatments, the neurochemistry of the condition is better understood hopefully leading to improved treatments. Forray and Sofuglu summarize the understanding ofmulti-level mechanisms and components of addictions, explaining how future developments can and should be focused on targeting particular aspects of the problem to increase efficacy and tolerability. Finally Perez de los Cobos et al and Niesters et al present us all with practical and ethical dilemmas in balancing evidence to inform our duty of care.

Selected by BJCP Guest Editor Yoon Loke:
Volume 77 issue 3

Are women more susceptible than men to drug-induced QT prolongation? Concentration-QTc modeling in a Phase 1 study with oral rac-sotalol?

B Darpo, D R Karnad, F Badilini, J Florian, C E Garnett, S I Kothari, G K Panicker and N Sarapa

This study set out to evaluate why women may be more susceptible to drug-induced arrhythmias. The authors used a therapeutic dose of sotalol and found that the change in QTc interval was steeper in women than men, thus suggesting a greater intrinsic sensitivity to sotalol-induced QT prolongation in women.

BPS Journals: on Twitter and Facebook

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Selected by *BJP* Senior Editors Andy Lawrence and Dave MacEwan
Volume 171 issues 3 and 4

Cannabidiol inhibits paclitaxel-induced neuropathic pain through 5-HT1A receptors without diminishing nervous system function or chemotherapy efficacy

SJ Ward, SD McAllister, R Kawamura, R Murase, H Neelakantan & EA Walker

An adverse effect of cancer chemotherapy can be the induction of neuropathic pain, a major drawback. This group has previously demonstrated that cannabidiol (CBD) may be protective in this regard. The current study was designed to examine the mechanism of action of CBD to prevent neuropathy. The authors found that this effect of CBD was not mediated by cannabinoid CB1 or CB2 receptors, but rather by 5-HT1A receptors, and they suggest CBD (or similar) as an adjunct to chemotherapy with agents such as Paclitaxel.

ADX71441, a novel, potent and selective positive allosteric modulator of the GABAB receptor, shows efficacy in rodent models of overactive bladder

M Kalinichev, S Palea, H Haddouk, I Royer-Urios, V Guilloteau, P Lluel, M Schneider, M Saporito & S Poli

This paper shows the power of modulatory agents to influence disease. This interesting compound shows good efficacy in an overactive bladder model—thus exemplifying the scope for new agents that are not just (agonist or antagonists) to treat human disorders.

Selected by BJP Senior Editor Sue Wonnacott:
Volume 171 issue 6

A role for PPARαin the medial prefrontal cortex in formalin-evoked nociceptive responding in rats

B N Okine, K Rea, W M Olango, J Price, S Herdman, M K Madasu, M Roche and D P Finn

In this study, administration into the medial prefrontal cortex of an antagonist (but not an agonist) of the nuclear hormone receptor PPARαmoderated nociceptive behaviour. As the medial prefrontal cortex has a role in both the cognitive-affective component of pain perception and in pain modulation, this result implicates PPARαin this region in mediating nociceptive responses.

In vivo characterization of the highly selective monoacylglycerol lipase inhibitor KML29: antinociceptive activity without cannabimimetic side effects

B M Ignatowska-Jankowska, S Ghosh, M S Crowe, S G Kinsey, M J Niphakis, R A Abdullah, Q Tao, S T O'Neal, D M Walentiny, J L Wiley, B F Cravatt and A H Lichtman

KML29, a highly selective inhibitor of monoacylglycerol lipase, an enzyme that catabolises the endocannabinoid 2-arachidonoylglycerol, has promising anti-nociceptive actions without cannabimimetic side effects.

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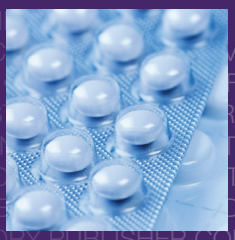


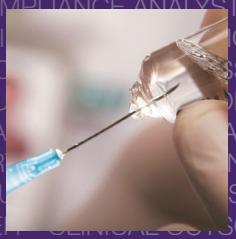








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