

PHARMACOLOGY mMATTERS



BRITISH
PHARMACOLOGICAL
SOCIETY

Today's science, tomorrow's medicines

ISSN No: 1757-8175

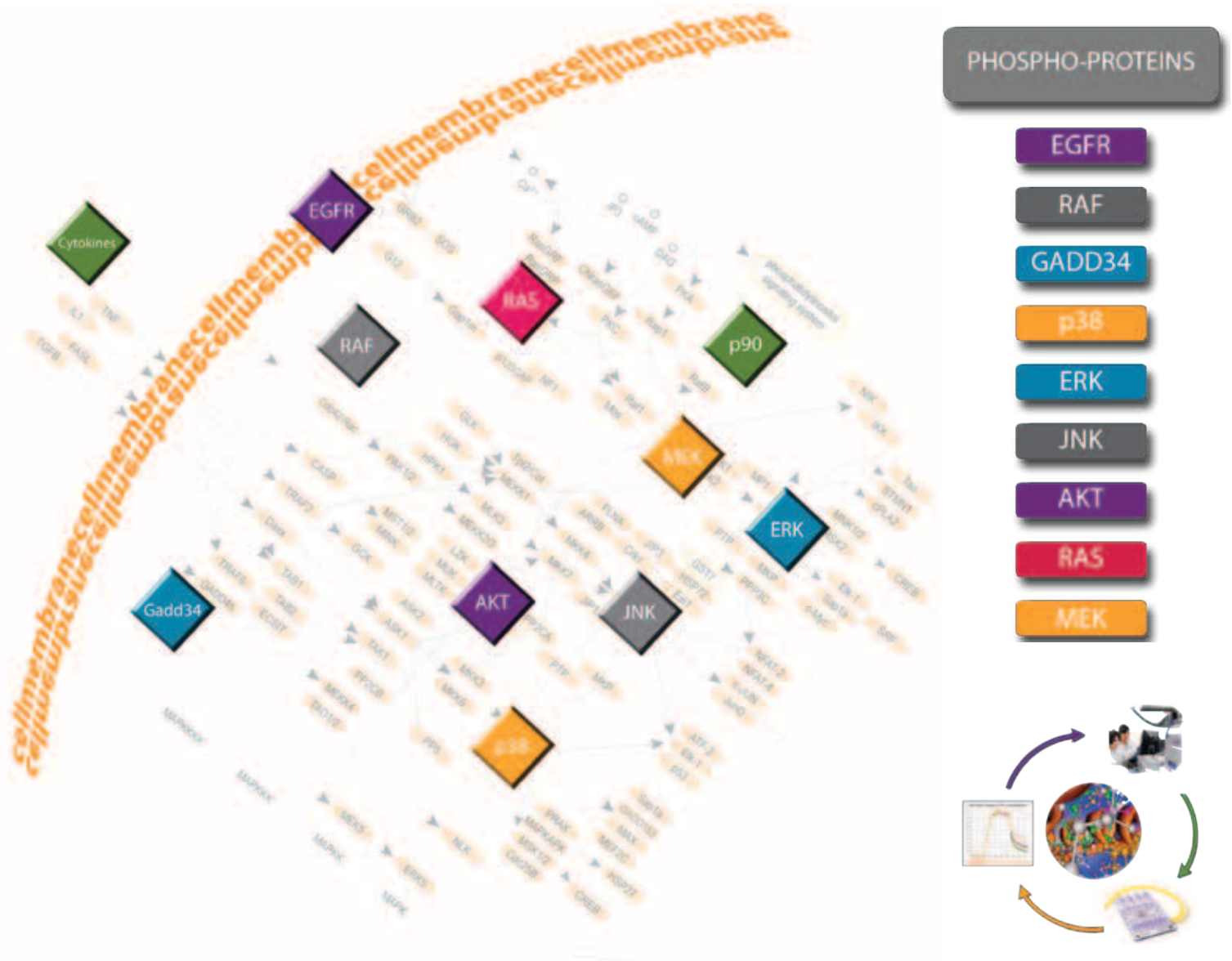
Volume 5, Issue 1 - April 2012

Developing new medicines

What are the hurdles?

does pharmacology matter? | prospects for clinical research | libel law reform | pharma R&D

Elucidating Biological Pathways with AMMP™ Assays



Ultrasensitive Detection & Quantitation of Proteins

BioScale's ViBE™ Workstation powered by AMMP™ assays should be an integral part of drug development research where measuring the levels of target proteins in complex samples is the rule. Whether analyzing potential recombinant protein drug candidates, monitoring and measuring protein biomarkers for drug efficacy studies or viewing the activation state of kinase pathways in cell or tumor lysates; it can all be done on one platform using off the shelf antibodies and reagents.

- Dramatic Detectability & Ultrasensitivity Levels
- Achieve Maximum Sensitivity with Fewer Cells
- Flexible & Rapid Assay Development with the AMMP Kinetic Advantage
- No Optical Interference from Complex Matrices



Visit Booth #1
BPS Cell Signaling Meeting

4 Maguire Road, Lexington, MA 02421
(P) 781.430.6800 www.bioscale.com info@bioscale.com

Editorial

Does pharmacology matter? David Trist's article not only reminds us all just how important pharmacology is to the drug discovery process, but it touches on some of the hurdles pharmacologists are facing as they play their respective parts in developing new medicines. In this issue, several of our pharmacological 'Olympians' address some of these obstacles in more detail.

Sir Michael Rawlins and Dr Morris Brown discuss clinical trials, or more precisely the regulations that need to be negotiated before clinical trials can proceed. Duncan Richards then invites us to consider what insights early clinical trials provide to a drug's potential, and Bob Coleman questions how good animals are in predicting the safety and efficacy of new medicines for man.

Pharmaceutical patenting and the public interest in libel law reform are examined on p17 and 19 respectively, followed by a sequence of articles about the pharmaceutical industry and what is being done to sustain it. Richard Green and Tom Blackburn review the rise and 'fall' of R&D and Humphrey Rang, motivated by the President's lecture on the *future of drug discovery in the UK*, which took place at the Winter Meeting in 2011, asks what is being done to sustain drug discovery during these tough times.

There is a very clear need for closer collaboration to safeguard the future of UK drug discovery, and with it the jobs, and livelihoods of a great number of pharmacologists. This collaborative message permeates through not only this collection of articles but previous issues of *Pharmacology Matters*. There have been steps forward, with over £350m of government money committed to pharma and biotech R & D in 2011, and a further £100m squeezing through the 2012 budget. At the time of writing GSK had just announced it will invest £500m in manufacturing in the UK and create up to 1,000 jobs, representing a significant long term commitment to a beleaguered industry. But there is clearly much, much more to be done, and we will continue to focus on this issue while it remains a preoccupation of our members.

Elsewhere in this edition, Michael Mulvaney responds to Nikolas Dietis' article *the domino that downgrades the PhD*, and you can catch up on our regular Education and Young Pharmacologists updates.

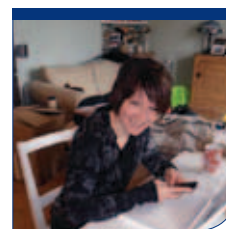
This will be last *View from Angel Gate* penned by Kate Baillie. Kate will be leaving BPS to take the helm of the Biochemical Society in June. Fortunately Kate will not be physically or spiritually too far away, and she leaves us in the very capable hands of our new CEO, Jonathan Brüün, see p6

Kate was instrumental in driving the early, critical changes to this publication and I will always be grateful for the advice and opportunity she gave to me as Managing Editor, thank you Kate.

If you have any comments or would like to discuss any articles in this issue please email me at hom@bps.ac.uk.

Disclaimer

Opinions expressed in *Pharmacology Matters* are not necessarily those of the BPS. The publishers, authors, and printers cannot accept liability for errors or omissions. All rights reserved. No parts of this publication may be reproduced in any form without the prior written permission of the copyright holder and the publisher, application for which should be made to the publisher, British Pharmacology Society. Registered office: 16 Angel Gate, City Road, London, EC1V 2PT. Tel: +44(0)20 7417 0110; Fax: +44(0)20 74170114; Website: www.bps.ac.uk. British Pharmacological Society is a company limited by guarantee, registered in England with No. 2877400, registered charity No. 1030623.



Hazel O'Mullan
Managing Editor BPS

Contents

View from Angel Gate	4
Themed Issues	
Does Pharmacology Matter?	5
Brightening prospects for UK Clinical Research	7
The Aftermath to Rawlins - Through the Looking Glass	9
Early clinical trials - what insight do they provide to a drug's potential?	11
How good are animals in predicting safety and efficacy of new medicines for man?	13
<i>In vivo</i> Pharmacology: Reaping the benefits of analysis at the cell type level	15
Pharmaceutical patenting	17
The public interest in libel law reform	19
Research and Development in the pharmaceutical industry	21
What is being done to sustain drug recovery and development	23
Collaboration between Learned Societies in support of Drug Discovery and Development	25
Features	
The Modern PHD	26
Education Update	28
News from the Young Pharmacologists	29

Cover image credit

iStock

Editorial Team

Editor-in-Chief

Jonathan Brüün

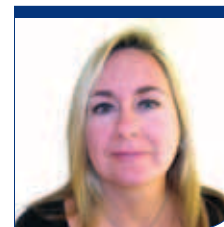
Managing Editor

Hazel O'Mullan

Editorial Board

Mike Curtis
Felicity Gavins
Jenny Koenig
Fraz Mir
Robin Plevin
Martin Todd
Hannah Watson

View from Angel Gate



Kate Baillie BA MA MBA
Chief Executive BPS

2011 ended on a high note for the BPS with a "sold out" Winter Meeting – for the first time pre-registrations were so high that a waiting list system had to be introduced! The meeting was preceded by Editorial Board meetings of both BJP and BJCP, as well as the opportunity for new Editors to receive training, and network with their colleagues. For the first time, we hosted a joint symposium with the Chinese Pharmacological Society (CPS), on *Clinical Pharmacology of Drug Development and Pharmacological Research in China* and welcomed around 40 delegates from the CPS who played an active part in poster and oral sessions. The next joint meeting is scheduled for July 2013, in Shanghai, and we hope to be able to field a strong delegation from the BPS membership.

We also used the occasion of the Winter Meeting to discuss plans for a future joint meeting with the Austrian Pharmacological Society in Graz in 2015. It is hoped that this meeting can provide a focus for celebration of the 140th Anniversary of Sir Henry Dale, who in 1936 received the Nobel Prize together with Otto Loewi, (head of pharmacology in Graz from 1909- 1938), for their work on the principles of chemical neurotransmission.

Another feature of this Winter Meeting was the mini symposium convened by Ray Hill to mark the end of his Presidency on *The future of drug discovery in the UK*. A detailed report of this session, prepared by Humphrey Rang is available on p23.

We have kept the momentum generated from this session going by entering into more detailed dialogue with the Royal Society of Chemistry and the Society of Biology. There is agreement that we should work collectively on presenting a single message to government around core requirements needed to maintain the UK's drug discovery capability. We hope to establish a series of joint meetings with government advisers and ministers, and to contribute to a potential series of articles for Research Fortnight.

As part of this initiative, BPS and the Society of Biology co-hosted a meeting on 8 February at the Linnean Society, attended by representatives from 22 organizations to look at collaboration across the skills agenda. There was a very positive spirit as well as vigorous debate at this meeting, and a willingness amongst participants to work together more closely on these issues in the future.

Also in the spirit of inter-Society collaboration, I was asked to co-organize and host a meeting on the impact of open access on Learned Societies on 11 January, along with co-organizers from the British Ecological Society and the British Society for Immunology. 35 Societies were represented at this meeting and included associations outside the bioscience sector to ensure a broad spectrum of opinions were represented. It was apparent that different disciplines were at different stages in their engagement with OA, but in general, there was limited data available on the uptake of OA across the sector. It was felt that topics for further research could usefully be identified, as it will be important to have

an evidence base available to present to policy makers when making the learned Society case.

The Prescribing Skills Assessment is continuing apace with the first Peer Review Meeting held in Warwick from 21-22 February. The 60 participants – pharmacists, clinical pharmacologists and doctors reviewed over 600 questions that will feed into the pilot exams. This year will focus on testing the new delivery system and helping the eight pilot schools develop protocols for an online exam. I'd like to thank everyone who is giving up their time to this exciting project which is set to make a real difference to the prescribing lives of junior doctors.

As mentioned in the last issue of Pharmacology Matters, a BPS strategy retreat was held between 1-2 March. The retreat was designed to provide an opportunity for free-ranging discussion that will help Council to fulfil its task of deciding the overall objectives and strategy for BPS to follow over the next 3-5 years. Following the retreat, Council will prepare a strategy document to guide the society's work over the next few years.

Finally, this will be my last *View from Angel Gate*, as members are probably aware, I will be leaving the Society on 1 June to take up the position of Chief Executive of the Biochemical Society, succeeding Chris Kirk who is retiring after seven years in post.

During my period as Chief Executive, the Society has seen many changes. I was appointed with a remit to make the Society more externally focused, and I hope that the strong links we now have with many other learned Societies both in the UK and overseas will continue to grow and develop. With the appointment of Jonathan Bruun in 2009 we were also able to develop a new website, communications and public engagement function. Re-negotiating our journal contracts to bring the journals together under one publisher enhanced and stabilized our primary revenue stream for a seven year period, enabling us to plan an ambitious programme of Meetings, Education and Communications activities. We were also able to refurbish the Angel Gate premises to provide meeting room space and hot desk facilities for members, as well as an office design more conducive to teamwork. I believe that we now have an excellent staff team in place at BPS to work with the Trustees, Officers and Members to take the Society into its next phase of development.

I would like to take this opportunity to wish the Society and my successor every success for the future and to thank the Members, Officers and Staff for all their help, support and forbearance during the past four years.

I hope to keep in touch with many of you, as I am sure there will be plenty of opportunities for continued collaboration between BPS and the Biochemical Society – and I will be just down the road at Charles Darwin House!

Does Pharmacology Matter?



David G. Trist
Independent Consultant

David Trist retired in December 2008 as Vice President and Head of Strategy and Operations for the Psychiatry Centre of Excellence for Drug Discovery within GlaxoSmithKline (GSK). He now occasionally consults in the area of Analytical Pharmacology.

David holds a first degree in Biochemistry and a PhD in Pharmacology from University College London and has been a member of the British Pharmacological Society since 1975. He worked for some years in Wellcome on targets in the Central Nervous System (CNS) and Cardiovascular System, before moving to Glaxo, Verona, as Director of Pharmacology. After the merger to create Glaxo Wellcome, David took on the wider international role of Disease Strategy Director for Psychiatric Diseases, whilst maintaining a responsibility for improving the Process of Drug Discovery in Verona.

David has published scientific papers and abstracts mainly in the areas of neuroscience, cardiovascular and bladder particularly in analytical pharmacology, with emphasis on the classification of drug receptors. He has a strong interest in studying the process of drug discovery, particularly in analysing and modelling its productivity.

The title of this magazine has always appealed to me because of its' double meaning. That is either topics/themes to do with pharmacology or that pharmacology is important/counts. The latter interpretation of this title actually provoked me to ask the question above.

As a young pharmacologist I would never have asked this question. The BPS was the most important society that I belonged to where future Nobel laureates and university professors still gave 10 minute oral communications. A time when drug discovery was mainly based on well established *in vitro* (organ bath) methodology and *in vivo* models, mainly in rodents. A time when biochemical methods were just beginning and molecular biology was not heard of, and when genetics was a completely separate discipline whose application to pharmacology was not even thought about.

