



Diseases Of Global Importance:

In this Issue:

BPS sans frontières

Translational pharmacology
at the heart of the challenge
to pharmaceutical industries

Innovative methods in teaching
pharmacology across the globe

Applied clinical pharmacology
(and public health) in rural Asia

University of Groningen: Rosalind
Franklin fellowship programme

Ensuring our graduates are
'fit for purpose' Sandwich
degrees in pharmacology at
the University of Manchester

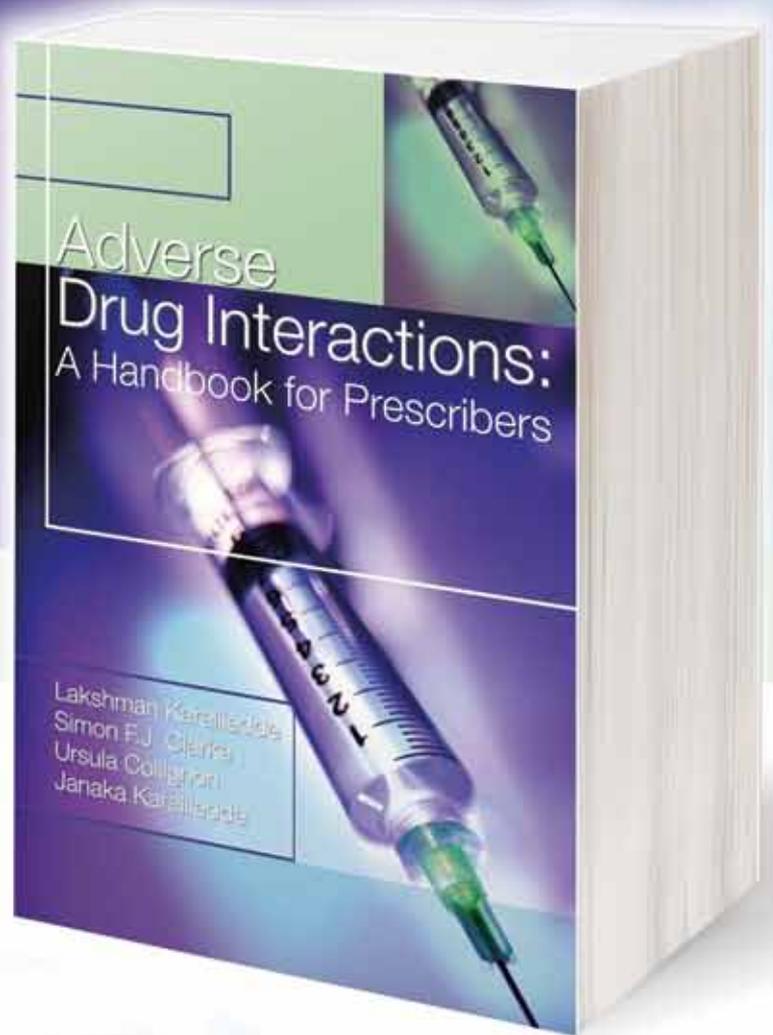
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academic and industrial researchers
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development struggles against
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Pharmacologists from across the globe will be debating the hottest topics in basic and clinical pharmacology at Worldpharma 2010. As a tribute to the 'global gathering' this issue of *Pharmacology Matters* focuses specifically on pharmacology and its

application around the world. Articles from a smorgasbord of drug discoverers include: the innovative methods employed by teachers of pharmacology (page 10), and applied clinical pharmacology in Sri Lanka (page 13). This issue also examines the progress that has been made in tackling diseases of global importance, focusing specifically on tuberculosis, malaria, cardiovascular diseases and HIV, four of the big killers. These articles can be found within the 'world diseases' section from page 21 onwards.

Keep up to date with the Society's activities by reading the 'view from Angel Gate' (page 4) and the regular updates from BPS meetings and the young pharmacologists' can be found on pages 33 and 34.

One of the greatest drug discoverers, Sir James Black, Nobel prize winning inventor of propranolol sadly died in March this year. The world lost an outstanding pharmacologist and the BPS lost a great friend. To celebrate the life and work of Sir James Black, BJP has put together a special issue illustrating the contributions he made, not only to science, but to BJP and to the BPS. This very special issue of BJP can be obtained from the BPS stand (20), or by emailing me at hom@bps.ac.uk.

The new year has brought several new additions to our editorial board, including Jonathan Brüün, Editor-in-Chief, and Dr Martin Todd, who replaces Cherry Wainwright as BPS Executive Committee representative. Dr Mike Curtis, Dr Annie Geraghty, and Dr Robin Plevin have also agreed to join the editorial team, and are already commissioning articles for future issues of PM.

Finally, I would encourage you to share your comments and thoughts about this issue, future issues, or the BPS more generally. You can email, phone, or post on the BPS Facebook page, we would love to hear from you.

Enjoy!

Hazel O'Mullan
Managing Editor

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Kate Baillie
Chief Executive,
BPS

Welcome to this internationally-themed issue of Pharmacology Matters, timed to coincide with WorldPharma 2010 which is being held in Copenhagen, from 17- 23 July. We are delighted that copies of this issue will be made available to all delegates and hope that it will raise awareness of the BPS's activities and benefits of membership to an international audience.

The Society has invested heavily in this Congress, both in terms of its financial support for the scientific programme, which includes three BPS-organized focused conferences, a contribution of nearly £60,000 towards bursaries, speaker costs, exhibition space and a Young Pharmacologists' networking event.

We are planning to meet with representatives from IUPHAR-affiliated national associations and will also take the opportunity to continue talks on future collaboration with our counterparts at ASPET, ASCEPT, EPHAR and the Chinese Pharmacological Society.

As the WorldPharma meeting takes place in July, BPS will not be holding a Summer meeting this year. However, we have been actively involved in the organization of events, beginning with the joint BPS/Physiological Society and NC3R's meeting on Cardiovascular Models, which took place in March. This event, which was sponsored by the Animal Welfare and Integrative Pharmacology Committee attracted over 90 delegates representing around 30 different organizations, and 11 speakers who delivered a diverse and challenging programme. Our second event, the first MRC/BPS Short Course in Translational Pharmacology, was heavily oversubscribed with 139 applicants for the 40 places on offer and the feedback received from participants has been extremely positive.

We were pleased to be able to use our newly refurbished offices to host the Women in Pharmacology (WiP) committee's Mentoring scheme training day, and the UKRC's workshop on presentation/voice skills, which was open to women with a completed PhD pursuing a career in pharmacology or clinical pharmacology.

I was also delighted to be able to sign the CEO Charter for Women in Science, Engineering and Technology (SET) on 11 March, on behalf of the BPS, as official recognition of the WiP's efforts to implement positive culture change in increasing the participation of women in SET.

In June, Annie Geraghty commenced in post as our new Education Manager. Annie will be working on a series of initiatives and is particularly looking forward to enthusing school children about Pharmacology, developing the careers section of the website, and looking



BPS signs the CEO Charter
Di Barber (UKRC) and Kate Baillie (BPS)

at ways to expand the Diploma in Advanced Pharmacology. Annie's first contribution to Pharmacology Matters is an industry based student's perspective which can be found on page 20.

Capitalizing on the success of BPS's second year at Cheltenham Science Festival, a team led by Clive Page and supported by the government's Science: So what? So everything campaign took a roadshow, The Science of Curry, to three London schools in March. A further BPS sponsored session - Chocolate, took place at Cheltenham Science Festival on 11 June and we hope to be able to develop this series in future years.

BPS continued to develop its social networking services and at the time of writing had over 550 fans on Facebook. The site has seen a marked increase in online interaction and several topics have been a focus for recent debate including the use of smart drugs, the classification of mephedrone as a class B substance and homeopathy. We have also launched a BPS YouTube Channel featuring vodcasts from the recent Winter Meeting and will continue to develop this resource.

BPS's presence in the media continues to grow, and we are now regularly asked to provide comments on drug-related stories. We are compiling a database of members willing to speak to the press - if you are interested in being added to this list, please contact Jonathan Brüün (jb@bps.ac.uk).