However, I believe that today pharmacology is in transition and that this started more than 30 years ago when major changes in the technologies itemised above started to have a profound effect on the way pharmacology was done. In introducing these new technologies, we have also heard opinion expressed that traditional pharmacology was old-fashioned and that the new biology counts for more. That is basically, pharmacology matters less.

We have even seen the name pharmacology removed from University and Industry departments. In 2006 Hollingsworth and Markham (Bioscience Education eJournal, **8**: article 3) compared Pharmacology employment to that reported by Bakhle *et al.* 10 years earlier (BJP, 1986, **87**:463-474). They showed, amongst others, that 'there has been subsuming of pharmacology

Departments within Schools and Faculties'. By looking at 20 top universities that offer undergraduate and postgraduate courses, I found only three had a Department of Pharmacology, three had a Department with Pharmacology in the title (never the first name however) and the rest (70%) offered courses within broader named establishments. This is why I think that this question is now more relevant than ever.

As someone who worked for more than 42 years in the pharmaceutical industry I naturally look at this pharmacology transition in the context of drug discovery, but I believe that it is also relevant in other contexts such as academic environments.

The revolution probably began back in the 1960's when pharmacology started to embrace biochemical methods. These methods began to replace traditional assay systems and bioanalysis and took us under the cell surface, the established home for drug discovery. Whole new targets began to be proposed, including adenylate cyclase, guanylate cyclase, inositol phosphates, and a host of phosphorylases and phosphatases. But the excitement really began when the name molecular biology appeared in the late 1980's. Now thanks to knowledge about their structure we can express human targets in cells (transfections) and animals (transgenics) to look at the pharmacology of the intended proteins for which drugs are being developed. The required leap from experimental outcomes in animals to man has been greatly reduced. At the same time, knowledge of biochemical pathways within the cell has been amplified offering thousands of new targets to the Drug Discoverer.

In parallel with this bioassays were becoming simplified, thanks to novel high-throughput technology developed to screen hundreds of thousands of molecules produced by combinatorial chemistry. IC50s have replaced KAs and PA2s, unfortunately reducing understanding of the types of agonism and antagonism that novel compounds might possess.

When genetics and genomics arrived the possibilities were raised that the molecular basis of disease would become apparent, allowing targets to be chosen that are unique to the pathology. Early optimism has dwindled in the understanding that most diseases are not simple but polygenetic making the choice of targets more difficult.

As mentioned above and addressed in part by Michael Williams (Current Opinion in Pharmacology 2011, **11**:496-500) the modern technology environment has led to reductionist approaches that often lead to surprises when molecules are put into integrated systems like man.

Yes, pharmacology matters. Especially today with drug discovery becoming more and more difficult (see Richard Hargreaves, *Pharmacology Matters*, December 2011, **4** (3):15-16). I believe the pharmacologist (both basic and clinical) needs to reapply

pharmacological principles to the systems being studied. It is heartening to see that in areas such as neuroscience, *in vitro* assays using human brain tissues are being advocated. Here one can look at the end target (receptor, enzyme, channel, etc) in an integrated system with target concentrations probably closer to that *in vivo* and connected to the right sub-cellular proteins. Williams gives a good example where both 5HT and N-MTPs bind to the 5-HT₂ receptor, but they differ markedly in the intracellular signalling pathway that they engage and their functional activity. Some years ago, we showed that expression levels of metabotropic glutamate receptors *in vitro* cause wide changes in agonism (Corrado Corti et al., Ann. N.Y. Acad. Sci (Receptor Classification Editors D.G. Trist et al.) 1997, **812**:231-233).

In a similar way, Adam Cohen talking at the Society's Winter Meeting 2011 suggested that clinical pharmacologists need to be doing human pharmacology and not simply First Time in Man studies, helping to translate novel targets and molecules into man. Carrying out more of these studies would aid translational medicine in general and further bridge the gap between pre-clinical and clinical results

In conclusion, by getting back to basics the pharmacologist can potentially reduce the number of failures in the clinic and help find the right target and the right molecule. Yes, Pharmacology not only matters but will continue to matter.

BPS CEO Appointment

We are delighted to announce the appointment of Jonathan Brüün as Chief Executive of the British Pharmacological Society, with effect from 6 June 2012.

Jonathan has worked with the BPS since the summer of 2009, when he was recruited to the position of Head of Communications and Development, going on to become Director of Communications and Business Development in 2011. He replaces Kate Baillie, who has served the Society as CEO since 2007. Kate joins the Biochemical Society as CEO in early June.

Over the last few years, Jonathan has played an important role in modernizing the public image of the BPS. One of his first tasks was driving the redesign of a new website catering to the developing needs and focus of our Society. Jonathan delivered a fresh, modern website providing a friendly and more straightforward user-experience. He also set up the Society's first social media engagement, through Facebook and Twitter, a development which has provided invaluable communication with a wide variety of stakeholders, and a tangible rise in our public profile. This work was supplemented by the introduction of a press policy and a strategy to engage proactively with journalists, providing comment and expert opinion as stories developed in the media. We are now very often the first call for comment on breaking stories.

In the past few years, Jono has worked closely with Kate and BPS members to develop closer links with other Societies in a variety of areas including meetings, public engagement and policy. We know that these collaborations will continue to flourish under his leadership.

Jono has also contributed to the management of our journals, the British Journal of Pharmacology, and British Journal of Clinical Pharmacology, as well as many of the Society's initiatives in areas including safe prescribing and outreach to the industrial pharmacology community. Jonathan offers the BPS continuity, energy and enthusiasm as we seek to build on the great many advances that have been made in the past few years.

We are sure you'll join us in congratulating Jonathan on his appointment, and wishing him well as he seeks to support, develop and grow our Society in the coming years.

With best wishes

Professor Phil Routledge
President, British Pharmacological Society

Professor Humphrey Rang
President-Elect, British Pharmacological Society

Brightening prospects for UK clinical research?

Sir Michael Rawlins

Emeritus Professor, University of Newcastle upon Tyne and Honorary Professor, London School of Hygiene and Tropical Medicine



Sir Michael Rawlins has been chairman of the National Institute of Health & Clinical Excellence (NICE) since its formation in 1999. He is also an Honorary Professor at the London School of Hygiene and Tropical Medicine, University of London, and Emeritus Professor at the University of Newcastle upon Tyne.

He was the Ruth and Lionel Jacobson Professor of Clinical Pharmacology at the University of Newcastle upon Tyne from 1973 to 2006. At the same time he held the position of consultant physician and consultant clinical pharmacologist to the Newcastle Hospitals NHS Trust. He was vice-chairman (1987-1992) and chairman (1993-1998) of the Committee on Safety of Medicines; and chairman of the Advisory Council on the Misuse of Drugs (1998 - 2008). He is President Elect of the Royal Society of Medicine.

Clinical research is embedded in the job descriptions of clinical pharmacologists. Whether it be experimental medicine (or "translational medicine" as it has now become), or randomised controlled trials, or studies of the effects of drugs in populations (pharmacoepidemiology), clinical research lies at the heart of our discipline. It is – to borrow an overused US phrase – in our DNA. The founding fathers of UK clinical pharmacology such as Colin Dollery, Paul Turner and Owen Wade were past masters at gleaning insights into both the beneficial, and adverse, effects of drugs using clinical investigative techniques. In so doing they were adapting the approaches pioneered by such luminaries as John McMichael, Peter Sharpey-Schaffer, Austin Bradford Hill and Richard Doll (1).

Yet over the past 25 to 30 years the UK's pre-eminence in clinical research has been badly eroded by an environment that has now become stifling. This has caused damage to both academic clinical pharmacology and the UK's pharmaceutical industry. The industry has responded – understandably – by moving much of its clinical research to countries with a more welcoming environment. UK academic clinical pharmacology has just withered. So what has gone wrong? And how can it be put right?

In April 2010 the outgoing Labour administration, recognizing the broad nature of the problem, asked the Academy of Medical Sciences to review the regulatory and governance environment for clinical research. I was asked to chair the review's Working Group and our report was published in January 2011 (2). We consulted widely and had over 300 responses to our call for evidence. Respondents – from both industry and academia – were almost unanimous in their view that clinical research had become unnecessarily and unreasonably over-regulated.

The Problems

Respondents to our call for evidence identified four areas where change was urgently needed:

- 1) All respondents agreed that the European Clinical Trials

Directive for the regulation of clinical trials has been a disaster for both commercial and publicly funded studies. As a consequence the numbers of patients in trials, in the EU, has fallen sharply as a proportion of global share with no discernible advantage to participants and much discernible disadvantage for the EU economy. There is also a widespread belief that clinical trials in the UK have been more damaged than those in most other EU countries because – in typical British fashion – we implemented the Directive with scrupulous attention to detail.

- 2) There are multiplicities of ethical approvals that are needed before a study can start. General bioethical approval is provided by the National Research Ethics Service and respondents to the Academy's review were generally complimentary about the service it provides. But for many studies additional specialist ethics approvals must also be sought. These include the Human Tissue Authority, the Human Fertilisation and Embryology Authority, the National Information Governance Board and its Ethics and Confidentiality Committee, the Gene Therapy Advisory Committee and more. All these bodies were introduced with the best of intentions but the cumulative effects of the idiosyncrasies of these different organizations – usually operating in series rather than parallel – leads to delays in obtaining approvals.
- 3) By common consensus, the most problematic area involved the research governance arrangements in the NHS. Much clinical research is carried out at multiple NHS sites and each Trust must give approval before a study can start. As independent legal entities, with overall responsibilities for the patients under their care, this is perfectly proper. The problem is that each Trust replicates the wide range of so-called "global checks" which increases the time and administrative burden without contributing anything extra to the protection of patients.
- 4) Added to these difficulties is the weak research culture in too many parts of the NHS. Although there are shining examples of NHS Trusts that foster research, too many see it as an unnecessary distraction or – worst of all – as an income stream.

The Proposed Solutions

The Academy made a number of recommendations based on four principles that it believed should underpin the regulation and governance of health research (see Box 1).

- 1) The report proposed the establishment of a new legal entity (as a Special Health Authority) to regulate UK clinical research. We suggested that the new Health Research Authority (HRA) should have two major roles: to streamline the current arrangements for ethical approval, and to provide a new research governance service.

We envisaged that the HRA would – over time – bring together all the research ethics responsibilities currently provided by a wide range of organizations. The National Research Ethics Service would be the natural base for this; but with time (and some of the changes would require legislation) the report indicated that all should eventually be encompassed by the new authority.

We also recommended that the HRA should either undertake all study-wide governance checks on behalf of individual NHS Trusts. These would include scrutiny of the arrangements for indemnity and processing of Criminal Records Bureau checks on the principle investigator and other research staff. Individual Trusts would only be expected to undertake local feasibility checks. These would include ensuring that appropriate arrangements were in place for handling clinical trials materials and to confirm their agreement to take part within agreed timelines.

- 2) The Academy's report also emphasized that although the establishment of the HRA was necessary it was not sufficient. And that the European Clinical Trials Directive needed a radical overhaul with the removal of its most egregious provisions and an approach based on proportionality. This, of course, is a matter that cannot be implemented by the government alone. Rather it will require discussions with the EU Commission as well as with other member states.
- 3) The report also sought a fundamental shift in the research culture of the NHS. It encouraged Trust Boards to take greater notice, interest and pride in the research activities of their institutions. As the report said, the NHS has obligations to future patients by fostering research as well as to those currently under its care.

The Outcomes

The government has moved with speed to implement the Academy's recommendations.

- 1) The HRA was established as a Special Health Authority on 1 December 2011 and the government should be given credit for having acted so speedily in setting up the new body. The HRA now includes the National Research Ethics Service and

has already taken responsibility for some of the other bodies which currently review the ethical aspects of clinical research. Although the HRA has yet to establish a research governance service, a number of Trusts have created "consortia" so that one Trust undertakes the global checks on behalf of others in its group. This, too, is to be welcomed; and the role of the HRA in respect of research governance will be made much easier if these consortia become widely established.

- 2) What of the European Clinical Trials Directive? Discussions between the MHRA (who lead on this for the Department of Health) and the EU Commission have begun and are continuing. Let's hope sensible and proportionate arrangements are put in place.
- 3) The climate and culture for clinical research, in the NHS, has been the subject of considerable discussion in the House of Lords as the health and Social Care Bill proceeds through parliament. I am hopeful that the Bill will place obligations on the National Commissioning Board and Clinical Commissioning Groups to promote clinical research in commissioning services from Trusts. If these obligations appear in the face of the Bill the pressure on Trusts to deliver will be profound.

Conclusions

I am much more confident about the future of UK clinical research, today, than I was a year ago. There seems to be mounting support for a sea change in attitudes. It is now for the clinical pharmacological community to deliver both for themselves but also for their trainees. I have been depressed at how many young academic clinicians retreat to wet laboratories, to try to make their research contributions, rather than undertake clinical research projects. Facilitating the regulatory and governance arrangements for clinical research will help them emerge from wet laboratories into the research world where they really belong!

References

- 1) Rawlins M. A new era for UK clinical research? *Lancet* 2011; 377: 190-192.
- 2) Academy of Medical Sciences. A new pathway for the regulation and governance of health research. London: Academy of Medical Sciences, 2011.

Box 1.

Guiding principles for the regulation and governance of clinical research

- 1) Safeguard the wellbeing of research participants
- 2) Facilitate high quality clinical research for the public benefit
- 3) Be proportionate, efficient and co-ordinated
- 4) Maintain and build confidence in the conduct and relevance of clinical research through transparency, clarity, accountability and consistency

The Aftermath to Rawlins - Through the Looking Glass



Morris J Brown, FMedSci
Clinical Pharmacology Unit
University of Cambridge &
Addenbrookes Hospital

Morris Brown is Professor of Clinical Pharmacology at the University of Cambridge and Honorary Consultant Physician at Addenbrooke's Hospital, Cambridge. He was President of the British Hypertension Society 2005-2007 and now chairs the BHS Research Working Party. This is undertaking a British Heart Foundation-funded programme of three trials in patients with hypertension. His other research interests include the endocrine profiling of patients with hypertension, in order to find secondary causes and personalise treatment for hypertension. Recent findings include the introduction of a non-invasive PETCT scan for the diagnosis of Conn's syndrome, and the recognition that most of the younger patients with Conn's syndrome are women with somatic mutations of the KCNJ5 gene. He was awarded the Lilly Gold Medal of the British Pharmacological Society (2002), and the Walter Somerville Medal of the British Cardiac Society (2006). His introduction of the AB/CD rule, and innovations in management of pheochromocytoma and Conn's syndrome, led to the Hospital Doctors' Award in 2003. In 2008 he co-hosted the International Symposium on Pheochromocytoma in Cambridge.

Which of the following quotations from Lewis Carroll's Alice is imaginary, with no relevance to current regulation of clinical trials?

*How do you know I'm mad?" said Alice.
You must be," said the Cat, "or you wouldn't have come here."*

"Curiouser and curiouser."

"If everybody minded their own business, the world would go around a great deal faster than it does."

"When I use a word," Humpty Dumpty said in rather a scornful tone, 'it means just what I choose it to mean — neither more nor less.'

"Now, here, you see, it takes all the running you can do, to keep in the same place. If you want to get somewhere else, you must run at least twice as fast as that!"

"Off with their heads!"

"Imaginary.... part of my dream, of course."

In January 2011, the Academy of Medical Sciences published the 'Rawlins' report on overcoming post-2004 obstacles to performing clinical trials. So with Pharma one of UKplc's three main earners, and clinical trials an area of research and medicine where the UK previously led the world, we can assume there has been an urgent welcome for Rawlins, that all is now hunky dory on the front-line of clinical research, and that men in white coats are no longer required to tend the sanity of those seeking to translate basic science into practical medical advances.

So let us peer at the two worlds of clinical trials regulation. In the real world, a young investigator – say a third year medical student, or academic clinical fellow (ACF), with three months to undertake a project, can write a single 5-6 page application seeking approval. This is submitted, together with an intelligible one side of A4 patient information sheet, to local ethics. Knowing the supervisor's track record and facilities, the Chairman gives permission to start recruiting subjects pending committee approval with the month. The investigator's responsibilities are, like any doctor's but more so, to put safety first, to ensure the patient receives the best possible treatment – either the best known with cost no object, or a new, maybe better treatment – and to keep accurate records. Research and Development (R&D), as the name implies and as in other walks of life, operate seamlessly to facilitate the research by ensuring support from the laboratories and pharmacy, who in teaching hospitals receive annual funding – 'service increment for teaching and research, SIFTR' – to compensate for any extra work.

By contrast, in the imaginary world, a substantial portion of welcome new funding for clinical trials would be diverted into paying ten jobsworths to obstruct clinical research, for every one masochist clinician trying to persevere. Even the simplest project with 50-year old drugs, would require 40-80 page applications to a minimum troika comprising: the National Research Ethics Service (NRES), the Medicines and Healthcare products Regulatory Agency (MHRA), and R&D. Separate R&D approval would be required for every participating hospital – 50 approvals if 50 patients with rare diseases are donating a blood sample. If patients are recruited from general practice, approval of each primary care trust's research management group (RMG) would be required. Medical students would no longer undertake vacation projects – they would be lucky just to receive their hospital's honorary contract by the end of the vacation. Trusts and their R&Ds would run scared of bullying ex-policemen employed by MHRA to undertake inspections – not of the quality of research but of the quantity of paper-trail. Some Trusts would set up star chambers of Executives and Medical Directors with no experience of clinical trials, but willing to close down research rather than face the MHRA policemen. They would collude with be-knighted medical school heads in 'constraining' senior professors who campaigned for the junior doctors and ACFs, or complained of delays, by threatening them with dismissal if they did not desist.

In this imaginary world, after nine months discussion among the great and good, the Academy review would announce what researchers already knew: that R&D is the most lawless part of the system, trebly so: they have no basis in legislation, they do the opposite to the job implied by their name, and make up the rules guiding their actions and time allowed for these. Yet, the review would compliment NRES, whose 80 page shop window turns first time applicants away at first base from clinical to bench top research; and fail to address the fundamental problem that Trusts are independent legal entities. Instead of hitting sponsoring Trusts and Universities in the only place that hurts, the pocket,

with a recommendation that research grants are withdrawn if not implemented within 30 days, the review would offer the time-honoured non-solution of a new over-arching body, comprised largely of the same people as are responsible for the (imaginary) collapse of UK trials. NRES used to claim a maximum 60-day turn-round – spurious to the extent that busy clinical applicants might need a month to complete the marathon forms, and then wait two months for a slot from which the 60-day clock can start. In the aftermath of Rawlins, and cocking a snook at the toothless recommendations, Trusts and NRES would conspire to reject submissions which have not first sat in an R&D queue – so much for the promise that all governance would run in parallel,

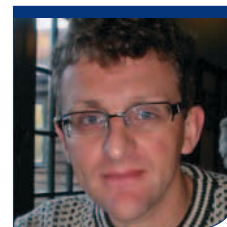
not series. In face of the correlation between job creation and work created (for researchers), Carrollian logic would demand that the mere four bodies previously holding up research (NRES, MHRA, R&D, and RMGs) be joined by a fifth, a new National Research Authority. With weary experience of Coordinated System Permission (CSP) in England, and NHS Research Scotland Permissions Coordinating Centre (NRSCC), researchers would be confident in the negative impact of extra coordinating tiers with no power over existing bodies.

The real world ended in 2004. And the imaginary quotation? The last.



An 'imaginary' look through the looking glass.

Early clinical trials – what insight do they provide to a drug’s potential?



Duncan Richards
Clinical Head, GSK Academic
Discovery Performance Unit

Duncan Richards leads the clinical group for GSK’s Academic Discovery Performance Unit (AcDPU). He trained in Clinical Pharmacology at the University of Oxford and joined GSK in 2003 to work at the Experimental Medicine unit in Cambridge, UK. He has since worked in early and late stage development before joining the AcDPU shortly after its launch in 2009. The clinical section of AcDPU manages a diverse and exciting portfolio of early drug molecules in partnership with academics from candidate selection to clinical proof of concept.

The chevron scheme of drug development would suggest that it is a linear process leading inexorably to registration and the market. The recent history of drug development has however been marked by a high number of late stage failures and poor productivity. A clear line of sight to what the medicinal product would look like (e.g. how is it administered, is it a course of therapy or a long term treatment?) is important to determine the key requirements for the discovery team to ensure that the candidate molecule is fit for purpose. This must however be balanced as an overly rigid view of the development plan leads to a cookie-cutter approach and a high risk of late stage failure.

Early drug development is accurately described as the ‘exploring’ phase, while late stage development should be the ‘confirming’ phase. In essence the exploration is of exposure (dose) response relationships, for both safety and efficacy. For example early clinical trials with H2 receptor antagonists measured the dose response in terms of gastric pH. Early studies in patients examined peptic ulcer healing and this was confirmed in large scale phase III trials. In this schema the translational and therefore highest risk steps are phase I and between phase I and phase II- does the drug reduce acid secretion (and so raise gastric pH) and then does the observed gastric pH profile lead to improved ulcer healing? Having shown ulcer healing in phase II it is relatively unlikely that this will not be seen in phase III. This type of approach may be ideal but is very uncommon for many of the targets currently in development, the number of phase I or II endpoints that can act as genuine surrogates for phase III is very low.

Treatments targeting A β in Alzheimer’s face a number of challenges but critically there is no straightforward measure that can be applied in a short term, small study that will reliably predict the response in efficacy studies of 1-2 years. Phase I studies might examine the effect of the drug on an aspect of A turnover, phase II might use imaging endpoints, while phase III will focus on clinical measures of cognition. Each of these transitions is associated with a significant translational step: does the effect on A β in blood also apply in the brain, does this alter plaque pathophysiology, and does this lead to a beneficial effect on cognition? None of these steps is guaranteed and as a result the drug development risk of translational failure is carried later and later into development. The huge costs of modern drug development mean that even the best financed Pharma companies can only support a small number of such development programmes. Indeed many have moved out

of therapeutic areas where this problem is particularly acute. The challenge for the clinical team is to ensure that, as far as possible, each development step is associated with one clear translational step as making several at once carries high risk of failure and importantly one may not be able to identify which one failed as so future development is not informed.

The types of clinical benefits that could result from many modern potential drugs are often unprecedented. While this is exciting, as it offers the potential to deliver a paradigm shift in disease treatment, it is also a challenge for the development process. There may well not be an established clinical endpoint. For example, a disease modifying treatment for osteoarthritis might ultimately deliver reduced pain, greater mobility, and/or reduced need for joint replacement. It may not be easy at the start of the drug development process to see which of these will be the main benefit of the drug. This is important as the value to payors and acceptability to regulators of these various indications may be very different.

Many modern drug targets have potential utility in a wide range of disease. For example a novel immune modulator could be beneficial in a wide range of autoimmune disease. These diseases are however complex and variable; it is a key challenge for the early development process to identify which are most tractable.

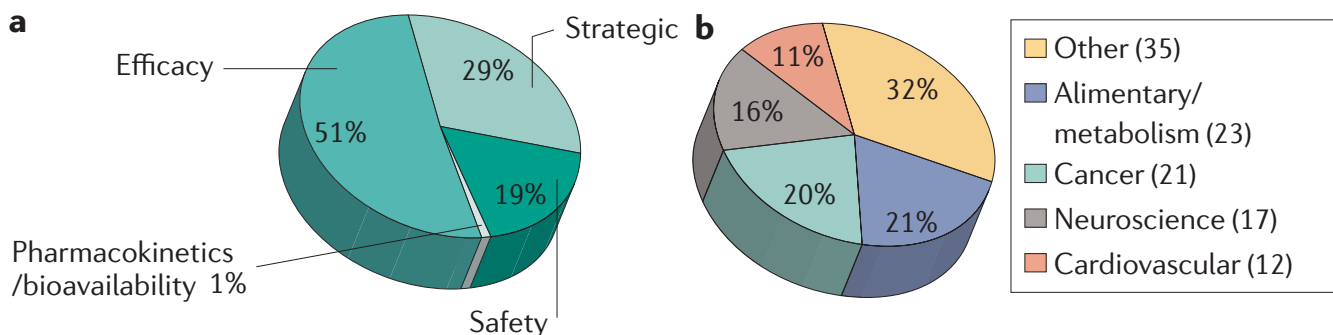
These challenges suggest that the scheme for drug development should be thought of in a different way. The early phase is an experimental one, determining not only the essential exposure response profile of the drug but also which disease or diseases are responsive to this effect; it also provides some idea of what clinical benefit might result. This information will guide the rational design of a proof of concept study in the right patient population with the right endpoint. Only then can one move to the confirming phase of large scale clinical trials. This scheme will likely take longer than the traditional scheme but it manages the high risk of failure in a staged way. The greatest risk of modern drug development is failure to show efficacy, taking a little more time to ensure you are studying the right thing in the right way is essential to reduce attrition.

The difficulty of effective translation of excellent science to effective medicinal products has reignited interest in experimental medicine. Experimental medicine suffers from a plethora of definitions but in essence it is a human pharmacology experiment. The promise of this approach is that one will be able to establish the nature and magnitude of a drug response in a relatively small number of well characterised patients. Appealing though this is it still relies on the availability of suitably robust endpoints for decision making. Suitably robust in this context should not be confused with statistical significance. In many cases one is seeking to gain sufficient evidence to inform the design of a more definitive (randomised, controlled) trial, not to formally test a hypothesis.

Nonetheless failure to establish the reliability of these endpoints can lead to erroneous decision making based on a small data set. It is therefore essential to invest in a rigorous understanding of the biomarkers or endpoints proposed. It is vital to understand whether this is a pure marker of pharmacology or whether it can also inform on disease progression. The scale of this work should not be underestimated, it can take millions of pounds and many years to identify a new biomarker.

In conclusion the purpose of early drug development is to establish the potential therapeutic utility of a new medicine (risk and benefit). Improvements in pre clinical development science mean that the single greatest risk of failure is now an inability to demonstrate adequate efficacy. The design of the early development programme should reflect this risk, and given the complexity of many contemporary drug targets, considerable investment may be required in identifying and characterising biomarkers and endpoints for these studies.

Fig 1.



Phase II failures: 2008–2010. The 108 failures are divided according to reason for failure when reported (87 drugs) (a) and therapeutic area (b). Thomson Reuters Life Science Consulting analysis.

About the BPS



With almost 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:

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

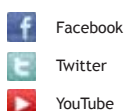
Undergraduate Member

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

Benefits

- free attendance to BPS scientific meetings including the Winter Meeting to be held in London in December
- enjoy access to the full online versions of the 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 GSK Prize for Young Investigators
- receive regular editions of Pharmacology Matters, the BPS newsletter
- opportunities to contribute to furthering pharmacology, across a range of activities, through the Society's committees, special interest groups and working parties

Follow us



Contact

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



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

How good are animals in predicting safety and efficacy of new medicines for man?



Robert Coleman
Independent Consultant

Bob Coleman is a pharmacologist with a keen appreciation of the value of using human cells and tissues in the search for new medicines to treat human disease. He worked for 30 years for the Glaxo group of companies, where he gained a wide experience of the drug discovery/development process. Bob is particularly associated with his contributions to the classification of prostanoid receptors and to the development of the long-acting β 2-agonist bronchodilator, salmeterol. In 1995, Bob left GlaxoWellcome, and joined a colleague in founding Pharmagene (now Asterand UK), a drug discovery and development company working exclusively with human tissues. In November 2003 he was awarded an honorary DSc by DeMontfort University, Leicester, in recognition of his scientific achievements and of his contributions to the experimental use of donated human tissues in drug research. Since 2006 Bob has operated as an independent consultant in drug discovery and in the use of human tissues in pharma R&D.

Ask many scientists and others involved in the discovery and development of new medicines, and they'll tell you that animals are essential for the development of safe and effective new medicines to treat human diseases, and that without them, there would be no new drugs (www.understandinganimalresearch.org.uk/; www.informatiedierproeven.nl/files/pdf/Artikelen/Scientific%20validity.pdf). But how well does such a position stand up to scrutiny?

My early work in the area of prostanoids made it abundantly clear to me that no one species could be relied upon to reflect any other in terms of the distribution and function of prostanoid receptors, and a number of blind alleys were encountered through too great a reliance on animals as predictors of responses of prostanoid agonists and antagonists in man. I became most excited by the observation that AH13205, an early selective EP₂ agonist, elicited bronchodilator activity, equivalent to that of salbutamol, both in potency and efficacy, when administered by inhalation to guinea-pigs (Nials *et al.* 1993). As this species had proved itself most useful for the identification and optimisation of β 2-adrenoceptor agonist bronchodilators, AH13205 was adopted as a development candidate, and tested along with salbutamol in human subjects with mild airflow obstruction. Unlike salbutamol, AH13205 failed to elicit any bronchodilatation, but cause an unpleasant irritant sensation in the upper respiratory tract. In contrast, guinea-pigs displayed no obvious discomfort on inhalation of AH13205. Development of AH13205 was discontinued. It is now of course well known that such inter-species issues are commonplace, and we are all well aware of examples of discrepancies in responsiveness of different species to chemicals, whether naturally occurring or synthetic. However, despite this, we still rely heavily on non-human animal species as a pointer to how a new drug is likely to behave when given to patients.

Alarming, despite the general acceptance of animals as human surrogates, there has never been a report of an objective, peer-

reviewed study demonstrating that animal tests have general value in predicting either safety or efficacy, although there are a number that demonstrate that they don't (Coleman, 2011). This is not to say that experimental animals don't have value, it is just that such value is not general, and therefore cannot be assumed. Thus, when attempting to identify novel approaches to treating a human disease, there is no certainty that animals are going to provide any relevant information. Failure to accurately predict clinical efficacy can result from a number of causes, including species differences in affinity for the drug target, in distribution and function of that target, in basic physiology, and from the use of inaccurate models of disease. Let us look again at asthma, a disease for which we have a number of very useful drugs and which is for the most part well controlled. What may not be appreciated is that almost none of the drugs in our current armoury originated from animal studies. Instead, they are either developments of natural hormones (glucocorticoids from corticosterone, and β 2-agonists from adrenaline), or known herbal remedies (muscarinic antagonists from belladonna, and theophylline from tea leaves). Interestingly, Intal® (disodium cromoglycate) was only identified because the synthetic chemist who made the drug, happened to be asthmatic, and had the habit of tasting each of his synthetic products. The only class of current anti-asthma drugs that may claim discovery primarily through animal studies are the LT₄-antagonists, and even here, the early observation that human lung produced large amounts of SRS-A on antigen challenge was critical to the initiation of programmes to identify inhibitors. On the other hand, there are many animal models of the disease in which a wide variety of drugs have demonstrated efficacy, including antagonists at BK, NK, TP, H₁, and PAF receptors, Ca²⁺-channel blockers, K⁺-channel openers, PPAR agonists etc, none of which has subsequently been found to demonstrate significant therapeutic benefit in clinical asthma (Coleman, 1999). But despite this, the models continue to be used and presumably believed in. Similarly in COPD, there is no shortage of animal models or of drugs showing efficacy in those models, but no clinically effective drugs have emerged; we still rely largely on antibiotics and modestly effective medicines borrowed from the asthma armamentarium. I am certain that such a situation will also be familiar to researchers in other disease areas.