On the clinical front, the project team behind the Prescribe e-learning resource, which is being developed by BPS in collaboration with the UK Department of Health, has now completed the first four e-learning modules, with around 300 planned for delivery by the end of 2013. The project aims to provide online resources for medical students, to help them develop a firm grounding in the principles of basic and clinical pharmacology.

At the time of writing, we were on the eve of a general election. BPS took the opportunity to make the case to over 230 prospective parliamentary candidates that pharmacology, which is at the heart of drug discovery and development, is of strategic importance to the health and wealth of the nation and to call for the protection of teaching and research in pharmacology in universities.

With Ray Hill as our new President, we are also looking at the provision of services for our members (and prospective members) in the pharmaceutical industry, biotech and contract research organizations. A working party chaired by Martin Todd has been established to focus on this area and I look forward to reporting on progress with this initiative in a future issue of Pharmacology Matters.

I hope that you enjoy the Summer and look forward to seeing some of you in Copenhagen at the BPS stand!

Kate Baillie MA MBA, Chief Executive BPS



Dr Mark Miodownik demonstrates to students how turmeric can be used to dye a bag during the science of curry to London schools in March.



Hold the date!

BPS Winter Meeting 14 - 16 December 2010 QEII Conference Centre, London

Registration and call for abstracts: Wednesday 25 August

For enquiries & expressions of interest, please contact: meetings@bps.ac.uk
First announcement available at WorldPharma (BPS stand 20), or online

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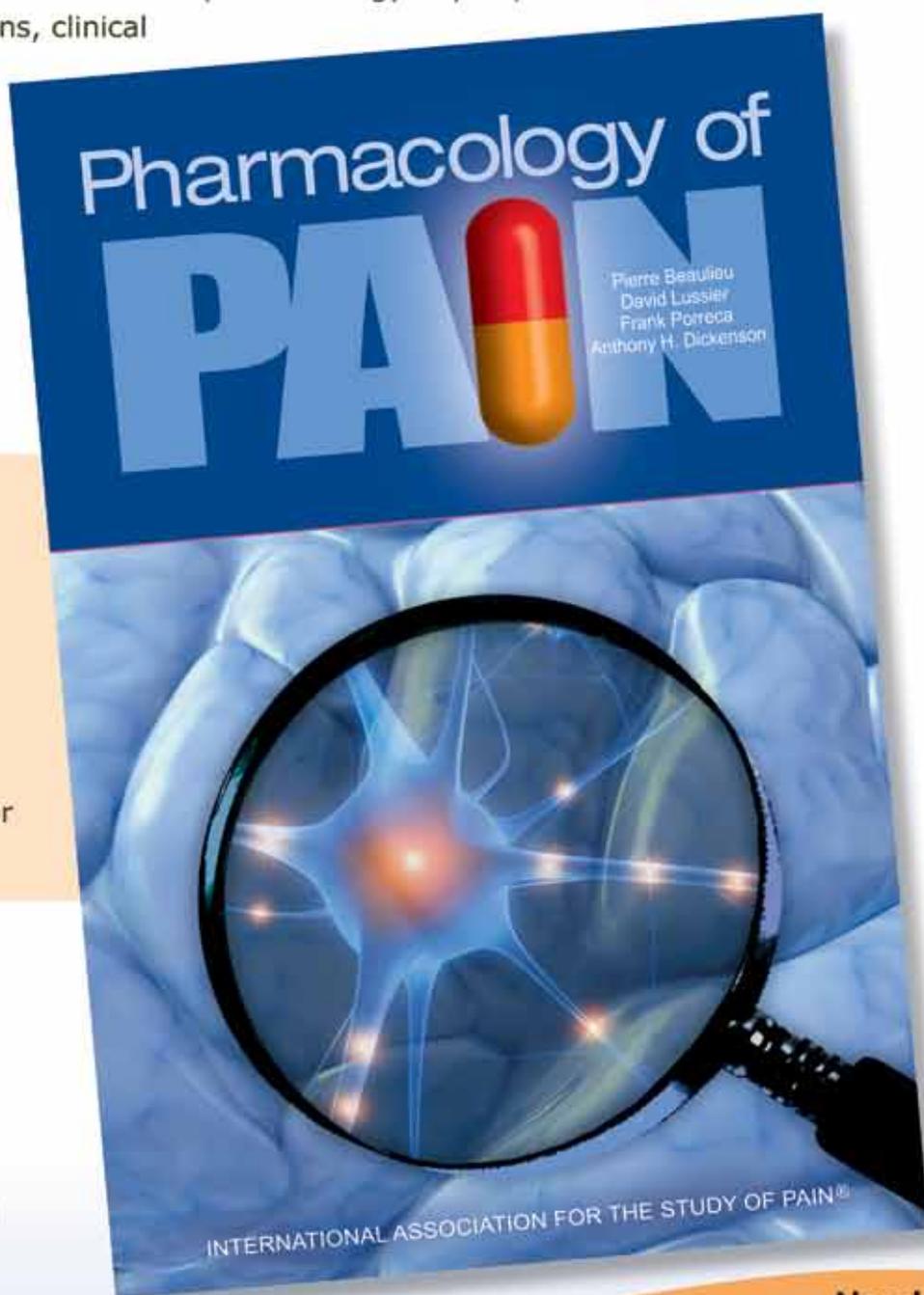
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Anthony Davenport
BPS Vice-President,
External Affairs

Since the foundation of the BPS in 1931 the Society has sought to support the international community of pharmacologists, and to foster the development of the discipline internationally. It is the remit of the External Affairs committee to coordinate these activities on behalf of BPS. The international community is reflected by our membership of over 2600 members (including many who are clinically trained) from over 60 different countries. So why do people join a UK learned society from so many countries?

A major function of the BPS is organizing meetings comprising invited plenary speakers, oral and poster communications, and the presentation of all aspects of basic and clinical pharmacology. A benefit of membership is that members can attend most of the meetings without paying a registration fee. Refereed abstracts arising from most meetings are published by the Society in PA2 online www.pa2online.org/. This provides an online forum for rapid communication of advances in pharmacological research to a wide audience.

During 2009, members could choose from over 20 days of meetings, including the flagship Winter meeting in December, which we held in London in the shadow of Big Ben and the Houses of Parliament. Over 700 delegates gathered over three days; the Summer meeting, another three day event held in Edinburgh; and smaller focused conferences of around 150 delegates or less. One of our regular focused meetings, Cell Signaling, Leicester, consistently attracts a strong international participation.

World Pharmacology

The BPS is a major sponsor and joint host with the Danish Pharmacological Society of WorldPharma 2010. This pre-eminent conference for pharmacology is under the leadership of Michael Mulvany (Secretary General) and Kim Brøsen (President) who have organized an eclectic and comprehensive programme seeking the fusion of basic and clinical pharmacology.

Three focused conferences at WorldPharma have been organized by the Society:

Mon 19 July FC 3 Ion channels in analgesia and anaesthesia. Conference leaders: Clifford Woolf & Nicholas Franks.

Wed 21 July FC13 Maximising benefits and minimising harms from drugs. Conference leaders: Kevin Park & Munir Pirmohamed.

Wed 21 July FC15 Endothelium in health and disease. Conference leaders: Chris Garland & Arthur Weston.

European Pharmacology

In July 2008, the BPS hosted and provided substantial financial support to the Federation of European Pharmacological Societies Congress (EPHAR) in Manchester under the chairmanship of the enthusiastic champion of pharmacology, Arthur Weston. Nearly 800 participants attended from 49 countries with BPS bursaries supporting the attendance of delegates from 16 countries. This enabled scientists, who might not otherwise have been able to present their work, gain exposure to cutting-edge science, and to take advantage of networking opportunities with colleagues from all over the world. The BPS also collaborates with cognate societies to host joint meetings, most recently with Deutsche Gesellschaft für Pharmakologie and Deutsche Gesellschaft für Klinische Pharmakologie und Therapie in Dresden, May 2009, organized by Karsten Schrör (Düsseldorf), Wilhelm Kirch (Dresden) and Mandy MacLean (Glasgow).