As a pharmacologist primarily interested in R rather than D, efficacy has always been my main consideration, but it is not everything, and other differences in the activities of drugs across species are highly relevant to drug R&D programmes, particularly pharmacokinetics (PK), pharmacology-related side effects and toxicity. In drug development programmes, pharmacokinetics is usually modelled in two species, very often rats and dogs, the problem is that these frequently give divergent answers, and the situation may not be helped if primates are employed. This problem is well illustrated in a report by Grass & Sinko (2002), where they reviewed PK data from clinical studies with those obtained in rats, dogs and monkeys, and found no correlation (see Fig. 1). Although such gross discrepancies are not seen in all

comparative PK studies, being a function of choice of compounds, it highlights the lack of certainty associated with the use of animals to predict likely bioavailability of novel drugs following oral administration to man.

Predicting likely adverse events and frank toxicities is a major challenge to the pharma industry. Again, much store is put by animal data, rodents and dogs being the primary test species. My experience is that most safety pharmacologists and toxicologists will claim that overall, animals do a reasonable job, but where objective measures are applied, this looks a rather difficult position to defend. In 2000, a review was published by ILSI-HESI of the concordance of the toxicity of a wide range of pharmaceuticals between humans and animals (Olson et al, 2000). The results provide rather sobering reading. They reported that overall, there is a positive concordance of 71%, which means that for 71% of the 1500 test compounds included, a specific human toxicity was also identified in at least one of the test species. This however, tells only a part of the story; a breakdown of the types of toxicity reveals that animals are far better for some systems than others, thus for toxicities related to blood, GI and CV systems, the level of concordance was between 80-90%, but for other systems, values were between about 35-60%, which by any estimation is poor. Also hidden in this analysis is the fact that concordance was recognised when data in a single animal species mirrored those in man, despite the fact that another species may have demonstrated no such toxicity, thus overall species-specific levels of human concordance were lower at 63% for non-rodents (mainly dogs) and 43% for rodents. An increasing realisation of the shortcomings of animal toxicity tests has prompted the US EPA and NIH along with the FDA to explore the possible benefits of using in human *in vitro* approaches in their Tox21 program (Shukla et al, 2010).

Despite the above, I am by no means against the use of experimental animals in pharma R&D as long as it is backed by sufficient validation, as for example the use of animals for safety or efficacy purposes where there is a history of predictive power in a specific area of biology or chemistry. However, it is difficult to see how this can apply to animal use for the identification of totally novel chemical or biological approaches, where by definition there is no prior art.

So if we can't rely on animals to identify potential efficacy and safety of new medicines, what should we do? I believe that the answer lies with the wider and more imaginative use of human-based technologies. Clinical microdosing, coupled with high sensitivity MS, is now accepted as a useful means of elucidating drug metabolism in man, and *in silico* approaches based on human-validated data are also being increasingly used to predict toxicity and efficacy. But the area that I wish to focus on is the use of human cells and tissues *in vitro*. In a recent review, Francis Collins, the physician-geneticist, who headed up the Human Genome Project, not only supported the use of *in vitro* technologies replacing animal toxicity tests, but also stated "With earlier and more rigorous target validation in human tissues, it may be justifiable to skip the animal model assessment of efficacy altogether." (Collins, 2011). With the Human Tissue Act now in place, the legal and ethical aspects of the research use of human donated materials are established, and there is no reason why researchers should not move on from surrogate biology to the real thing. And the criticism that it is not possible to model the complexities of the whole human body by looking at isolated parts is becoming an increasingly hollow objection. Through the application of ever more ingenious approaches, involving such things as tissue slices, 3-D culture and the application of

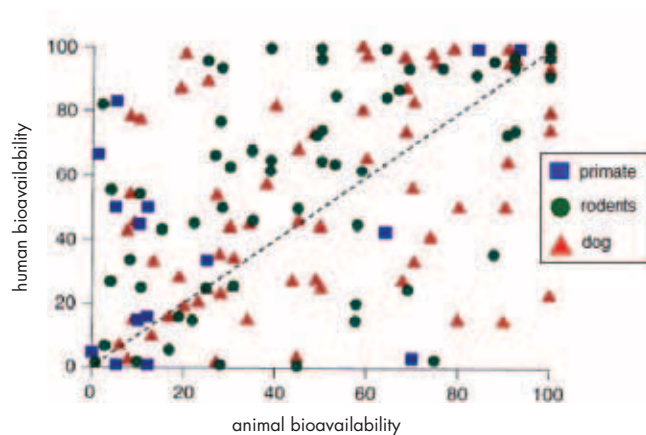
microfluidics to body-on-a-chip technologies (Esch et al, 2011), particularly where cells and tissues are maintained under constant flow conditions, more complex questions can be addressed.

My final thoughts relate to the source of the cells and tissues required for such human-based test methods. While both cadaveric and surgical sources have their roles, they will never supply a sufficient range and volume of viable materials. This can only ever be achieved through the increased access to non-transplantable samples acquired, with appropriate consent from transplant donors. This of course requires an understanding and commitment on the part of scientists, medical intermediaries, regulators, ethicists, politicians and the general public. This will be tough, but it must and will happen.

References

- Coleman RA. Current animal models are not predictive for clinical asthma. *Pulm Pharmacol Ther.* 1999; 12(2): 87-9.
- Coleman RA. Human tissue in the evaluation of safety and efficacy of new medicines; A viable alternative to animal models? *ISRN PHARM.* 2011; 2011: 806798. Epub 2011 Jul 6.
- Collins F. Reengineering Translational Science: The Time Is Right. *Science Translational Medicine.* 2011; 3(90).
- Esch MB, King TL, Shuler ML. The role of body-on-a-chip devices in drug and toxicity studies. *Annu Rev Biomed Eng.* 2011; 13:55-72.
- Grass GM, Sinko PJ. Physiologically-based pharmacokinetic simulation modelling, *Adv Drug Delivery Rev.* 2002; 54(3): 433-451.
- Nials AT, Vardey CJ, Denyer LH, Thomas M, Sparrow SJ, Shepherd GD, Coleman RA. AH13205, a selective prostanoid EP2-receptor agonist. *Cardiovasc Drug Rev.* 1993; 11 (2): 165-179.
- Olson, H., Betton, G., Robinson, D., Thomas, K., Monro, A., Kolaja, G., Lilly, P., Sanders, J., Sipes, G., Bracken, W., Dorato, M., Van Deun, K., Smith, P., Berger, B., Heller, A. Concordance of the toxicity of pharmaceuticals in humans and in animals. *Regul. Toxicol. Pharmacol.*, 2000; 32(1):56-67.
- Shukla SJ, Huang R, Austin CP, Xia M. The future of toxicity testing: a focus on *in vitro* methods using a quantitative high-throughput screening platform. *Drug Discov Today.* 2010;15(23-24):997-1007. Epub 2010 Aug 11.

Fig 1.



A comparison of human vs animal oral bioavailability (Grass & Sinko, 2002).

In vivo Pharmacology: Reaping the benefits of analysis at the cell type level



Sterghios A. Moschos
University of Westminster

Dr Sterghios A. Moschos, M.S.B. obtained his BSc (HONS) Molecular Biology at University of Portsmouth in 1999 and PhD in Pharmaceutics at the School of Pharmacy, University of London in 2004. His post-doctoral work at the School of Pharmacy and subsequently the National Heart and Lung Institute, Imperial College focused on *in vivo* evaluation of liposomal formulations and cell penetrating peptides as delivery solutions for siRNA therapeutics, their utility in antiviral biodefence applications and the characterization of the role of small non-coding RNAs in lung disease. Recruited to lead oligonucleotide therapeutics exploratory research for the lung at Pfizer UK, his expertise was applied to liver diseases such as hepatitis C virus infection and novel biomarker discovery. Following the closure of the Pfizer site in Sandwich, he has been appointed Reader of Industrial Biotechnology and Biochemistry at the University of Westminster where he is currently setting up his independent research group.

Introduction

In the last 20 years the bulk of drug candidate selection and optimization work has shifted from animals to tissue and/or cell culture. However, *in vivo* studies remain key to obtaining confidence in drug safety and mechanism of action prior to clinical use. Typically, this is quantified by measuring changes of molecular markers (biomarkers) related to the disease in question, such as cytokines, the extracellular signaling molecules of inflammatory networks. These factors change in concentration both in the disease-afflicted tissue and at the whole organism level. Thus, whether targeting inflammation in the injured liver or the asthmatic lung, cytokines can be quantitative indicators both in affected organs and in circulating blood.

However, the contribution of individual sub-populations of cells in a diseased organ to the biomarker signature might vary considerably. Much of this information has been accumulated through studies in isolated cells *in vitro*. These have shown that 1) the levels of a drug target might vary considerably between distinct cell types found in a tissue and 2) each of these cell types might contribute biomarker signals in substantially different ways. Nevertheless, current methods measure biomarkers either in tissue fluids such as lung lavage fluid or homogenates of whole tissue samples, agglomerating biomarker contribution by cell type into a tissue-wide average. Thus, the biomarker signal becomes diluted and more variable, translating into a requirement for larger groups of animals to obtain a statistically meaningful result. Similarly, lack of knowledge around the range of drug target expression among different cell types *in vivo* might increase toxicity risks: an excess of drug in cells expressing the drug target at low levels could allow drug binding to other factors, increasing off-target effects.

Doing *in vivo* pharmacology by the cell type

Presently, these concerns can be partially addressed by histology. The methodology is sufficiently discriminatory to have reached the clinic: the recommendation for Herceptin treatment in cancer

is decided on histological evidence for estrogen receptor 2 expression. Alas, substantial inter- and intra-laboratory variance in sample and result interpretation even at the clinical level (Choritz *et al.*, 2011) belies the main drawbacks of this technique: poor scoring range and bias-prone, subjective interpretation of results. Image analysis algorithms are partially addressing this problem however the technology has not matured sufficiently to facilitate true automation and objectivity. Alternatively, laser capture microdissection is used in combination with downstream analytics. Though the post-histology methods somewhat overcome the inherent operator bias in cell subtype sampling, this technique has been met with poor uptake due to high cost, considerable complexity, very low throughput and extremely low quantities of assayable material.

Thus, the reliability of information commonly obtained from animal testing might indeed be presently compromised. Is the effect of a drug actually sufficient in disease-relevant cells, or is it masked by seemingly mediocre changes measured at the tissue level? Does sufficient drug reach the target cell type, or is the quantity recovered from the tissue homogenate apparently inadequate? Is a tissue unaffected by a substance, or is a particular cell sub-type impacted in a way that optical examination by histology cannot discern? These questions become more significant in the context of biological drugs such as antibodies, stem cells and gene therapy, including molecular therapeutics such as antisense and short interfering RNA (siRNA), which often benefit from tissue/cell type targeting to maximize efficacy and safety.

A new approach: Tissue Disruption and Cell Sorting (TDCS)

In an effort to overcome these problems, a new method was developed at the now defunct Pfizer research laboratories at Sandwich UK. This work was spurred by the need to resolve a long-standing controversy: if siRNA and antisense are administered via the respiratory tract, do they actually deliver and operate in cells lining the lung airways (Moschos *et al.* 2008)? To achieve this we proposed using primary cell isolation methodologies in pharmacology studies in mice. Coined tissue disruption and cell sorting (TDCS), the method aimed to quantify the amount of drug and effect achieved in individual cell types of the lung after these had been exposed to the drug *in vivo* (Moschos *et al.*, 2011).

To test the technique, a transgenic mouse model was used. The genetically modified mice expressed the light-emitting gene luciferase. Thus, luciferase served as a drug target for siRNA and antisense, and light emission as the biomarker of successful treatment. Efforts were focused on two key cell types of the lung: epithelia and macrophages (figure 1a). Preliminary studies sought to optimize the cell isolation process and evaluate throughput: a single cell sorter operator could prepare a total of 48 separate cell populations per day (mixed cells; macrophages; epithelia; macrophage and epithelia-depleted cells, or 'other' cells from 12 separate lungs).

Pilot work assessed baseline levels of light emission by luciferase at the whole animal, whole tissue or cell type-specific level. The results indicated that variability was substantially reduced when measurements were made in cell sorter-isolated cells (figure 1b). To measure a 50% reduction of luciferase in the lung tissue, as many as nine mice would be needed with an 85% chance of success. To measure the same change in lung macrophages only, as little as three mice would be sufficient with a 91% chance of success. In other words, the TDCS technique could answer the same question using a staggering 2/3 fewer animals compared to classical approaches.

Luciferase light emission could be also quantified independently in each of the cell types examined across at least a 4-log range (figure 1b). These results contrasted the range and granularity of manual scoring methods used in histology. Moreover, they were underscored by a total lack of operator bias in data accumulation and vetting: identification and sorting of cell sub-types and signal measurement was a fully automated process yielding consistent data in separate studies (figures 1b, c).

With these exciting results in hand, we tested the activity of luciferase-targeting siRNA and antisense. In culture, both compounds had been shown to reduce luciferase light emission by up to 90%. After dosing luciferase mice via the trachea, we collected individual lung cell types by TDCS and quantified luciferase light emission and drug loading (mass spectrometry) in each of the cell sub-types. Intriguingly, no cell sub-class could be loaded with siRNA, whereas antisense loaded only in macrophages. Nevertheless, antisense had no impact on the level of luciferase in drug-loaded macrophages. Follow on studies indicated that both of these drug classes rapidly access systemic circulation after topical dosing to the lung. Moreover, they showed that whilst a quantity of either drug might appear to accumulate in the tissue when assessed at the tissue level, this is not in the disease-relevant cells, at sufficient quantities, or within the appropriate sub-cellular compartment for the drugs to function.

Implications and Future directions

These results raise a number of important questions for the fields of *in vivo* experimentation. The TDCS technique yielded remarkably concise biomarker data, which translated into a 2/3 reduction in animal use. Notwithstanding the value of objectively quantifying change within individual cell types *in vivo*, the reduction of animal use that can be achieved by TDCS is in itself a substantial driver for wider implementation of the technique. In addition, information on drug target levels and response at the cell type level would be useful in improving *in vitro* drug optimization studies, identifying sources of *in vivo* risk and indicating mitigation strategies such as dosing route selection or use of delivery systems/targeting approaches. Taken together, the data confidence and value gain afforded from these ethical and scientific refinements merit the cost associated to accessing automated cell sorter technologies for carrying out *in vivo* pharmacology by TDCS and further expansion of the technique.

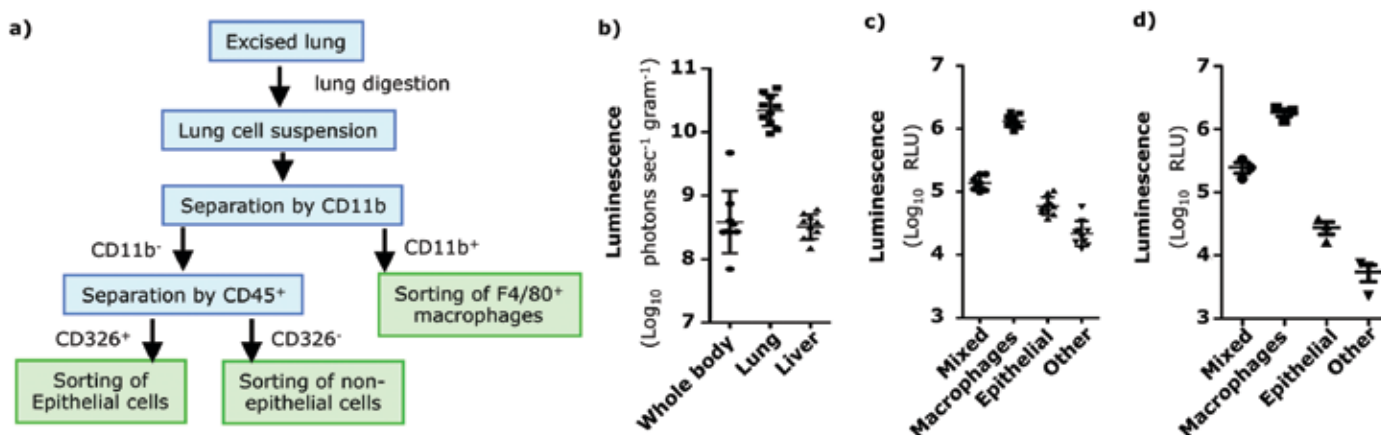
References

Choritz H, Busche G. and Kreipe H. Quality assessment of HER2 testing by monitoring of positivity rates. *Virchows Archiv* 2011; 459(3): 283-9.

Moschos SA, Spinks K, Williams AE, and Lindsay MA, Targeting the lung using siRNA and antisense based oligonucleotides. *Curr Pharm Design* 2008; 14(34): 3620-7.

Moschos SA, Frick M, Taylor B, Turpenney P, Graves H, Spink KG, Brady K, Lamb D, Collins D, Rockel TD, Weber M, Lazari O, Perez-Tosar L, Fancy SA, Laphorn C, Green MX, Evans S, Selby M, Jones G, Jones L, Kearney S, Mechiche H, Gikunju D, Subramanian R, Uhlmann E, Jurk M, Vollmer J, Ciaramella G, and Yeadon M. Uptake, efficacy, and systemic distribution of naked, inhaled short interfering RNA (siRNA) and locked nucleic acid (LNA) antisense. *Mol Ther* 2011; 19(12): 2163-8.

Fig 1.



Pharmaceutical patenting

D YOUNG & CO
INTELLECTUAL
PROPERTY



Garreth Duncan & Kit Wong
D Young & Co LLP

Garreth is experienced in all types of chemical subject matter, including pharmaceuticals, food chemistry, petrochemicals, agricultural chemistry, polymer chemistry and chemical synthesis and processes. He has particular experience in obtaining Supplementary Protection Certificates and other forms of patent term extension. He acts for a wide spectrum of clients, ranging from large multinational companies to universities and associated spin-out companies. Prior to joining D Young & Co in 2007 Garreth worked both in private practice and in Pfizer's European Patent Department and his experience there included a secondment to the Pfizer site in Ann Arbor, US. He became a partner at D Young & Co in 2011.

Kit has had experience in private practice since 1997, having handled portfolios for a large number of clients in the chemical field, in diverse areas such as upstream and downstream petrochemical processing, polymer chemistry, pharmaceuticals, cosmetics, hair dyes and other consumer products, chemical processing, chemical synthesis and catalyst chemistry. In the pharmaceutical field, Kit has had extensive experience in working directly with small generics, as well as large innovator companies. Kit has a broad academic background in chemistry, with a particular interest in organic chemistry. Her PhD research in the field of pharmaceutical/medicinal chemistry has provided a strong background upon which her main practice areas at D Young & Co have developed. Kit joined D Young & Co in 2004 and became a partner in 2008.

As the regulatory requirements to obtain marketing authorisation of medicines become more stringent, the research required becomes ever longer and more costly; it can typically take 12-14 years and cost up to \$1bn to bring a new drug from its initial discovery to the market. Patent protection is therefore critical to protect this investment: both small molecule and biologic drugs are routinely patented, and it is rare in the pharmaceutical industry for a drug to be developed and marketed without patent protection for the molecule itself.



Most major pharmaceutical companies are currently facing the expiry of patents covering blockbuster drugs: examples include Pfizer's Lipitor (atorvastatin), whose extended patent terms of which expired in 2010 and 2011, and AstraZeneca's Seroquel (quetiapine), whose extended patent will expire in March 2012

in most countries. As the compound patent application is typically filed at an early stage in the R&D process, the innovator is often left with a short term of exclusivity before generic entry, even when patent term extensions and regulatory data protection are taken into account. With many pharmaceutical companies currently facing a weak pipeline with few strong new drug candidates, the need exists now, more than ever, for innovator companies to manage and extend the life cycle of existing products.

Patenting Formulations

One way commonly used by innovator pharmaceutical companies to extend the exclusivity of a drug product is to patent new formulations of the drug. The basic compound patent typically contains general text indicating possible formulations of the drug such as tablets, capsules, injectable formulations and transdermal patches, and lists typical excipients used in these formulations. For a formulation of a known drug to be patentable, the formulation must be both novel and exhibit an inventive step (typically by providing a technical effect or advantage) over and above these generally described formulations.

Extended release formulations of a drug are particularly common in the pharmaceutical industry. Such extended release forms can be used to reduce dosing frequency from twice or three times a day to once a day. Solving this problem can require additional invention and therefore allow the formulation to be patented in its own right. Provided the new formulation is launched and established on the market before the basic compound patent expires, it can provide valuable additional exclusivity for the innovator.

A good example of how such a strategy has been successful is AstraZeneca's Seroquel XR, which is an extended release, once a day quetiapine formulation. This formulation was launched in 2008 and by 2011 was achieving worldwide sales of over \$1bn in its own right. The patent for the XR formulation expires in 2017: although a number of generic companies are challenging the patent, if upheld it may provide AstraZeneca with exclusivity for an additional five years after expiry of the basic quetiapine patent.

Patenting Polymorphs

Another common way to extend the exclusivity of a product is to protect new crystalline forms (polymorphs) of the drug. Patent protection for a new crystalline form of a compound can be extremely valuable, for example, if the new form possesses a desirable physical property, such as improved stability, or if it is an unavoidable component of a commercial drug product, so that competition is postponed whilst third parties try to design around the patent to avoid making this polymorph and avoid infringement. Increasingly, the use of polymorph patents has also become an important strategy for generic companies vying to

keep their competitors off the market for as long as possible. The European Patent Office's practice in respect of claims to crystalline forms has evolved with time and over recent years it has tightened its approach to the allowance of such claims.

Where an invention relates to a crystalline form of a known compound ('compound X'), but which was only known in amorphous or oil form, it was formerly possible to obtain a broad claim to 'crystalline compound X' at the EPO. However, such claims are now routinely objected to by the EPO as unclear, and it is now generally necessary to characterise crystalline forms by suitable experimental parameters (such as powder X-ray diffraction, IR spectra or DSC thermograms). Therefore, the first consideration in drafting claims to a new polymorphic form is the selection of a suitable set of experimental parameters with which the crystalline form can be characterised and distinguished over the prior art. Only the minimum number of parameters essential to distinguish over the prior art should be included in the claim to ensure a broad claim scope.

It is not always possible to predict whether the selected parameters will be sufficient to distinguish over prior art uncovered after filing. It is therefore essential to include in the patent application a raft of other parameters (eg, alternative and secondary XRD peaks, XRD peak intensities, IR absorption bands, and DSC thermograms) that can be relied on to provide basis in the event that amendment is needed in view of prior art. The experimental conditions used to produce the new polymorph (eg, temperature, solvent quantities and proportions, seeding step, heating or cooling rates, water content, etc) and obtain the measurements (eg, the wavelength of the X-ray source in the case of XRD, the disc material in the case of IR, and the heating rate in the case of DSC) should also be included to ensure sufficient disclosure.

The assessment of novelty can also present a challenge in polymorph cases. Owing to the fact that characterisation of a particular crystalline form is typically reliant on its internal structure the problem of inherent disclosures can arise when assessing novelty. This is particularly the case where the prior art discloses the same compound and a similar crystallisation procedure or solvent. The EPO and many national courts may then take the view that, although the prior art is silent on the existence and characterisation of the claimed polymorph, it is nevertheless considered to be disclosed. The onus would then switch to the patent applicant to demonstrate that carrying out the prior art process does not inherently result in the same polymorph.

The most significant area in which EPO has tightened its criteria for allowance of claims to new crystalline forms is inventive step. The EPO's current approach to assessing inventive step for polymorph claims starts from the assumption that polymorph screening experiments are a routine part of the drug development process. Thus, it is becoming standard practice for the applicant claiming a new polymorphic form to be required to demonstrate the existence of an unexpected effect or advantage by the provision of comparative data. It is good practice to provide a discussion of the potential advantages of the claimed polymorphic forms, at least in general terms, so that the description provides support for later-filed experimental data showing an advantage.

Patenting second medical uses and dosage regimes

Claims to further medical uses of known products ('second medical use claims') have long been acceptable before the EPO. The wording for second medical use claims currently accepted by

the EPO is as follows:

"Substance X for use in the treatment of disease Y".

The EPO has also permitted second medical use claims directed to new treatments of a disease where the use of substance X to treat disease Y was already known in general terms. Examples include those relating to a novel group of subjects to be treated and those relating to a novel mode of administration.

In 2010, the Enlarged Board of Appeal, which is the EPO's highest legal authority, decided second medical use claims are also permissible where the only novel feature relates to a dosage regime. Examples of dosage regime claims include the following: *"Substance X for use in the treatment of disease Y, wherein substance X is administered every morning for a 10 day period."*

"Substance X for use in the treatment of disease Y, wherein substance X is administered at a dosage of 50 to 100 mg/day."

However, the Enlarged Board has indicated that, in order to meet the requirement of inventive step, the dosage regime defined in the claim must also exhibit a technical effect (such as an improvement or advantage) over the prior art which discloses substance X for treating disease Y in general terms.

Granted second medical use patents prevent generics from packaging and labelling pharmaceutical products for the claimed use. As the indication must be specified on the label to satisfy regulatory requirements, use patents can therefore provide valuable additional exclusivity to pharmaceutical products. Dosage regime claims can be particularly valuable when the claimed dosage is the only one which obtains marketing authorisation, so a generic cannot market the drug without infringing the dosage regime claim.

In summary, formulation, polymorph and second medical use patents can be valuable tools to enable innovator pharmaceutical companies to extend the lifecycle of marketed drug products beyond the expiry date of the basic patent. Generics companies in turn aim to design around such patents or revoke them to clear the way to market, and the consequent disputes between the two will continue to develop the law in this area.

View IP articles online

www.dyoung.com/knowledgebank

The public interest in libel law reform



Síle Lane
Sense About Science

Síle Lane joined Sense About Science in 2009 from a career as a stem cell researcher. Sense About Science works with scientific bodies, research publishers, policy makers, the public and the media, to change public discussions about science and evidence. As Campaigns Manager Síle is developing a new dedicated campaigns unit to popularise our approach to standing up for science and manages Sense About Science's Keep Libel Laws out of Science campaign to reform the UK's outdated libel laws. www.senseaboutscience.org.

Freedom to criticise and question in strong terms and without malice is the cornerstone of scientific argument and debate, whether in peer-reviewed journals, on websites or in newspapers. But the libel laws of England and Wales discourage debate and merely encourage use of the courts to silence critics. The laws are unnecessarily complicated and unduly costly. Anybody can bring a case without having to prove they were damaged or that allegations are untrue. The outcomes of libel cases are difficult to forecast (although, out of 154 cases identified in a 2008 review, zero were won by defendants).

While human rights groups have long protested that English libel law is among the most restrictive in the world, it is only recently that its impact on scientific discussions has come to light, helping to catalyse a public campaign and change libel law reform from an esoteric issue to something for which scientists are leading the charge.

Several high profile cases brought in London against doctors, science writers and scholarly journals recently provoked a groundswell of public objection. These include:

- Medical writer Ben Goldacre who was sued for writing about a German vitamin salesman who promoted vitamin cures for HIV in African countries.
- A Swedish Professor of linguistics whose peer-reviewed review of a new scientifically untenable lie detector technology under consideration by several Governments was suppressed following a libel threat.
- Cardiologist Dr Peter Wilmshurst who was sued by an American device manufacturer for commenting to a Canadian journalist about a trial in which he was the principal investigator.

Even though Dr Wilmshurst faced bankruptcy he fought for four years to defend his words. This is rare. When Sense About Science objected to the cases above we were inundated with hundreds of stories of scientific researchers, patient groups and publishers around the world who had been threatened with libel action in London. Every week researchers and editors withdraw their articles, hold back material from public discussion and, in the end, stop asking vital questions of public interest.

As patients we expect health professionals making decisions about our treatments to have access to complete information but the peer reviewed medical literature has felt libel chill. Dr Fiona Godlee, editor-in-chief of the BMJ, told us the BMJ Group of medical journals has had to refuse to publish scholarly articles in response to legal advice. Dr Godlee said in an editorial(1) calling for reform of the laws that, "scientific claims [must] be exposed to critical scrutiny before they are accepted" but these discussions too, have felt the chill. A survey of GPs by the magazine *Pulse*(2) found 80% of the doctors who responded said that fear of being sued for libel by a large company was restricting open discussion of the potential risks of drug treatments.

Dr Philip Campbell, editor-in-chief of *Nature*, told us the libel laws impact on the reporting of issues of importance to the scientific community, such as research misconduct. He said "either we chose not to cover a story because the impact is not worth the incredible effort and time it takes or we suffer by covering the story." Our recent survey of medical and scientific journal editors(3) showed that scholarly editors regularly consult libel lawyers and that it was the non-peer reviewed content – the opinion and comment pieces, letters page and book reviews – that cost them the most time and money.

It is not just rarefied debates among specialists that libel laws are affecting. The everyday discussions all of us as voters, consumers, citizens and patients have are under threat too. An online patient support forum for sufferers of the condition chronic fatigue syndrome (M.E.) told us they had to bar members from sharing their experiences of unproven treatments because the people promoting the treatments have threatened to sue. Citizens Advice spent an entire year's research and campaign contingency budget to libel-proof a report on firms employed by High Street stores that it still can't publish in full. A mother told us how she had to take down a Facebook page she had created to discuss a change in school uniform policy with other parents when the school threatened her with a libel suit. Consumer magazine *Which?* regularly battles legal threats, sometimes unsuccessfully, to be able to print critical reviews of double glazing companies, debt management firms and unsafe child safety seats.

There is no accessible public interest defence for people discussing medical treatments, consumer products or the behaviour of companies. That is why Sense About Science, a charity founded to promote good science and evidence in public debates, joined free speech organizations English PEN and Index on Censorship to co-found the Libel Reform Campaign in 2009. Sense About Science works with scientists to respond to misinformation and encourage scientists to get involved in debates on controversial issues. When scientists are reticent to speak out research doesn't move on and the public's ability to make informed decisions is damaged.

Nearly 60,000 people support the campaign and hundreds of commentators, comedians, historians and authors as well as scientists and doctors have spoken out. More than 50 organizations including medical Royal Colleges, human rights NGOs, parenting organizations and medical and science publishers support us. Thousands of our supporters wrote to MPs with their concerns about the libel laws and at the last general election all three main parties included a commitment to reform the laws to protect public interest discussions in their manifestos. In March 2011 the Government published draft legislation(4) which may become law if a Defamation Bill is included in the next Queen's Speech.

The Government's proposals do not go far enough to protect public interest discussion. Scientists and scientific organizations will need to keep pushing to make sure reforms included in the Bill include a strong public interest defence.