Future meetings in 2010 include:

- Cutting Edge Concepts in Lung Pharmacology (October)
- 8th James Black Conference - Platelets (November)
- General and Advanced Receptor Theory Workshop and Pharmacology in Stem Cell Research and Regenerative Medicine Workshop. Part of the BPS Winter meeting. (December)

International Meetings in 2011 that the BPS will host include the 12th International Conference on Endothelin, (ET-12) in Clare College, Cambridge and, to coincide with the Olympic Games in 2012, a Human and Exercise Physiology themed meeting jointly with the Physiological Society.

Publications

The Society publishes two journals that cover the whole spectrum of pharmacology; the British Journal of Pharmacology (BJP), published bi-monthly; and the British Journal of Clinical Pharmacology (BJCP), published monthly.

The decision to publish both journals with Wiley-Blackwell has led to the re-launch of BJP in 2010 covering all aspects of pharmacology from molecules to man; translational and integrative bioscience; and a host of new features including:

- Free to author colour in print and online and no handling or page charge
- Open Access policy that meets all funding body requirements

- PowerPoint downloads of all figures, downloadable movies and other supporting information files
- Linked commentaries on exciting or controversial papers
- Press releases on newsworthy papers

These new initiatives ensure the widest readership of papers in a journal that already has a highly competitive impact factor of 4.902. BJP continues to retain its international appeal with half the editorial board, under the Editor-in-Chief, J.C. (Ian) McGrath, drawn from outside the UK, with original submissions during 2008-9 coming from 52 countries.

A key feature of both journals are themed issues and sections on hot topics in pharmacology, many arising from original manuscripts and reviews linked to specific conferences and meetings organized by BPS, and other organizations. Recent examples in BJP include:

Molecular Pharmacology of G Protein-Coupled Receptors
www3.interscience.wiley.com/journal/123317001/issue

Edited by Roger Summers, many of the papers arose from material presented at the 5th International Molecular Pharmacology of G Protein-Coupled Receptors meeting held in Sydney, Australia in late 2008.

QT Safety

www3.interscience.wiley.com/journal/123244325/issue

This themed section focuses on drug-induced toxicities associated with prolongation of the cardiac QT interval based on communications presented at a symposium organized under the auspice of EPHAR 2008 by Jean-Pierre Valentin.

Imaging pharmacology

www3.interscience.wiley.com/journal/123300981/issue

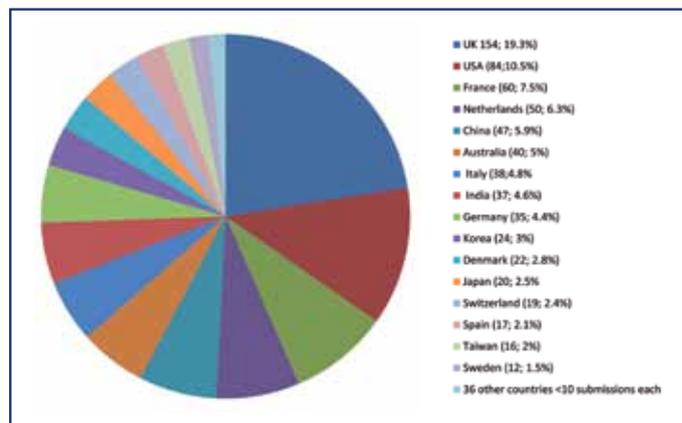
Reviews and original articles from two symposia at BPS Summer Meeting, Edinburgh 2009 on Developments in Receptor Imaging and Imaging and Targeting Inflammation in Stroke and Atherosclerosis edited by Anthony Davenport and Craig Daly.

The BJCP, under Editor-in-Chief Jim Ritter with a management board covering Australasia, Europe, and America, together with an international editorial board, seeks to bridge the gap between the medical profession, clinical research, and the pharmaceutical industry. Papers and reports are published on all aspects of drug action in man, including invited review articles, original papers, short communications and correspondence. Submissions in 2007-8 came from 47 countries. The journal features lively editorials and articles which regularly elicit press releases and media interest, and awards an annual prize of £1000 to the author of the best published paper.

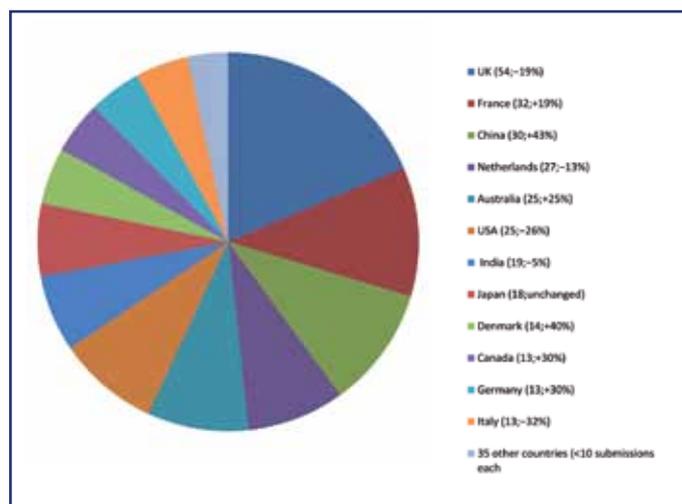
Guide to Receptors and Channels (GRAC)

GRAC is now in its fourth edition under the editorship of Stephen Alexander, Alistair Mathie and John Peters with input from international consultants. Through the support of Pfizer the paper version can be on every member's desk or free online via www.brjpharmacol.org/view/0/GRAC.html.

This Hitchhiker's Guide to Pharmacology in 254 pages is divided into seven sections. Pharmacological targets are mainly restricted to one page with concise information on nomenclature, pharmacological tools, suggestions for further reading and a buyers guide. The aim is to provide information succinctly, so that a newcomer to a particular target group can identify the main elements 'at a glance'.



BJP Article submissions by country of origin



BJCP Article submissions by country of origin

IUPHAR-DB

The IUPHAR database (www.iuphar-db.org/) has been developed by a team, led by Tony Harmar (University of Edinburgh), on behalf of the International Union of Basic and Clinical Pharmacology Committee on Receptor Nomenclature and Drug Classification (NC-IUPHAR) with donations from a number of pharmaceutical companies, grants from ICSU and the BPS in a joint initiative with GRAC. This publicly-accessible relational database contains all the essential pharmacological, chemical, genetic, functional, and anatomical information data for 77M GPCRs and voltage-gated ion channels, with ligand-gated ion channel and nuclear receptor data under development. The content of the database represents more than a decade of work by ~60 subcommittees (comprising over 700 international experts from academia and industry) and members of NC-IUPHAR peer-review the content. The site is regularly used by scientists from >100 countries.

Joining the Society

If you are not already a member, the Society offers membership at all career stages Undergraduate, Postgraduate, Associate, Full and Fellowship and enjoy free access to the full online versions of BJP and BJCP, free or discounted attendance at meetings, publication of abstracts in pA2online. Details of how to join can be found on the back page.

Visit us at Worldpharma, (stand 20) to pick up free copies of the current editions of BJP, BJCP and GRAC.

Anthony Davenport, Vice President, External Affairs

Discovering and developing new medicines that will benefit patient lives is the ultimate goal for people entering a career in the pharmaceutical industry. Unfortunately, the introduction of new medicines has decreased during the last decade despite increased investments. The role of translational pharmacology in drug discovery and development will be discussed as an area of future focus.

Scientific knowledge and information is increasing continuously, and technologies are advancing in a way that some years ago we were not able to imagine. Investments in research and development (R&D) by the pharmaceutical industry and others have increased tremendously during the last decade. Despite the financial investments and expanded scientific and technological knowledge, the benefits of delivering new and better medicines to patients and society have not followed the same trend. The approval and introduction of new drugs has not increased but unfortunately follows a more downwards looking trend. In particular this has been the case for new drug classes introduced by the biggest companies in the industry.

It is always possible, and tempting, to focus on explanations outside an area of immediate control. Regulatory requirements have changed with an increased focus on benefits in relation to safety risks, but another area with more challenging requirements is the demand for a clear differentiation between already available medicines related to benefits for patients versus the pressure to achieve a satisfactory reimbursement position.

If we instead focus our attention on aspects under the control of a R&D organization and the pharmaceutical company itself, we should pay attention to how tremendous advancements in science and technologies are used, and integrated, to discover and develop new medicines.

The cornerstone of drug discovery and development is the need to define biological mechanisms and readouts that will give beneficial effects to patients if modulated in an appropriate way. Translational pharmacology is the integrated theoretical and practical fundament to: establish these biological ideas; select the appropriate molecule needed to modulate them in the right manner based on pre-clinical models; and subsequently to study the hypothesis to see if it will give the desired benefits in patients. These basic principles were used in the past to bring new medicines to patients and they still apply today, but with the advantage of the more extensive scientific information and technical capabilities that are now available.

The most interesting aspects of working in the area of translational pharmacology are the true multidisciplinary elements of the work, covering understanding of pre-clinical and clinical disease biology and the knowledge around specific compound properties. To successfully discover new molecules that may have the potential to treat patients, you are required to understand the patient's situation, the disease biology, and how the disease is currently treated. This information will make it possible to define novel mechanisms that may benefit patients if they are influenced by molecules in a certain way. You will need to define how compounds will be documented in order to build confidence around, and to ultimately prove the hypothesis validity.

The interplay between disease biology and the pharmacological properties of compounds in different *in vitro* test systems, animal models, and ultimately patients make translational pharmacology truly fascinating. The true challenge is to be able to predict from pre-clinical experiments and data if a compound will have the desired attributes, and profile to influence the disease biology in a way that will achieve beneficial effects in patients. By today's ever increasing scientific and technical knowledge a key question is how to bring these aspects together and integrate them in a drug project. In order to do this one needs to understand the technology and the science, but even more importantly be able to integrate and conceptualize testable hypotheses. By establishing these hypotheses, suitable compounds could be selected based on *in vitro* assays and models. In order to understand the pre-clinical and clinical experimental results concentration effect relations need to be defined.

It is equally important to understand the duration and concentration effect relationship to the primary desirable effect as possible side effects. By doing this in a rigid manner you will be able to decide if the compound(s) available will modulate the mechanism in order to deliver beneficial effects according to your hypothesis.

This important area of integration between science, technologies and compounds is the key to translational pharmacology, and enough attention has been applied to advance this area in the same way as science and technology have progressed.

Why would an emphasis on translational pharmacology increase success rates in R&D? The reasons for high attrition rates are of course multiple and difficult to predict e.g. lack of efficacy, toxicology and clinical safety.

A key component that an increased focus on translational pharmacology will deliver is an improved and more robust understanding of the interplay between the biology and the properties

of compound(s) brought forward in clinical testing. This will address the key questions, based on an understanding of effect concentration and duration relationships. By focusing on this, together with the definition of a testable translational hypothesis based on an understanding of the disease, and utilization of cutting edge technologies, the likelihood of success will increase by addressing the questions in a more stringent way.

Stop/go decision for projects could be made at an appropriate time based on well defined criteria and experiments. Risk will be more clearly articulated in relation to both biological aspects and compound properties. By being aware of these risks, experiments will be done to reach conclusions on the prospects allowing compounds to be taken forward. This integration will address key biological questions so that early decisions can be taken to move forward or not for a specific mechanism and/or compound.

In an environment where the demand for innovation is increasing, a key challenge is to select biological mechanisms and compounds that jointly have the best possibility to create successful medicines. A focus on translational pharmacology will be a major factor in achieving this.

Håkan Wennbo, MD, PhD

Innovative methods in teaching pharmacology across the globe



Ian Hughes
Leeds University

Ian is a Fellow of the British Pharmacological Society and has been involved in developing computer-based learning programs since 1978. He directed the 'pharma-CAL-ogy' project and a European network of pharmacologists supported by EU funding. Ian has written software simulating various pharmacological preparations, and currently holds a part-time appointment as Professor of Pharmacology Education in the University of Leeds.

We teach pharmacology in a multitude of contexts and circumstances, for example, to students of medicine, dentistry, nursing and pharmacy and also as a science discipline in its own right. In addition, pharmacology is taught as service teaching to students taking degrees in other science disciplines, and to a variety of healthcare disciplines such as optometry, osteopathy, veterinary science and others. Pharmacology is taught at Masters level and in a number of professional development contexts, nurse prescribers for example. One size does not fit all and the content, pace and style of courses for this variety of students is very different.

The aims of teaching pharmacology are shown in Box 1. Few would disagree with aim 1. Aim 2 is more contentious but increasingly there is a need to make sure that the student customers, paying increasing fees, perceive they are getting value for money. There is often a reluctance to acknowledge that aims 3 - 7 have to be considered but, acknowledged or not, they are part of the world in which we live.

Across the globe, to greater or lesser extents, pharmacology is under a variety of pressures as shown in Box 2.

With regard to changes in educational tools and styles, it is not just the availability of new technologies and methods as learning aids which has brought their use to the fore

but also the extent to which they enable different sorts of provision of teaching. Thus distance learning, franchised courses, provision on split (international) sites, short or long term placements, partial course provision and satellite campuses have all become common, and the increasing use of English as the language in which teaching is provided is promoting competition between universities.

With regard to changes in learning opportunities, the changes in educational tools, styles and needs fall into four categories:

1. Technical

The changes in information technology have made available: video on disc; video conferencing; simulations; interactive computer-based-learning and tutorial/self-directed learning packages; the internet; social networks; virtual labs and lectures; virtual teacher; distance learning; mobile phones; blended learning; virtual or managed learning environments; student response indicators (clickers); blogs and podcasts. How best to use these resources to promote learning is the question.

2. Person based

Students themselves have become a learning tool and participate in the learning process not just to learn but also as a resource. The formation of teams with responsibility for shared learning is developing quickly.

3. Teaching/assessment methods

Peer teaching, peer assessment, self directed learning, independent learning, Problem-based learning (PBL), scenario based teaching, integrated medical course, extended matching set questions, computer marked assessment are also used increasingly.

4. Learner's needs

Differentiated learning, interprofessional teaching, generic skills (including ethics, sustainability, team working, communication, information handling), individualized teaching, feedback and pastoral care/support (monitored, prompted and controlled by computerised system delivered through a virtual learning environment/mobile learning environment).

Most of these will be familiar to some extent but three are worth some clarification:

1. Differentiated learning

This is where it is expected that students will have different levels of achievement. It is important because each student (the truly exceptionally able individual and the more able group present in any cohort) should be developed to their limit. It is not clear how this can best be achieved within resource constraints, or how it interacts with peer pressures to conform, these pressures are very strong in countries that do not have a student body which values excellence. Full development of these students is essential if the discipline is to advance and the country benefit from the economic potential of these students. Individualized teaching is likely to become an expectation as education follows consumerised services, such as healthcare and social care, all of which have become focused on individual provision, choice, and user needs. As students pay more fees they will increasingly demand value for their money.

2. Interprofessional teaching

This is where different professional groups are taught together so they each get a better perspective on the others' role in the healthcare process which is of course increasingly delivered in multidisciplinary teams. Pharmacology in particular is involved in the professional interplay between medicine, pharmacy, nursing, and other healthcare professionals who apply pharmacological knowledge. It is not clear how the objectives of interprofessional teaching can best be delivered and if this should be done at all at an undergraduate disciplinary level. It may be better achieved by qualified professionals each bringing their own knowledge to a disease focused forum.

3. Peer assessment

Literally, students marking other students' work. There is now evidence to suggest this is a win-win scenario. Staff time is saved and students get better feedback and learning, not only of the subject area, but also around critical appraisal and self criticism of their own work (surely the bedrock of any scientific worker).

For the individual teacher (who may also be expected to be a researcher, entrepreneur, administrator and contributor to the local community), the issue is around having the time, and developing the expertise to make changes and utilize these developments in their courses. However, these developments have been made and are already in use somewhere in the world. Rather than spend time developing them from scratch, it is better to utilize the work already done by others, or to collaborate with others to share the load. National and international collaboration is routine in research but much less common in teaching, possibly because other universities are seen as competitors in the increasingly fierce global competition for able students.

In spite of this, many pharmacologists have made their teaching developments available to others (sometimes at a cost). The problem is that there is no effective mechanism by which pharmacologists can share this material which is currently located on dozens of different sites. It would be useful if, perhaps through a web-based mechanism, a repository of useful resources or website locations could be maintained for use by all. Until such a facility becomes available the trick is how to find teaching resources.