For more on the campaign see www.senseaboutscience.org/pages/keep-libel-laws-out-of-science.html, follow @FreeDebate on Twitter or contact Sile at slane@senseaboutscience.org

References

- 1) Godlee, F, Keep libel laws out of science, British Medical Journal, 2009,339,b2783
- 2) Kenny, C, Libel laws stifling debate on drug safety, say GPs, Pulse, 27 January 2010
- 3) Libel Reform: http://www.ringgold.com/uksg/si_pd.cfm?Pid=10&Articleid=5927&XSection=Business&issueno=237 (accessed 10 February 2012)
- 4) Ministry of Justice, Draft Defamation Bill Consultation, Printed by The Stationery Office Limited on behalf of the Controller of Her Majesty's Stationery Office (Consultation Paper CP3/11), March 2011



BRITISH
PHARMACOLOGICAL
SOCIETY

Today's science, tomorrow's medicines

Our Programme:

23-24 April 2012

4th Focused Meeting on Cell Signalling
Leicester, UK

27 April 2012

Time for Change
Addressing Changes to the Animals
Scientific Procedures Act by
Transposition of Directive
63/2010/EU
London, UK

11 May 2012

Rational and Safe Prescribing
the Way Forward
Dublin, Ireland

25 May 2012

Pharmacokinetics &
Pharmacodynamics Workshop
London, UK

7-9 June 2012

Focused Meeting on
Neuropeptides
King's College London, UK

20 June 2012

Safety Pharmacology Workshop
Harrogate, UK

Hold the date!

To register or find out more
about our events, please call:
+44 (0)207 239 0176

or email meetings@bps.ac.uk
or visit www.bps.ac.uk

Research and Development in the pharmaceutical industry



Richard Green
Nottingham University and
President Emeritus BPS



Tom Blackburn
TPBioventures LLC and
President Emeritus BPS

Dr Richard Green is Honorary Professor of Neuropharmacology at Nottingham University His PhD was with Gerald Curzon and following two years at NIMH Washington DC he joined David Grahame-Smith at the MRC Clinical Pharmacology Unit in Oxford where he undertook psychopharmacology research, becoming Assistant Unit Director in 1981. In 1986 he was appointed Director of the new Astra Neuroscience Research Unit in London and also became Meetings Secretary for the BPS and subsequently General Secretary in 1989. In 1996 he was appointed Director, Global Discovery CNS & Pain Control for Astra and was involved in the preclinical development of novel neuroprotective agents for stroke. After retiring from AstraZeneca in 2007 he has continued psychopharmacology research in Nottingham investigating recreational drugs such as MDMA. He has published around 280 papers and was given the Lifetime Achievement Award by the British Association for Psychopharmacology in 2010.

Dr Tom Blackburn is a highly accomplished pharmaceutical/biotech executive with 30+years of international and domestic success in drug discovery and development with start-ups and growth organizations. An innovator with proven successes in drug discovery and clinical development of multi-billion dollar products, that's gained him international recognition. He has published over 100 papers in the field of neuroscience and is a named inventor on over 20 patents. His entrepreneurial approach for creating original concepts has been acknowledged as a recipient of awards for drug discovery/development and training. He is founder and CEO of Translational Pharmacology BioVentures (TPBV) LLC a 'virtual' drug development company in the USA & UK. Tom holds a Ph.D., D.Sc., from the University of Manchester, President Emeritus and Fellow of the BPS.

The President of the Royal Society of Chemistry David Phillips recently proclaimed "It's a fact that the easy targets in the body for the production of drugs have, essentially, all been used up." This is one view of the complex pharma industry we live in today. However, there are those who would submit that many of those easy chemistry targets developed in the 1970s to 1990s would have stumbled and fallen by the pharma 'waste-side' given the rigours of today's regulatory environment, and also been stifled and suffocated in the current overwhelming government bureaucracy. More importantly, the culture has changed dramatically in drug discovery and development from the times when David Jack at Glaxo, Keith Mansford at Beecham and Paul Janssen in Breese, Belgium interacted with researchers on a daily basis. Such people led the industry through a period where innovation was fostered and nurtured in small teams of scientists and where the bean counter and matrix and process management culture were still in their infancy.

It is surely not chance that this earlier era was the most productive period for drug discovery ever. In those days most pharmaceutical companies (of which there were then many) were of modest size and there was a close association between management (many of whom were scientists) and bench workers. Research teams were small and worked together closely, as one would expect in any small group.

It is now abundantly clear to all that this former creative productivity was largely due to small groups working closely together. It should also be mentioned that in this same period several companies also set up new research units embedded in, or closely associated with, universities in order to increase brainpower and therefore productivity. These units included those set up by Astra (Institute of Neurology, London), Sandoz (University College, London), Reckitt's (Univ. Bristol), Parke -Davis (Univ. Cambridge), SmithKline Beecham (Univ. Oxford) and Glaxo (Univ. Cambridge) - there were others. However by the mid-1990s all had changed. Companies were merging in every direction and the number of distinct companies decreased dramatically. In addition, almost all the university embedded units closed, the reason being given that one needed 'critical mass' to conduct modern pharmaceutical research. There seemed (and seems) to be a herd mentality in the industry; once one company makes a change all others follow suit. Consequently the new 'centres of excellence' or like-titled organizations emerged. Instead of having small groups of dedicated and often senior scientists working together at the bench, one had more junior staff in the laboratory and senior scientists spending most of their time in meetings. The age of innovation and, crucially, the ability to undertake 'I wonder if' or the 'Friday afternoon' experiments had gone.

The reasons and complexity for this major change are probably many. However the rise of 'The City' in the late 1980s is probably the major one. Companies used to report financial results yearly, now it is quarterly, and 'The City' expects instant gratification, which does not jibe well with the long process of drug R&D. The emphasis on the day-to-day share price, dividend and bonus culture further resulted in the rise to prominence of the Finance Director in controlling research activity.

This same period saw the rise of robotics (again how this must have gladdened the heart of the Finance Director, machines that can work for 24 hours a day and don't demand holidays or a pension at the end of it). Robotic screening also encouraged the idea of target-based research, an idea that with hindsight has major weaknesses, particularly in CNS research as has been discussed elsewhere (Green AR and Aronson JK, *Br J Clin Pharmacol*; in press DOI: 10.1111/j.1365-2125.2012.04246.X).

Many of the aircraft hangers built to handle this robotic platform technology of the day now remain in moth balls at many of the redundant UK/global big pharma sites. The failure of this approach to produce innovative new drugs over the last 15 years is now evident.

The pharmaceutical industry does appear to have now realized that overall large 'centres of excellence' have been a failure in terms of discovery of effective new medicines. Small research teams are now the mantra of today and are being promoted by companies like GSK (see DPU strategy <http://invivoblog.blogspot.com/2012/02/gsk-dpu-scoreboard-three-fewer-four.html>) and others as the answer to the NME drought that we have seen over the last decade. Some major companies are now also interacting with small innovative biotech companies that have maintained the flexibility that large organizations have lost. So, full circle in 25 years!

Until the industry rebalances the power base, finance will still drive every R&D decision. Research is now being cut severely with many excellent pharmacologists and other scientists being made redundant. The head-count and facilities are being decreased in an effort to save money and often to ensure the share price/dividends can be kept artificially high with company buyback schemes. Culling high quality scientists is helping to feed the share price. The weakness of this approach should be evident to even the most financially naive observer, and it is affecting the future of UK R&D.

AstraZeneca is now undergoing its third major restructuring since 2007. Such changes may not seriously disrupt the functioning of a company making light bulbs, but they play havoc with the culture and productivity of staff involved in the creative business of discovery. One is again reminded of the situation 20 years ago when management consultants wrote books talking enthusiastically about 'downsizing'. Airport bookshops were full of them and these ideas were followed eagerly by many companies. A few years later the same consultants were then able to make more money by writing further books that filled the same bookshelves that pointed out the damage that had been done by companies that had cut back too severely and thereby damaged the effective running of the organization.

What also remains worrying however is the way that almost every company has pulled out of research in major therapeutic

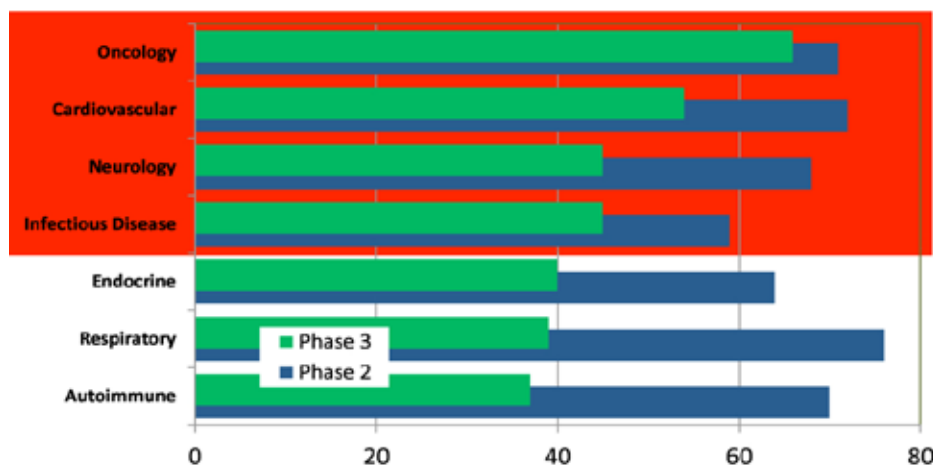
areas such as neuroscience because of lack of progress, not realizing that this lack of productivity might be due primarily to the changes management has imposed on the R&D process rather than a deficiency of good neuroscience. This is clearly shown in Figure 1 where the attrition rate is far greater in areas of research where 'funding' is given a higher profile in risk management assessment of therapeutic targets (oncology, infectious diseases and cardiovascular disorders).

The dominance of finance in directing research priorities is based on risk analysis and is not going to change, so is there anything that is going to encourage long term thinking and planning and help boost innovative research in areas of perceived high risk, like neuroscience? One idea would be to lengthen the period of patent protection. The patent period is generally 20 years. A research and development period of 12-14 years is usual. One must then add the time for approval by the regulatory authorities such as the FDA and their reliance on 30 year old diagnostic criteria (DSM IV). Regulatory approval takes at least 18 months, and since they then often ask for further information which is then considered for another six months or more, this means that a further two years is invariably added before launch and this time is totally outside the control of the company. There then remains 5-6 years of exclusivity (although we acknowledge this can be extended modestly by clever patenting techniques). That is little time in which to recoup the costs of discovery and development and make a good financial return. Compare this with the average period of copyright for a book or music of 50+ years and one realizes how unbalanced the 'discovery' exclusivity is between drug discovery and the arts. A longer period of exclusivity would allow lower prices to be charged for new drugs since the company would have more time to recoup costs and get a realistic profit. Crucially, for the matters we are discussing in this polemic, it would allow a return to underwriting high risk research because the money would be there to cover it. Plans in pharma to "share cost, risk and reward" with other institutions such as small companies and universities are rapidly being adopted, so that the bigger companies then do what they are best at - picking up the promising leads and making products that fill an unmet medical need, have significant efficacy and work well enough to become a commercial success.

Time will tell if these new collaborative initiatives will see the industry "strike back" or whether it continues to fail, becoming unable to maintain its position as a viable commercial empire.

Fig 1.

Drug Failure Rates by Therapeutic Area. Overall Failure Rate at P2 and P3.



BIO-BioMedTracker Study handout on DRUG APPROVAL RATES: presented at The 13th Annual BIO CEO & Investor Conference in New York City (February 14-15, 2011).

What is being done to sustain drug discovery in the UK?



Humphrey Rang
BPS President-elect

The President's Lecture, organized by Ray Hill at the BPS Winter Meeting in Dec 2011, took the form of a mini-symposium on the future of drug discovery in the UK, with three well-known industry-based scientists presenting their analysis of the pharmaceutical industry, and their vision of the future.

The speakers were Tom Blackburn (ex-BPS President, and CEO of Translational Pharmacology Bioventures LLC), Simon Campbell (ex-RSC President, former Senior Vice-President for Worldwide Discovery at Pfizer, and author of the RSC position paper on Healthcare Innovation in the UK (www.rsc.org/ScienceAndTechnology/Policy/Documents/healthcare.asp), and Dave Allen (Head of the Respiratory Therapeutic Area at GlaxoSmithKline). Recordings of their presentations are now available on the BPS website.

Despite serious problems confronting the pharmaceutical industry, all of the speakers agreed that the various constituencies that make up the world of drug discovery – industry, academia, funding bodies, investors, healthcare providers – are determined to find ways of working together to develop the necessary new structures and organizations, and there is a spirit of cooperation that we have not seen before.

What are the problems?

The pharmaceutical industry is facing increasing costs, long development times, stubbornly high attrition rates and diminishing new drug approvals, coupled with a 'patent cliff', increasingly stringent regulatory requirements, and pressure to reduce drug costs. The rate of new drug approvals has decreased over the last decade and there is a real risk that drug discovery could slow to a trickle at a time when healthcare demands are increasing. All speakers agreed there was urgent need for change within the UK healthcare industry.

Tom Blackburn told us that the market capital of pharma companies, which had increased dramatically until 1990, had steadily declined by over 30% over the last decade despite rapidly increasing R & D expenditure. Mental illness, which comprises an estimated 35% of the global burden of disease, is an area from which most companies have largely withdrawn their efforts, while investing more on orphan indications where development costs are less. Investment in antibiotic research has decreased massively, despite the growing problem of resistant organisms. This loss of investment, coupled with restrictive and cumbersome approvals procedures for clinical trials in the UK, has caused a rapid decline in the number of UK-based clinical trials – now less than 2% of the world total. The exceptional UK clinical trials expertise and resources will be lost to the UK economy in consequence.

Pharma industry research in the UK has shrunk and continues to shrink, with closure or major contraction of research establishments by all of the large companies, and little or no expansion of biotech companies. Government is placing much reliance on future development of biopharmaceuticals, which have made

impressive progress recently, to fill the innovation gap. But, as Simon Campbell argued, small molecule therapeutics will continue to have major advantages for affordable oral medication, and the special medicinal chemistry expertise needed to develop them is something at which UK excels, and which must be nurtured. Medicinal chemistry is particularly at risk, because expertise in universities and research institutes is very limited, UK pre-eminence in this area residing mainly in pharma industry laboratories that are under threat.

Encouragingly, the seriousness of the problem, which affects both the healthcare and the economy of the UK, is recognized at the highest level; an additional £800m government funding for medical research was announced last August.

The background

For 50 years or more, up to the end of the 20th century, the industry was sailing along beautifully, creative in inventing new drugs that met real needs, and very profitable. Pharma industry products introduced over the last few decades – many of them coming from the UK - have transformed healthcare (see *Pharmacology Matters* 4 (3) 2011, for a list of important drugs developed over the last 40 years). About 40% of the increase in life expectancy in the developed world is attributed to improvements in therapy. In these boom years, the big companies established large centralised laboratories, highly managed to develop profitable new drugs in line with company policy which was to develop enough highly profitable 'blockbusters' to finance the many unsuccessful projects. They were efficient, controllable, and delivered the goods.

Many of the blockbusters were me-too drugs (often dressed up as 'second generation' drugs) aimed at large markets. Concerned to sustain innovation, companies were alert to ideas coming from academia, and able to direct their drug discovery and development capabilities on to new targets quickly and effectively. To varying degrees, they set up collaborations intended to gain early and exclusive access to knowledge about emerging mechanisms and targets, but by and large they kept themselves to themselves and were concerned to reveal nothing that might help the competition. However, the blockbuster model gradually failed, partly because regulatory authorities became increasingly reluctant to approve me-too drugs, and too few innovative drugs were developed to fill the gap, mainly because of failure in clinical trials of drugs directed at poorly validated targets.

When the human genome was sequenced, it was widely believed that a splendid new avenue of success had opened up, producing novel, better drugs more quickly and more cheaply than ever before. Important though genomics undoubtedly is, it has not yet produced a drug discovery bonanza. Nevertheless, the need for better drugs is as great as ever, so what is to be done to make the discovery process work better? That is the question that the three speakers addressed, and there was a great consensus in what they said.