BOX 1 - Aims of teaching pharmacology

1. To ensure the students have what they need for their varied careers. Knowledge (subject specific and non-specific), skills (subject specific and generic), attitudes (ethical, professional, personal)
2. To provide the students with what they want (satisfied customers, National Student Survey ratings, competition for students)
3. To generate income for the faculty (income or surplus? General drugs/medicines teaching as well as specialized pharmacology?)
4. To meet employers' needs (speed of job market change?)
5. To enable more research to be carried out (minimize staff time involvement in teaching, appoint on research criteria, subsidize research funding)
6. Widen participation (while maintaining standards)
7. Meet the needs of the regulator (General Medical Council, General Pharmaceutical Council, etc)
8. Provide a satisfying and enduring career for professional academics (clinical and non-clinical)

BOX 2 - Pressures on pharmacology around the world

1. Changes in the discipline
2. Changes in educational tools and styles
3. Changes in the environment
4. Changes in customers expectations
5. Changes in academic pharmacologists

Good starting points in addition to Google are:

- **IUPHAR Section on Teaching website**

www.IUPHAR.org freely available, editable and hangeable, no copyright problem; simulations; teaching scenarios; tutorial materials; links

- **Higher Education Academy Subject Centres in the UK Centre for Bioscience**

www.bioscience.heacademy.ac.uk imagebank; searchable knowledgebase; also www.heacademy.ac.uk for other centres (medicine; health subjects)

Higher Education Academy Centre for Health Sciences and Practise

www.health.heacademy.ac.uk/

Higher Education Academy Centre for Medicine, Dentistry and Veterinary Medicine

www.medev.heacademy.ac.uk/

- **British Pharmacological Society**

www.bps.ac.uk
computer assisted learning packages; MCQ; practicals; teaching scenarios; clinical pharmacology; links

Some varied resources are listed below, though for full access you may have to contact the named owners:

DOG LAB Vincenzi

courses.washington.edu/chat543/cvans/

CVS MODULE Cracowski

www.sante.ujf-grenoble.fr/SANTE/alpesmed/index.htm

COURSE Allain

www.med.univ-rennes1.fr/

LABS Dempster

spider.science.strath.ac.uk/sipbs/staff/John.Dempster.htm

DATA EXERCISE Jarrott & Davies Pharmacologist, 44, A4(9.2)(2002)

HYPERTENSION RESOURCE Hughes & Atkinson
CD download from BPS website

Try it out and see what a rich set of resources, developed by pharmacologists across the globe, are available to help you teach and your students learn.

Ian Hughes, Leeds University

Alternatively, AND MUCH BETTER, get the students to find materials for you. They are amazingly effective in pulling out excellent resources for pharmacology teaching from all over the world. An ability to find and assess information on the internet is a required generic skill, and this requirement can be exercised by giving the students a set task, to find and critically assess a pharmacology teaching resource from the internet.

This task exercises searching skills (the student should document the search strategy they utilized), criteria setting (what makes a good teaching aid?), critical evaluation (how were these applied?) and, especially if done in a small group other generic skills, and ultimately,

provides you with a host of resources you can use.



Michael Eddleston
University of
Edinburgh

Michael Eddleston studied Undergraduate medical sciences at Cambridge before going to La Jolla, California, to do a PhD at the Scripps Research Institute with Professor Michael Oldstone on the brain's response to infection. He returned to Oxford to clinical school - where he met David Warrell and was sent to Sri Lanka to study snake envenoming during a summer holiday. Michael witnessed self-poisoning for the first time and became fascinated by clinical toxicology/ pharmacology. Michael returned to Sri Lanka twice over the next year before finally taking a year off to write an Oxford Handbook. During this year, Michael carried out his first RCT on anti-digoxin Fab. He was awarded a Career Development Fellowship in Tropical Medicine by the Wellcome Trust in 2002 with which he set up a cohort of acutely poisoned patients, into which he nested two randomized controlled trials (RCT). Michael returned to Edinburgh in 2005 to complete training in CPT and is now a Scottish Senior Clinical Research Fellow, carrying out clinical and public health research in Sri Lanka and animal research using minipigs in Edinburgh. He is also an honorary consultant in clinical toxicology working for the National Poisons Information Service in Edinburgh.

When one thinks of tropical medicine, one does not usually think of poisoning and suicide. But in parts of rural Asia, intentional self-poisoning with plants and pesticides causes more deaths than all tropical infectious diseases combined. Every year, at least 250,000 people die from pesticide self-poisoning and several thousand die from plant poisoning. The World Health Organization (WHO) now considers pesticide self-poisoning to be the single most important means of suicide worldwide.

I first came across the problem during a medical school project carried out in Sri Lanka. Professor David Warrell of Oxford University and Professor Rezvi Sheriff of Colombo University had invited me and a friend to work on a clinical trial of an antivenom for Russell's viper (*Daboia russelli*) envenoming. Unfortunately, the season was wrong, with little rainfall, meaning that people were not out in the paddy fields and few bites occurred. However, sitting on the adult medical wards in Anuradhapura district hospital, it was obvious that the major clinical problems were self-poisoning with seeds of the yellow oleander (*Thevetia peruviana*) tree or with organophosphorus (OP) and organochlorine pesticides. It was my first exposure to self-poisoning and to clinical toxicology; fifteen years later I am still working on these same problems.

The oleander poisoned patients developed digoxin-like toxicity, due to cardiac glycosides in the seeds. Patients vomited and defecated the vilest green-coloured liquid, while complaining of abdominal pain. Cardiotoxicity took the

form of severe bradycardia, developing into second and third degree blocks, and sometimes DC-cardioversion resistant VF. Treatment was restricted to isoprenaline or atropine infusions and an urgent transfer to a tertiary hospital for temporary cardiac pacing. Many patients did not survive the transfer or the pacing. OP poisoning was dramatic to see. Overstimulation of muscarinic receptors due to inhibition of acetylcholinesterase caused production of fluid - patients were covered with sweat and their lungs filled with fluid, some even frothed at the mouth. Atropine was able to bring these features under control but failed to prevent acute respiratory failure. The unfortunate ones then developed neuromuscular dysfunction, sometimes called the intermediate syndrome. These patients required mechanical ventilation for 1-3 weeks until the neuromuscular junction had repaired itself. During this time, they were at risk of pneumonia. Around half of the patients intubated and admitted to intensive care did not survive to discharge. Overall, the case fatality for OP poisoning was around 20%.

This high case fatality for OP poisoning was actually better than it used to be. The Pesticide Registrar in Sri Lanka, the government official who determined which pesticides could be used in agriculture, had taken an active role in trying to prevent pesticide-associated deaths. Due to the introduction of pesticides into practically all rural households in the Green Revolution in the 1950s and 60s, the suicide rate in Sri Lanka and other rural Asian countries rose exponentially through to the 1980s. A Sri Lankan rate of 5/100,000 throughout the first half of the 20th century rose to a peak of 43/100,000 by the end of the 1980s, one of the highest in the world. Of note, this was not due to a high rate of self-poisoning or attempted suicide but to a high lethality of self-poisoning - 10-20% compared to <0.5% in the UK.

The Registrar, Dr Gamini Manuweera, responded to this major public health problem by banning the most toxic WHO Class I OP pesticides in the early 1990s. Immediately the suicide rate began to fall. Unfortunately, an unpredicted consequence occurred - farmers switched to a less toxic (WHO Class II) organochlorine pesticide called endosulfan. Poisoning with this pesticide, unlike the highly toxic OPs, was completely untreatable. Patients presented with status epilepticus that usually did not respond to any combination of anticonvulsant drugs. Around 30% of patients died.

One knew in advance when these patients were being brought to the ward since they rattled against the metal trolleys, a sound that could be heard from some distance. Intravenous diazepam and phenobarbital could then be drawn up in the two minute warning we were given.

Dr Manuweera again responded to this problem by banning endosulfan three years after the problem began to grow. Following these two bans, the suicide rate fell by more than 50% - the greatest fall in suicide seen anywhere in the world. This government official's actions have saved an estimated 17,000 lives in Sri Lanka over ten years. However, even with these effective bans, people continue to die from pesticide and plant self-poisoning in Sri Lanka. The case fatality for acutely poisoned patients in Anuradhapura is still around 7%, with much higher case fatality for particular compounds. Better treatments are urgently required.