The way ahead

All three speakers agreed that translational medicine, to work properly, needs academia and the pharmaceutical industry to work together in new ways. A critical need is to improve target validation and patient selection, and thereby reduce the rate of failure in clinical development. Robust target validation needs convergent evidence from several experimental approaches, often beyond the capabilities of a single company. Collaborative enterprise, and sharing of information in the public domain, is the way forward.

Dave Allen described the way companies have moved from the model of large centralised discipline-based functions to small autonomous multidisciplinary units with a less corporate, more biotech-like culture. At the same time, external collaborations are coming to be seen as necessary, rather than ancillary. Indeed one of GSK's teams operates exclusively through external collaborations with no internal research, serving to provide leads and starting points for the various therapeutic areas. The Stevenage Bioscience Catalyst – a new incubator facility for start-up companies – is on GSK's doorstep, and its tenants will have access to much of GSK's expertise and communal facilities. Another important joint initiative by MRC, Cancer Research UK, the Wellcome Trust and UCL is the new Francis Crick Institute (www.crick.ac.uk), on which high hopes rest. Simon Campbell stressed the need for expert medicinal chemistry in the new institute. The UK Drug Discovery Consortium (www.ukddc.org), sponsored by pharmaceutical companies, funding agencies and research centres is another recent innovative development. These are just two examples of similar initiatives aimed at decentralising drug discovery research away from the 'big pharma silos' by creating Therapeutic Centres of Excellence.

Two key phrases have entered the lexicon in recent years: open innovation and pre-competitive space. [Google them and stand back!] Both refer to the fact, which may seem obvious, that the common ground of published research provides the knowledge base on which drug discovery projects are built. But whereas in the past pharma companies sought to build on it, while avoiding adding to it anything that might assist their competitors, they have realised that cooperation and sharing knowledge with their competitors should enable them to use their resources much more efficiently. This is, of course, in tune with initiatives such as GenBank, SwissProt and many other public domain databases (including the BPS/IUPHAR-sponsored Guide to Pharmacology database, www.guidetopharmacology.org) that have so facilitated biomedical progress in recent years. Actually building open innovation platforms for drug discovery, and defining exactly where precompetitive space ends and proprietary space begins, is no easy task, but many worthwhile ideas are being pursued. Our speakers agreed that we will soon see a much more productive and open relationship between academia and the pharmaceutical industry than in the past.

The pharmaceutical industry can be justly proud of what it has contributed to improved medical care over the last 50 years or so – imagine medical practice stripped of any drugs introduced since 1960 – yet it has a dark side and often attracts a bad press, accused of profiteering, unscrupulous marketing practices, concealment of clinical trials results, failure to address global health problems and much besides. A ruthless commercial culture, that seeks to sequester scientific knowledge as intellectual property, exists alongside a vibrant and creative scientific one. Many scientists in academia feel alienated by this. Obtaining from a company a sample of one of its compounds to test a hypothesis generally means signing a draconian 'material transfer agreement' that allows only agreed experiments to be performed, and the

results to be published only if the company agrees to it. Practices that impede the acquisition and publication of knowledge about the natural world have to change if 'open innovation' is to become a reality. Will the new spirit of cooperation, and developments like the Francis Crick Institute, succeed in creating an environment in which drug discovery science can take place at arm's length from commercialism? Let us hope so. Real changes, with powerful sponsors, are happening, and optimism is emerging from the gloom.

What is the BPS doing?

The BPS, which has long been a meeting ground for academic and industry-based pharmacologists, is keen to encourage the kind of open collaboration that our speakers presented as the way ahead for drug discovery. It is surely the dream of any pharmacologist to see his or her discoveries translated into effective ground-breaking medicines. Dale, Black and Vane, our three Nobel laureates, all had this vision, and worked in pharma companies to realise it, but nevertheless made a huge impact on drug discovery well beyond the confines of the companies that employed them. It was simply in their nature as outstanding scientists to share their ideas, and they were unstoppable.

There is no question that pharmacology is an essential discipline in the quest for new drugs. The role of the BPS is to ensure that it thrives, providing able and well-trained scientists to drive drug discovery in the UK. To this end the BPS is a founder member of a new group formed in partnership with the Society of Biology and the Royal Society of Chemistry, which aims to link the learned societies representing the disciplines needed to build the skills base to cover all aspects of pharma R & D, and to provide a single authoritative voice in advising policy-makers and funding agencies. We will make sure that the voice of pharmacology comes over loud and clear.



What does the future hold for healthcare innovation?
Dr Simon Campbell (Past President, Royal Society of Chemistry).

Collaboration between Learned Societies in support of Drug Discovery and Development



Martin Todd
BPS Industry Committee Chair



Jess Strangward
BPS Head of Education

In the second half of 2011 the BPS contributed to a Royal Society of Chemistry paper and follow up workshop on 'Innovation in Healthcare' which aimed to support the identification and development of key drug discovery skills in the UK. There is no doubt that the UK has the strong scientific skill base in those biological, chemical and clinical skills but the BPS Industry committee saw this scheme of work as an opportunity to preserve and develop UK Drug Discovery by proposing that a number of our fellow UK Learned Societies explore the potential of working together to ensure greater impact and a coordinated approach.

For our learned Societies there is the potential to support members' careers, training and development, to attract young people to science and to promote a culture of innovation and collaboration. Discussions with the Society of Biology and the Royal Society of Chemistry led to a proposal for a meeting which we called 'Pharma and Biotech Learned Societies: Collaboration across the skills agenda'. The meeting was held on 8 February at the Linnaean Society in London and representatives from 24 Learned Societies attended.

The aim of the meeting was to identify a number of common themes and messages which could be used to gain support from Government, Research Councils, Trade Associations and Pharma and Biotech to support the maintenance and development of a skilled scientific workforce that can excel in delivering novel medicines through innovation and collaboration.

David Allen, Senior Vice President for Respiratory therapy at GlaxoSmithKline (GSK) introduced the new Drug R&D landscape and noted the emergence of a 'gap' between the excellent basic science and the publication of innovative scientific concepts taking place outside Pharma and the difficulties experienced in moving effective and safe compounds into man. The solution to this problem at GSK has been to develop a strategic research agenda grounded in the needs of patients linked to developments in emerging science.

This strategy means that the trend in Pharma companies has moved to an organizational shape where activities are decentralised, internal groups have strong autonomy and where collaboration with external partners is an essential part of the new research landscape. In order to create effective partnerships scientists need excellent collaborative skills, confidence to develop new networks, an ability to take on scientific leadership and an ability to understand the criteria on which decisions are made about how new targets and compounds are progressed in the R&D process.

This overview of the landscape acted as an excellent background in promoting discussion from all of the attendees. These sessions were facilitated to identify some key themes which are summarized here:

1) Policy headlines - Support for training and skills development in areas relevant to Pharma R&D – a set of key policy headline areas summarizing key actions from the three areas below which could form the basis of a shared position building on the

Royal Society for Chemistry Healthcare Innovation paper, to create a positive dialogue with government, stakeholders, funders and key bodies in supporting Drug Discovery R&D.

- 2) Practical skills – support for the further development and provision of practical skills training at graduate and postgraduate level. There is a real opportunity to utilise the concept of Centres of Drug Discovery Excellence to offer practical skills experience using real life drug discovery projects. The excellent summer schools programmes in practical skills offered in some areas like *in vivo* skills could be extended to other areas to ensure that students can gain the kind of experience that potential employers would value.
- 3) Placements – support for increased placement opportunities for graduate and postgraduate students in Pharma, Biotech and CROs. Potential for the creation of a 'clearing house' for placements that could coordinate and promote opportunities. There is also an opportunity to influence professional bodies and employers in promoting and valuing the opportunities for academics to work in Industry and vice versa to promote innovation and an increased understanding of the needs and opportunities within each sector.
- 4) Continuing Professional development – the new R&D landscape shows us that there is a need for our members to develop new skills both in science and in aspects relating to collaboration and partnership. The Learned Societies could promote and contribute to activities pioneered within the Innovative Medicines Initiative EMTRAIN programme to provide their members with high quality learning opportunities throughout their careers. There may be an opportunity to develop a mentoring programme for all of our members to promote cross disciplinary interactions by the provision of mentors from complementary areas of science.

These four areas were seen as squarely within the remit of Learned Societies and their membership and areas where we could work together to share experience and make some proposals for future action. We clearly need to have the support of a number of key stakeholders including Research Councils, Government Departments, employers organizations and interactions with them will be part of our next steps.

The spirit of enthusiasm to see and experience the changed landscape and to start to develop new ways of delivering key skills through existing or new channels was very encouraging. We would like to encourage BPS members to bring forwards new ideas for discussion so that we can support our existing members, our new members and our potential members of the future.

The Modern PhD



Michael J Mulvany
Aarhus University



Zdravko Lackovic
University of Zagreb

Michael graduated in 1962 from Oxford in Mathematics and Engineering Science. PhD (1978) and Doctor of Medical Sciences (1983), Aarhus University. Since 1997, he has been Professor of Cardiovascular Pharmacology Aarhus University. Head, Aarhus Graduate School of Health Sciences (2002-2011). His interests are structure and function of small arteries and their role in the development of high blood pressure.

Zdravko Lackovic, MD, PhD Professor of Pharmacology at School of Medicine University of Zagreb. A Visiting Scientist at the Laboratory of Preclinical Pharmacology, NIMH, Washington D.C. (1979-1981) and in 1994-1995 he spent a sabbatical as an Established Visiting Scientist, Abo Akademi University, in Turku, Finland. Beside research in the field of neuropharmacology, leadership of several Croatian and collaborative international projects, he held shortly the Chair of the Department of Pharmacology (1983-84). Vice Dean for Science in the period from 1985-1991 with a task to make criteria for the academic advancement in line with European standards. President of Croatian Pharmacological Society 1998-2002. Founder and director of the PhD Program at the University of Zagreb, School of Medicine (founded in 1998), and the Deputy Dean for PhD education. After organizing two European conferences (2004 and 2005) on harmonisation of PhD program in biomedicine and health sciences, he became originator and the first president of ORPHEUS (Organisation of PhD Education in Biomedicine and Health Sciences in the European System, <http://www.orpheus-med.org>).

In the December edition of Pharmacology Matters(1), Nikolas Dietis raises important points about the future of the PhD. His concerns fully support the series of articles he refers to in Nature from 21 April 2011(2). That series raised well-argued criticism of the PhD: "Fix the PhD: no longer a guaranteed ticket to an academic career, the PhD system needs a serious rethink" and "Most doctoral programmes conform to a model defined in the middle ages", were just some of the comments. And also the Economist(3): "One thing many PhD students have in common is dissatisfaction. Some describe their work as 'slave labour'. Seven-day weeks, ten-hour days, low pay and uncertain prospects are widespread". Nikolas Dietis' comments suggest that these points are not exaggerated. Particularly when it is recalled that only a small minority of PhD graduates will end up in permanent academic positions (some say only 15%, some say less than 5%).

Something is clearly wrong, and unless something is done, the PhD will decline – doing a PhD will not be attractive to the best students, and where then is the feed line for our research and our future researchers?

Nikolas Dietis suggests that it is the PhD itself which is the culprit. In support of this he compares the US PhD (lasting up to eight years or more) and the UK PhD (lasting three to four years). Both appear to be dysfunctional, and Nikolas Dietis concludes that this indicates that it is the PhD that is the problem. Another provocative interpretation could, however, be that there are some institutions in the US and the UK where the PhD has become restrained in the old apprenticeship model. In contrast to new forms of the PhD that have been developed, particularly in Continental Europe. The apprenticeship model was fine when practically all successful PhD graduates embarked on an academic career. Three-four years in a laboratory culminating in a thesis describing the experiments and an examination where the thesis is argued line by line is an excellent foundation for academia. But for the 85-95% of PhD graduates who proceed to careers outside of academia, it is not sufficient.

What are the options? One possibility would be to retrench and reduce the number of PhD students to the number needed to supply academia. Who then would do the research? Academics do not have time to do research themselves, they are too busy with grant-writing, administration and all the other countless demands on their time. University research is therefore often driven by PhD students. Somehow the requirement that the PhD is a research degree should be equated with the need to ensure that undertaking a PhD is a route to a good job inside or outside of academia.

This question has been taken up by the European Council for Doctoral Education(4) who have recommended that PhD education needs to be structured, so that it is based on a research project but also provides instruction in so-called *transferable* skills: courses in advanced methodology and ethics; how to make presentations orally and written; how to manage a project; and how to teach.

These are aspects that are important not only for a scientist, but of value in other walks of life. Being able to set-up a three-year project, perform it, present it, and combine it with critical evaluation of work done by others, is in itself a *transferable skill*. The skills learnt would be valuable in any job where creative synthesis, initiative and resourcefulness are needed. Thus PhD education is a valuable contribution to the knowledge society – which we will need in the future if Europe is to contend with competing economies.

This solution requires a new attitude to the PhD, moving away from the idea that it consists only of learning scientific method and laboratory techniques towards having responsibility for a project. The student will not necessarily do all the work

themselves (previously such an idea was anathema), but they will learn to manage the job, define the protocols, ensure the protocols are followed, write it up, get it published and present it at international conferences and in other fora. In this the student is supported by specific courses. This approach has been the aim of ORPHEUS(5) over the past seven years, where more than 100 biomedical faculties from virtually all European countries, including the UK, have worked on defining what is meant by a PhD in biomedicine, and how to ensure that the PhD graduate will be of use both inside and outside of academia. This has resulted in a set of recently published standard from ORPHEUS together with AMSE and WFME(6). These are not intended as a straitjacket, but as a way of ensuring the value of the PhD, both to the institution in terms of research output and to the student in terms of relevant training. The document provides considerable detail with flexibility about how PhD programmes can be organized, but the major points can be summarized in the following "seven pillars":

- 1) PhD programmes require a strong research environment.
- 2) Admission to a PhD programme requires a level corresponding to a bachelor and, 1-2 year master's, and based on research potential rather than past experience.
- 3) PhD programmes are structured and based primarily on a 3-4 year hands-on, original research project.
- 4) PhD programmes should include project-related course work covering at most about 6 months, including courses on ethics and transferable skills.
- 5) PhD students should have qualified and regular supervision.
- 6) A PhD thesis should demonstrate an intellectual ability to be expected from completion of a 3-4 year research project at international level (e.g. equivalent of 3 papers/ manuscripts).
- 7) The PhD thesis should be evaluated by an assessment committee consisting of active scientists, who should be independent and preferably international.

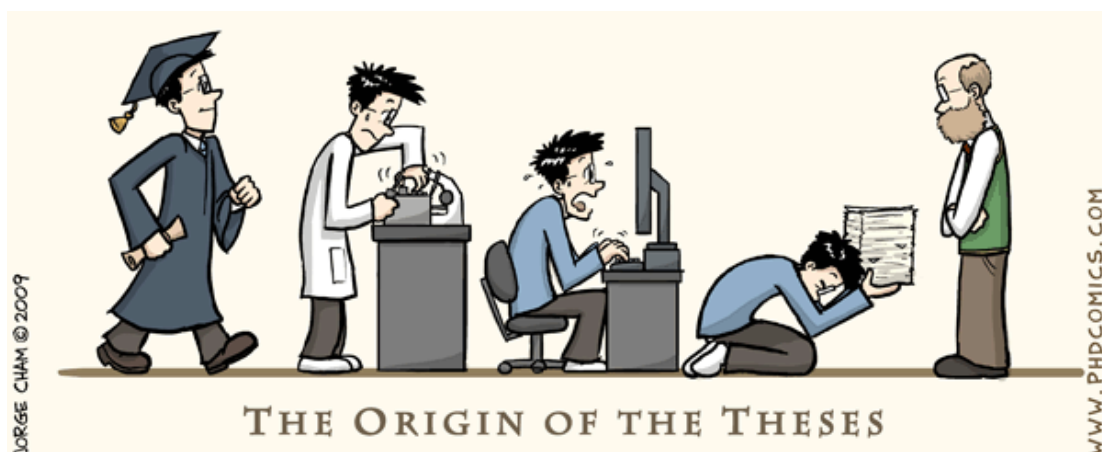
As pointed out recently(7), there are several aspects where the UK PhD differs importantly from the Continental European PhD. Admission to a PhD in the UK can be on the basis of a bachelor degree, whereas on the Continent, the student must already,

through their master's thesis, have demonstrated research ability. In the UK it is not a requirement or even necessarily expected that the work is published. On the Continent, PhD theses in more and more countries consist of papers and a review. In the UK, examination is a closed event between the student and the examiners. On the Continent, defence of the PhD is public; the student must demonstrate ability to make an oral presentation. In the UK, coursework is minimal; on the Continent this is an integral part of a PhD programme, the courses supporting the student to complete the programme within the allotted time.