Over 30 years ago, anti-digoxin Fab fragments were developed in New York for the treatment of digoxin poisoning. Although used for a few cases of poisoning with the related common oleander (*Nerium oleander*), there was insufficient knowledge about their effectiveness in yellow oleander poisoning for these expensive drugs to be used in Sri Lanka. I therefore took a year off medical school in 1996-7 to return to Sri Lanka to perform a RCT comparing the effectiveness of anti-digoxin Fab with placebo, in addition to standard treatment, in moderate-to-severe yellow oleander seed poisoning.

Working with colleagues from Professor Sheriff's department, we first performed a small dose-finding study in the Colombo CCU. This unit was busy, receiving oleander-poisoned patients 24hrs/day from across the island for temporary cardiac pacing. To do this study, I slept on Professor Sheriff's examination couch, a short walk from the CCU to which I was called whenever a potential patient arrived. An ECG was rapidly carried out to determine whether the patient had substantial cardiotoxicity and eligible for the study.

A pacing wire was inserted into all patients with cardiotoxicity; those that gave consent to the RCT were randomized to either placebo or Fab. Despite the trial being blind, there was an obvious and near immediate effect in those receiving Fab. They felt rapidly better, with their abdominal pain fading. Their cardiac rhythm started improving over the next 30 minutes, with a sharp rise in heart rate; subsequent unblinded analysis showed that 50% had returned to normal sinus rhythm (judged as a completely normal three minute rhythm strip) within three hours compared to 30 hours in those receiving placebo.

The anti-digoxin Fab was briefly introduced into clinical practice and found to be effective. But unfortunately, the company was taken over twice after the study was done and, although the price was reduced compared to the cost in the West, it was still considered too expensive for Sri Lanka. Hopefully, an Indian antivenom producer will start making the antitoxin one day, allowing it to be used affordably across south Asia.

An alternative, cheaper treatment for oleander poisoning might be activated charcoal since cardiac glycosides have an enterohepatic circulation. We therefore planned a large RCT comparing no activated charcoal with multiple doses of charcoal in 2800 patients (1400 per arm) with pesticide or oleander poisoning. To determine whether any effects were due to all six doses or to the first dose, we added a third single dose charcoal arm to the study.

We aimed to recruit these patients from 2-3 hospitals, expecting to recruit up to 20 patients a day. To do this we developed a programme for a handheld computer that would allow us to collect patient data on recruitment and randomize them. This system worked well, allowing us to collect baseline data and randomize a patient within five minutes of them giving consent. This speed and simplicity was essential as patients often needed urgent treatment, charcoal administration and the patient flow was relentless.

This study went well until personal politics intruded. A doctor in one of the study hospitals disliked me, my Sri Lankan head of department and a cardiology colleague. I was accused of killing an OP-poisoned patient by giving him activated charcoal. This news was first announced on national radio before being taken up by national newspapers; the local coroner ordered the study to be stopped. However, he did not follow correct legal procedures and the hospital refused to follow the order. Therefore, the local doctors' union made a decision that no doctor could work with me on the study. This effectively prevented the study from continuing in this hospital.

Attempts to stop the study in the two other hospitals did not succeed due to local support from the hospital staff. However, it was finally shut down in these hospitals after pressure by the doctors' union resulted in a central order from the Ministry. The next three months were difficult, as we tried to find out what changes were needed to restart the study. We did eventually restart; a colleague who had faced similar troubles doing clinical trials elsewhere in SE Asia predicted, "you can only start again if the local doctors and people make the decision that they really want you to start". It was finally the provincial government that made this decision, bypassing the national government.

This study ran for 29 months and recruited 4,632 patients. Unfortunately, we found no significant benefit from routine provision of either single or multiple doses of activated charcoal to acutely poisoned patients.

We have continued to do RCTs in these hospitals through the South Asian Clinical Toxicology Research Collaboration (SACTRC). A study of the antidote pralidoxime in OP poisoning showed that it offered little or no benefit for moderately toxic Class II OP pesticides. A public health cluster RCT will start later this year, randomizing 162 villages to receive a storage container for their pesticides to see whether this approach can reduce the incidence of pesticide poisoning. Future RCTs will include novel therapies for the lung complications of aspiration.

Pesticide and plant poisoning in Asia will remain important areas of study for many years to come.

**Michael Eddleston, Scottish Senior Clinical Research Fellow,
Clinical Pharmacology Unit, University of Edinburgh**



Martina Schmidt
University of
Groningen

The worldwide Rosalind Franklin Fellowship Programme at the University of Groningen (RUG) is named after the female English scientist Rosalind Elsie Franklin and her pioneering discoveries that led to our understanding of the structure of deoxyribonucleic acid, DNA. Based on her X-ray photographs of DNA, James Watson, Francis Crick and Maurice Wilkins received the Nobel Prize for the double-helix model of DNA in 1962. The Faculty of Mathematics and Natural Sciences of the RUG introduced, in 2002, the Rosalind Franklin Fellowship to attract ambitious female researchers. Equipped with considerable financial start-up support and a personal position for five years, successful Rosalind Franklin Fellowships end up in full Professorships. The Rosalind Franklin Fellowship initiative is unique in Europe and aims to raise the presence of women at the highest levels of the institution.

The Helsinki report (2002) indicated that in the Netherlands, women comprised less than 8% of the permanent scientific staff in exact and life sciences. This represented one of the lowest percentages in the European Union, although Dutch women contribute to a similar proportion of PhD degrees compared to other European countries. Due to this programme, currently 13% of professors at the RUG are female. In particular, the Rosalind Franklin Fellowship programme succeeded in enlarging the international research carried out at the University of Groningen, as top female researchers were recruited during the last selection process, to the most northern city of the Netherlands, Groningen.



Rosalind Franklin Symposium: May 2009,
Academic Building RUG

To date 23 Rosalind Franklin Fellows have started their careers at the University of Groningen, and exceptionally successful candidates have been promoted to (full) professors. Thereby, the RUG re-defined the rejoinder, "Women simply do not apply, we would like to appoint women, but they do not seem to out there", often used by selection

committees when questioned why no women were interviewed. The Rosalind Franklin Programme from the RUG reports a completely different story. Top women scientists are "out there" and if the positions are attractive and allow a wide spectrum of scientific endeavour, women most certainly do apply.

The RUG advertisement of the Rosalind Franklin programme appeared in Nature, Science and several Dutch newspapers. Despite, or maybe due to, the high pre-requisites such as postdoc experience abroad, publications in top international journals, and evidence of international recognition, hundreds of applications from all over the world reached the RUG. Applicants came from the Netherlands, other European Countries, and from the US, representing a broad spectrum of disciplines including biology, mathematics, chemistry, physics, biochemistry, pharmacy, astronomy and computer sciences. Selected candidates were invited to Groningen to present a "Rosalind Franklin lecture" and to envision their future research ambitions to the selection committee. The committee was supplemented with additional scientific experts from the faculty to cover the distinct disciplines of the top female scientists. This procedure led to a considerable increase in the percentage of women in the permanent staff in the faculty, thereby making the participation of women at the RUG more visible. The Rosalind Franklin initiative succeeded in creating a nucleus of ambitious female scientists who serve as role models for female PhD students aiming for a career in science. To maintain the highly-dynamic inspiring scientific research atmosphere at the RUG, Rosalind Franklin Fellows are supported by a special mentoring system (further information at www.rug.nl/gmw/onderzoek/rff/index).

The RUG agreed, with the Faculty of Mathematics and Natural Sciences, the Medical Faculty, the Faculty of Applied Linguistics and the Faculty of Art, to continue with the Rosalind Franklin fellowship programme to further increase the percentage of female professors by 2012 to 25%. The programme is supported by initiatives of the Netherlands Organization for Scientific Research, the Koninklijke Nederlandse Akademie van Wetenschappen and the Dutch Government.

The Rosalind Franklin Programme has proved that sufficient numbers of talented women are engaged in science, and are ambitious enough to climb the academic ladder. A Rosalind Franklin Symposium, in conjunction with representatives of the Dutch Royal family and the Dutch government, was held at the RUG in May 2009.