We would respectfully propose that this new approach to the PhD will make PhD programmes more attractive thus recruiting better students, as well as ensuring that PhD graduates have the competencies that will enable them to contribute to Society at large. The approach may be seen as safeguarding the reputation of the PhD and strengthening career opportunities for those with PhD degrees. Additionally, in scientifically less developed European countries, application of ORPHEUS/AMSE/WFME standards can prevent overproduction of low level PhD. ORPHEUS hopes that this approach can be the basis for further discussions about how to ensure that the PhD continues to have its rightful place as a distinguished research degree.

References

- 1) Dietis N, The domino that "downgrades" the PhD. *Pharmacology Matters* 2011; 4(3): 17-19.
- 2) *Nature* 2011; 472:259-384
- 3) *The Economist*, 16 December 2010
- 4) www.eua.be/cde The Council for Doctoral Education is an organization under the European Universities Association
- 5) Organisation for PhD education in Biomedicine and Health Sciences in the European System www.orpheus-med.org
- 6) Standards for PhD education in biomedicine and health sciences in Europe. A publication from ORPHEUS, Association of Medical Schools in Europe, and World Federation for Medical Education. 2010. Aarhus University Press. ISBN 978 87 7934 600 0. Available on www.orpheus-med.org.
- 7) Mulvany MJ, Goulding N. Safeguarding the PhD. *Pharmacology Matters* 2011; 4 (2): 7-8.



Education Update



Jess Strangward
BPS Head of Education

“Education is what remains after one has forgotten what one has learned in school”.

~ Albert Einstein

When does your educational life finish? When do you make the decision that enough is enough and there are certain areas you don't need or want to know about anymore: Twitter? Justin Bieber? Quantum Mechanics?

At work this decision is sometimes more tricky, especially in science. A PhD can often be exploring a niche within a niche. As you progress you have to build and expand your area of expertise – quickly assimilating new techniques and more importantly new scientific knowledge that can transform the way you view your subject. If this wasn't enough to deal with increasingly the boundaries between disciplines begin to blur, mesh, and meld. This is why the focus nowadays is on skills – what can you practically do, not what do you know – often at a moment's notice you're going to need to 'know' something else. Moreover as the 'job for life' in whatever realm becomes a thing of the past, employees need to be adaptable and be able to demonstrate this.

To this end the BPS, with the Society of Biology recently hosted a meeting with a variety of other bioscience Learned Societies to discuss skills in drug discovery. The day began with a lecture from Dave Allen from GSK who advised that it wasn't that Industry needed certain skills to succeed in drug discovery, what it needed was new ideas and fruitful collaboration based on exciting ideas. The discussions were proactive and we'll be updating everyone over the year as to our next steps. One thing that many representatives thought very important was providing members with ways to access Continuing Professional Development (CPD). It became apparent that BPS is already making strides in this area with our Diploma in Advanced Pharmacology and its accompanying workshops. A more detailed summary of the day can be found on p25.

Looking across the suite of workshops it is interesting to note that the relentless popularity of our workshops such as Statistics, General & Advanced Receptor Theory (GART) – real nuts and bolts scientific concepts – never wanes. I think this demonstrates something that the BPS hold dear – a robust knowledge of basic pharmacological principles can help any scientist involved in drug discovery.

Diploma

Congratulations to Oladipupo Adeyemi, Juan Antonio Gilabert and Darren Riddy who all received their Diploma in Advanced Pharmacology at the Winter Meeting. The Diploma now has 27 students and we wish them all the best with their studies.

We have a really diverse and exciting Workshop line up for 2012. Starting with *sold out* Statistics, Pharmacokinetics and Pharmacodynamics, Safety Pharmacology, Drug Discovery and Neuroprotection. We look forward to seeing you there.

Science in Schools

The BPS now sits on the SCORE (Science Community Representing Education) with the Society of Biology who make direct representations to Government about how the new curriculum could be structured to benefit the Life Sciences. This gives the Society a real opportunity to influence and drive new ideas about what they feel school leavers should know to ensure they are ready and able to work in a scientific field.

EU Directive Meeting: Time for Change

The BPS, The Physiological Society, Understanding Animal Research (UAR) and the Society of Biology are co-hosting a meeting on the 27 April at the Wellcome Trust, keynote speakers Judy MacArthur Clarke and Martin Walsch to prepare the community for the changes as the Directive becomes part of UK law. The Directive will inevitably act as a way for anti-vivisectionist to claim that standards are slipping. It is important that as a community we continue to be transparent and open about the use of animals – if you need any support please contact BPS or UAR.

The year is already rushing by and I'm looking forward to updating you on all our Outreach activities soon!



Darren Riddy and Oladipupo Adeyemi receive their diplomas from Professor Nick Goulding

News from the Young Pharmacologists



Hannah Watson

Young Pharmacologists Representative

Another successful Winter Meeting

After months and months of planning, the Winter Meeting 2011 was a huge success! The Young Pharmacologists' scientific symposium inspired by "Stem cells: Pharmacology and Therapeutics" was praised with great reviews and excitement for next years' event. Thank you to the committee members who dedicated so much time to the cause, and to our speakers who made the day so special. A review from Dan Reed follows this article.

"I love pharmacology" Merchandise

Our "I love pharmacology" T-shirts are as popular as ever. They are being sold in aid of the IUPHAR 2014 congress to help fund bursaries for young African scientists to attend the event in South Africa. Please support this great cause by donating just £5 per T-shirt. T-shirts will be available at all BPS events, or contact the BPS office if you would like to order one. Watch this space for more "I love pharmacology" merchandise in 2012!

If there are any queries on events or bursaries please don't hesitate to contact Hazel O'Mullan at hom@bps.ac.uk

Stem Cells: Pharmacology and Therapeutics

A Review by Daniel Reed

It is a pleasure to review our symposium on Stem Cells: Pharmacology and Therapeutics held at the Winter Meeting 2011. The symposium was an incredible success, attracting some 300 delegates resulting in a truly packed and broad audience.

This year's symposium was opened by Professor Sian Harding, past-president of the International Society for Heart Research and member of the scientific advisory board for 'Stem Cells for Safer Medicines'. What followed was a series of awe-inspiring presentations ranging from discussions on the first successful stem cell tracheal transplant to applications of stem cells in drug safety, neuroscience and cardiovascular disease. There truly was something for anyone.

The symposium concluded with our greatly anticipated keynote lecture by Professor Doris Taylor of the University of Minnesota, USA. With Professor Taylor attending, the young pharmacologists committee and the BPS were able to attract the interest of Channel 4 documentaries, which were producing a programme with burns survivor Katie Piper, who, with Professor Taylor, has supported the advancement of stem cell therapy. We were flattered to receive such interest and hope to continue to be a part of such events in the future.

There are few words to describe the truly amazing nature of Professor Taylor's work which is sure to change how we think about pharmacology and develop therapies, be it drugs, cells or whole organs, forever. The future of pharmacology and therapeutics for young scientists will be exciting indeed.

During the meeting Professor Taylor took part in an interview with Young Pharmacologist Committee member, Daniel Reed, where she gives us an insight in to the future of regenerative pharmacology and her next 'crazy idea'. The interview is now available on the BPS website.



Speakers and Chairs of the Stem Cell Pharmacology Symposium. (Left to right): Professor Giles Hardingham, Professor Sian Harding, Mr Daniel Reed, Professor Doris Taylor, Professor Jane Mitchell, Professor Sara Rankin, Dr Sally Dickinson, Mr Thomas Mercer.



Professors Sian Harding and Doris Taylor love pharmacology!



BPS Focused Meeting on Neuropeptides

In association with the European Neuropeptide Club and American Summer Neuropeptide Conference. Local organizers: Professor Susan Brain and Professor Helen Cox

Bursaries are available for BPS members who are presenting an abstract at the meeting



**e: meetings@bps.ac.uk
w: www.bps.ac.uk
t: 020 7239 0176**

Sessions include:

TRP channels: from cough to pain
CGRP receptor and vascular mechanisms
Ghrelin
Elucidating roles for novel neuropeptides in
pathophysiology
VIP and PACAP

Confirmed Speakers to date:

Professor Maria Belvisi (UK)
Professor Piero Geppetti (Italy)
Professor Zsuzsanna Helyes (Hungary)
Dr David Poyner (UK)
Professor Steve Bloom (UK)
Professor Inge Depoortere (Belgium)
Professor Birgitte Holst (Denmark)
Professor Erika Pinter (Hungary)
Professor Illana Gozes (Israel)
Professor David Vaudry (France)
Dr Graeme Cottrell (UK)
Professor Jo de Mey (Netherlands)



**BRITISH
PHARMACOLOGICAL
SOCIETY**

Today's science, tomorrow's medicines



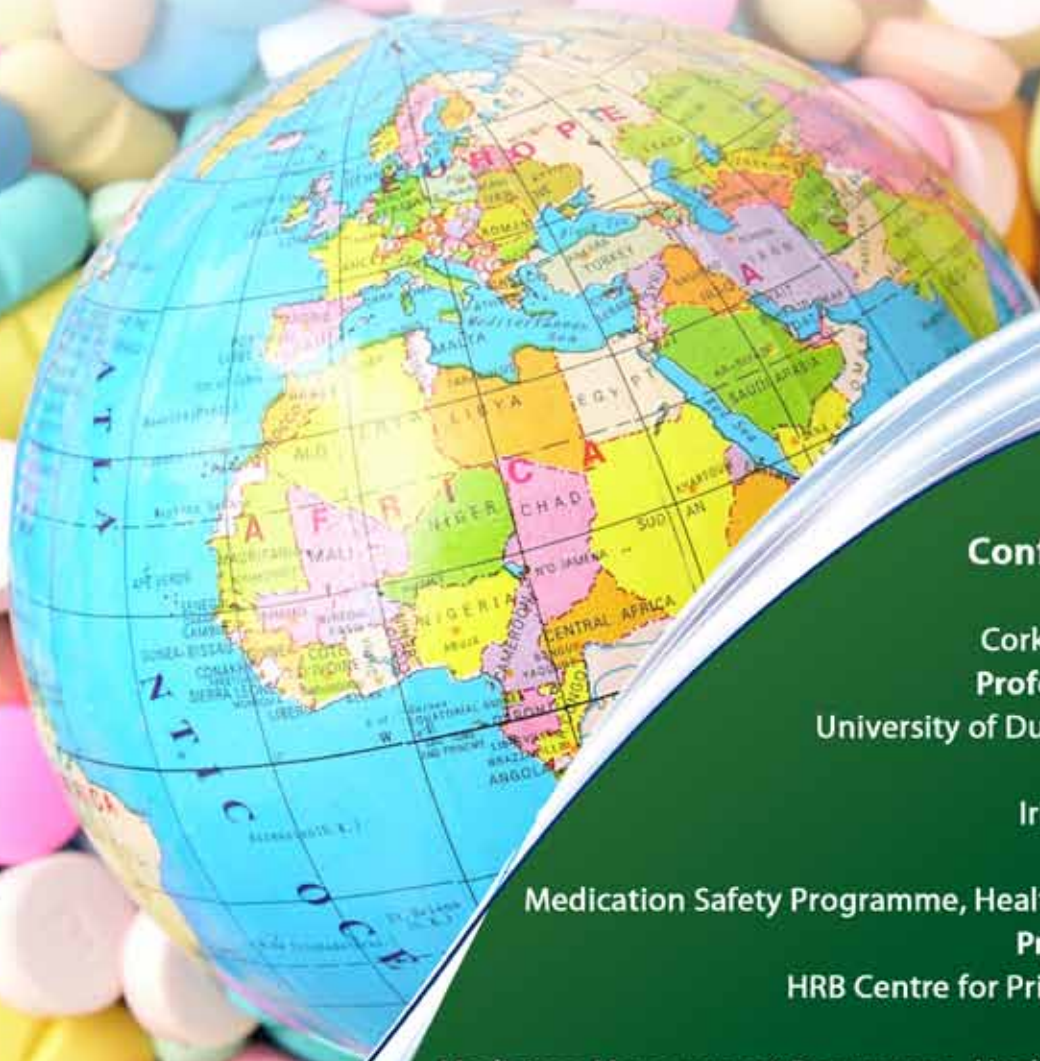
**ROYAL COLLEGE OF
PHYSICIANS OF IRELAND**

11 May 2012

Rational and Safe Prescribing- the way forward

This meeting brings together experts in the field of rational prescribing. It will appeal to all healthcare professionals involved in the prescribing of medicines in the modern era.

Venue: Royal College of Physicians Ireland, No 6 Kildare Street, Dublin 2



e: rachelmaguire@rcpi.ie

w: www.rcpi.ie

t: +353 1863 9760

Confirmed Speakers:

Dr Paul Gallagher

Cork University Hospital

Professor Michael Barry

University of Dublin, Trinity College

Dr Joan Gilvarry

Irish Medicines Board

Mr Tim Delaney

Medication Safety Programme, Health Service Executive

Professor Tom Fahey

HRB Centre for Primary Care Research

Dr Helen Flint

Medicines Management Programme, Health Service Executive

Professor Philip Routledge

BPS President; University of Cardiff

Professor Simon Maxwell

University of Edinburgh

Keynote speaker:

Professor Sir Michael Rawlins

Chairman of the National Institute for Health and Clinical Excellence (NICE)

Online registration is open (www.bps.ac.uk/meetings)

Bursaries will be available for BPS members

Publish
or
Perish

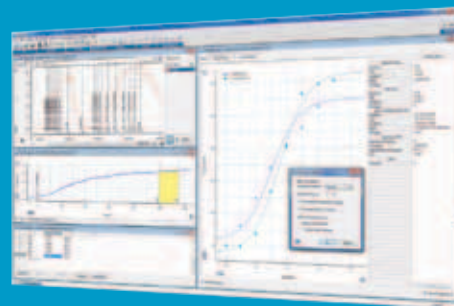
Fast track your pharmacology research to publication

Accelerate your research with the data acquisition systems already cited in thousands of published papers*. PowerLab® systems are flexible, powerful and seamlessly connect to a wide range of instruments including tissue baths, isolated heart systems, wire myographs and small animal telemetry systems. PowerLab's comprehensive software, LabChart® Pro speeds up analysis with specialised modules including Dose Response, ECG, HRV and Peak Analysis. You can automate calculations, generate dose response curves instantly and produce GLP (21CFR11) compliant data that is indisputable.

What's more, we'll keep you on track with expert support from our Europe-wide network and diverse web resources. When there's no prize for second place, ADInstruments PowerLab systems help you to publish. First.

To find out more, visit adstruments.com/publish

*According to Google Scholar, ADInstruments systems are cited in over 50,000 published papers.




ADINSTRUMENTS
making science easier