Since its foundation in 1614, the University of Groningen has enjoyed an international reputation as a dynamic and innovative centre of higher education offering high-quality teaching and research. Balanced study and career paths in a wide variety of disciplines encourage the 25,000 students and researchers to develop their own individual talents. Belonging to the best research universities in Europe and joining forces with prestigious partner universities and networks, the University of Groningen is truly an international place of knowledge.

The broad spectrum of the applicants perfectly matched the intentions of the Rosalind Franklin programme to further increase the international reputation of the RUG, and to improve its state-of-the-art research institute, the European Research Institute on the Biology of Ageing and Healthy Ageing. Indeed, the University of Groningen was recently ranked fourth on the international list of 'Best Places to Work in Academia 2009'. It has been proposed that the RUG owes its high ranking, in part, to the Rosalind Franklin fellowship programme.

As a Rosalind Franklin Fellow and a woman in pharmacology, it is worth emphasizing that at the RUG top female researchers experience a unique scientific research environment, where feminine skills; conflict management, tolerance, and communication, are naturally integrated.

Rosalind Franklin Fellow: Department of Molecular Pharmacology

In 2006, I started as Rosalind Franklin Fellow in the Department of Molecular Pharmacology. Based on my scientific record, international achievements, and reputation in the molecular regulation of phospholipases, G proteins, and lipid and protein kinases by membrane receptors, and the discovery of novel signaling cascades in various cellular systems, I was also appointed as Professor in Molecular Pharmacology at the Pharmacy, Faculty of Mathematics and Natural Sciences. The hugely inspiring scientific atmosphere at the RUG contributed tremendously to my research. My current research focuses on signaling pathways being executed after clustering of molecular partners in defined subcellular compartments (signalosomes) that enables cells to exert highly specialized tasks. Since 2006, we unravelled the organization of recently discovered signaling components within functional units by biochemical, molecular and cell biological methods, and defined how these novel pathways regulate physiological processes in cell, tissue, and organ systems areas of integrative pharmacology, and translational medicine. We have directed our attention to chronic inflammatory disorders, as evidence exists for a role of our signaling components - exchange protein directly activated by cAMP, phospholipase D - in vascular smooth muscle cells, neuronal cells, immune cells as well as cardiomyocytes and airway smooth muscle cells (Oude Weernink et al, 2004; Peters et al, 2006; Schmidt et al, 2007; Oude Weernink et al, 2007).

Many devastating diseases, e.g. cancer, type-II diabetes mellitus, Alzheimers's dementia, cardiovascular and airway diseases are associated with defective or derailed signaling processes, and research into the control of these processes is clearly of great public and social importance (Grandoch et al, 2010). Our research benefits from the multidisciplinary approach at the RUG, which is organized with the Graduate School of Drug Exploration, TopMaster Medical Pharmaceutical Drug Innovation (MPDI), International Research Training Group GRK880, the Centre for Behavioural and Neurosciences, and the Groningen Institute of Asthma and COPD (GRIAC). In addition we are continuing and forming new collaborations with local, national and international groups.

As a Rosalind Franklin Fellow and a woman in pharmacology, I am a board member of the Dutch Pharmacological Society, board member of GRIAC, chair of the MPDI programme and speaker of the GRK880. Such functions will certainly help to further increase the visibility of female researchers.

**Martina Schmidt, Rosalind Franklin Fellow
Professor of Molecular Pharmacology
University of Groningen**

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Sandwich degrees in Pharmacology at the University of Manchester



Arthur Weston
and Gill Edwards,
University of
Manchester

Gill Edwards is a Fellow and Council Member of the BPS. She recently took over from Arthur Weston as placement officer for many of the undergraduate Industrial Placements (including pharmacology) in the Faculty of Life Sciences at Manchester.

Arthur Weston is Leech Professor of Pharmacology in the University of Manchester and for the past 13 years, he has had major responsibility for Manchester's undergraduate Industrial Placement Programme. A former Honorary Treasurer and Council Member, he is a Fellow of the Society and currently a Senior Editor of the British Journal of Pharmacology.

Introduction

For more than 50 years, some British universities have offered four-year Bachelor of Science (BSc) degree courses in which undergraduates spend 12 months away from their parent University (usually in an industrial environment) in order to gain approved practical experience relevant to their degree. Since these industrial placements are typically between the second and third academic years, the associated degrees have become known as 'Sandwich Degrees' since the 12-month period of practical training is sandwiched between two periods (two years + one year) of formal academic study.



Figure 1: Mountain views in America or the delights of rural Germany await some of the Pharmacology placement students

The current BSc degree course in Pharmacology within the University of Manchester's Faculty of Life Sciences has roots that are more than 50 years old.

For approximately the past 15 years, students of not only pharmacology but also of related subjects like biomedical sciences, physiology and neuroscience have been able to graduate with a 'Sandwich' degree in their major subject (now known formally as a BSc degree in XX with industrial or professional experience).

In this article, we highlight the key features of the Manchester model of this uniquely-British four-year degree concept, the graduates of which, because of their high academic achievements and 12-months' research experience, are in great demand by employers throughout the world.

The course

Manchester BSc degree programmes with industrial or professional experience are four-year courses with years one and two comprising traditional lectures, practicals and tutorials. Year three is the 'Sandwich' or industrial training year while in year 4, students return to Manchester to complete their academic studies.

Within the Faculty of Life Sciences, any BSc course can have a sandwich component, depending on the availability of an approved placement and a suitably high-achieving undergraduate. With an annual undergraduate intake of approximately 600 students, up to 150 per year perform well enough (see Selection, below) to be allowed to try for a 12-month placement. On average, 80 of these will be successfully placed each year and around 40 of these students will undertake undergraduate programmes in which pharmacology is a significant study component. Of these, approximately 15 will graduate with a BSc in Pharmacology (or the joint degree of Pharmacology & Physiology) with industrial or professional experience.

The Placements - an eclectic mix in locations throughout the world

The majority of placement opportunities, particularly for pharmacology students, are within industrial organizations involved in the life sciences and particularly within the drug discovery industry. A significant minority, however, are at specialized research institutes located on a university campus. Pharmacology students can therefore find themselves at the heart of an industrial research complex or within a university environment with views over mountain ranges (**Figure 1**).

The degree programme is very much international and although more than half the placements are typically in the UK, the remainder are scattered throughout the world (**Figure 2**).

In respect of foreign languages, German is the key with 20% of students being located in German-speaking laboratories in Germany itself, in Austria and in Switzerland.

Goals

Universities are sometimes criticized for producing graduates who are unfit for purpose. The objective of the Manchester four-year BSc courses is to produce graduates who will be future leaders and wealth creators and who will specifically be:

- Industry-aware
- Independent thinkers
- Confident team players
- Innovative and motivated
- Aware of (and in some instances, skilled in) *in vivo* techniques
- Unequivocally employable

Selection - choose only the best

Preliminary screening in Manchester. The four-year degree course with industrial or professional experience is elitist and is only available to those students who perform exceptionally well in their first-year studies. Actual selection begins at the start of the student's second year; a minimum requirement of an 'upper second' performance in all key first-year study modules is a sine qua non as are excellent A-level grades (some companies require at least an AAB score). A tough interview with the placement officer weeds out any candidate who lacks motivation or who simply seeks a year of foreign travel outside the UK.

Interview by the placement giver. In general, most company placement givers begin to advertise their 12-month placements in late September/early October. Individual companies have their own specialized selection procedures that usually involve searching interviews and aptitude tests at the company's premises. A key Manchester 'rule' is that all students must immediately accept the first offer that is made to them; this greatly simplifies procedures and ensures that especially high-performing students are unable to benefit at the expense of others.

Special pre-placement training - *in vivo* preparation in Manchester

For decades (and generously supported with financial assistance from the BPS), all Manchester pharmacology students have completed the Home Office modules 1-4) in-house during their second year. Successful completion of the training enables them to obtain an Animals (Scientific Procedures) Act 1986 Personal Licence and to undertake the advanced pharmacology practical course in their final University year. An increasing number of placements involve *in vivo* techniques and thus prior completion of the Home Office course represents an invaluable benefit and is much appreciated by placement givers.

Manchester's special requirements: research projects and their assessment

A key feature of the Manchester sandwich degrees is that placements must not be simply 'work experience'.

Although students may spend some time doing routine procedures for the placement giver, each student must be given ownership of a specific project within an on-going research initiative.

The student's contribution is written up during their



Figure 2: Typical annual world-wide distribution of placements for Faculty of Life Sciences students from the University of Manchester

placement and submitted to the university as a completed 10,000-word document. Two faculty members independently assess this and, together with the outcome of a 45-minute oral examination, the combined mark contributes approximately 10% towards the student's final degree classification. Many of the project reports are strictly confidential; binding legal agreements cover their handling by the university using tight procedures that have been developed over the years.

Student support and duty of care

Although students are away for a 12-month period, Manchester retains significant responsibility for their welfare and it takes its 'duty of care' very seriously. The Faculty support team comprises a full-time administrator who assists the two placement officers. The students' Senior Advisor, together with the Faculty's Business Development Manager is also involved.

Every student remains in email contact with their placement officer and is visited once during their placement (usually after about 4 months) by a faculty member. This individual (often the student's personal advisor) makes a report and obtains a numerical performance assessment from the student's placement line manager. Towards the end of the project, there is a virtual visit by video link. During this, students present the results of their work (in Keynote or Powerpoint) and there is a further check on progress and performance.

Financial aspects - support from the EC's Erasmus programme

Students are paid during their placement and the exact amount varies from placement to placement. Manchester itself covers all the students' special insurance costs and seeks to ensure that all the student's reasonable living expenses are covered by the placement giver. Placements outside the UK and within the EC receive special support from the Erasmus Life-Long Learning Initiative. This currently amounts to a stipend of approximately €400 per month; it ensures that the additional costs associated with living within the EC (and outside the UK) are covered.

Publications and prizes

Through the generosity of Boehringer Ingelheim and Novartis Pharma, two prizes, each worth €500, are awarded during the students' final university year for the two best placement-project reports and their verbal presentation to a live audience.

The competition for these prizes is intense and the standard achieved is always remarkable. In 2009, Yiwen Dong (AstraZeneca; First-class honours, July 2009) went on to receive the GlaxoSmithKline Award for the Best Pharmacology Student in the Science Student of the Year SET Awards Ceremony in London (Figure 3). Furthermore, every year, the results of some placement projects are published in peer-reviewed scientific journals.

What happens to placement students?

Without exception, all students return for their final year having achieved the goals listed at the start of this article. In 2009, 40% graduated with first-class honours and the remaining 60% with upper seconds. Many also return fluent in a foreign language that bodes well for their future role in a global economy.

One of Manchester's first pharmacology placement students was Luisa Betts (Thomae, Germany). She graduated with first-class honours and completed her PhD in Pharmacology in the University of Oxford. She is now a senior analyst in the pharma team of a multinational merchant bank in the city of London.

Annie Geraghty is a more recent placement student (AstraZeneca). After graduating with the 'top first' in Pharmacology, she has just completed her PhD studies in Manchester and took up her appointment as Education Manager at the BPS Offices in Angel Gate on 2 June 2010. Her personal view of a 'Sandwich Degree' in Pharmacology follows this article.

Personal note

For one of us (AHW), it has been a real privilege to be involved in forming the careers of so many clever and highly-motivated young people.

With their enthusiasm and commitment, I know that pharmacology will continue to flourish not only in the present but also in the days that I will not see.

Gill Edwards* and Arthur Weston
Faculty of Life Sciences
University of Manchester

*Correspondence

gillian.edwards@manchester.ac.uk



Figure 3: Placement training can lead to prizes (eg. Yiwen Dong, GlaxoSmithKline SET Award Pharmacology Student of the Year 2009) or peer-reviewed publications (eg. Mageean & Büttner, 2010, Comb Chem High Throughput Screen 13:229-41). Yiwen and Craig are now PhD students at the Universities of Manchester and Liverpool, respectively

Annie Geraghty: industry placement. A student's perspective



Annie Geraghty, BPS Education Manager

Annie graduated from the University of Manchester, with a degree in Pharmacology, in 2006. she spent the third year of her degree on an industrial placement at AstraZeneca, looking at the effects of novel, anti-angiogenic anti-cancer agents on healthy bloody vessels. After finishing her degree, Annie started a PhD in Vascular Pharmacology, working with Professor Arthur Weston and Dr Gillian Edwards, again at the University of Manchester.

When I applied to study Biomedical Sciences at Manchester University I had no idea what the word 'pharmacology' meant. Studying some pharmacology units in my first year at Manchester opened my eyes and I became fascinated by the way that drugs work and their potential for making ill people better. In my second year I switched to a pure pharmacology degree and decided to take the opportunity to spend my third year on an industrial placement working for a pharmaceutical company, to see the application of pharmacology in action.

Manchester University sends a large number of students on industrial placement each year and I had friends who went all over the world, from Florida to Germany, Switzerland to the Gambia. However, having fallen in love with Manchester during my first two years at university I chose the slightly less exotic option of applying for a placement at AstraZeneca in Alderley Edge, Cheshire. The application process was competitive and was very good preparation for future job hunting. I had to submit a CV and a covering letter and then attend an intense assessment day during which we were interviewed by different panels, tested on our scientific knowledge, and shown around the site. Subsequently I was offered a place working in the Cancer Department.

At that time, AstraZeneca were developing drugs to target tumour vasculature, with the hope of cutting off blood supply and starving the tumour of nutrients and oxygen. The team I worked in was examining the effects of these novel anti-cancer agents on healthy arteries to study what other effects they might have in patients. A number of experimental techniques were used, including giving these drugs to radio-telemetered and anaesthetised rats, to measure their effects on blood pressure and heart rate.

My role was to test these drugs on isolated rat aortae in an organ bath. I started the placement without much consideration of the potential benefits; it seemed like a good idea to experience working in a 'proper' job and to earn some money. Looking back, however, it was a uniquely beneficial experience.

My team was incredibly welcoming and friendly and, importantly, treated me like a true member of the group. I was given a project and advice on how to get started, but I was allowed to manage my own work with the support of people around to help and answer questions whenever I needed. They really helped to boost my confidence and start to think more independently about the science and the possibilities for my project.

Starting at AstraZeneca with a cohort of placement students from different universities provided a ready-made friendship group with plenty of opportunities for socializing. This also offered a support network if experiments weren't working out the way you might have hoped. Some of the people I met in that year are still close friends now.

During my placement, I gave a presentation about my work to a departmental meeting which included some senior members of staff. At the time it was very daunting, but again, the atmosphere was very friendly and supportive. As part of my four-year BSc degree I had to submit a detailed scientific report on my research to Manchester University, which was examined in a viva and I was also invited to give a presentation as part of a university competition. These experiences helped my written and presentation skills and improved my confidence in public speaking immensely, all of which prepared me very well for my fourth year and my subsequent PhD.

Working in industry for a year not only taught me valuable lab skills but, far more importantly, helped me to mature, become more independent and taught me how to think for myself. Going back into university it was clear that having spent a year working in the 'real world' was a real advantage. The ability to take responsibility for your own work and get a greater sense of perspective was invaluable. And three hours of lectures a day no longer seemed like such a long day!

During my fourth year at Manchester I decided to apply for a PhD Studentship. Having had the experience of working in a lab for a year and completing a research project meant that I had at least a small idea of what a PhD might involve, and what I was letting myself in for: the satisfactions and the frustrations. It also looked great on my CV when applying for PhDs as I had a year's more lab experience than many people in my position.

It was fascinating to see from the inside how a multinational company worked and to compare the working styles and priorities of Industry and Academia and I really enjoyed the buzz of working in a large, corporate environment. I would really recommend anyone who has the opportunity for an industrial placement year to take it. It is a unique chance to experience a 'proper' job, particularly one within a very specialized industry, in a supportive environment. It's amazing how much you can learn and how much fun it can be.

Annie Geraghty, BPS Education Manager

Ken Duncan, Senior Program Officer
Global Health Discovery, Bill & Melinda Gates Foundation

Tuberculosis (TB) is a disease that in most of the developed world has been consigned to history, and yet globally it remains one of the major infectious disease killers. In 2007 there were an estimated 13.7 million chronic active cases, 9.3 million new cases, and 1.8 million deaths, mostly in developing countries (WHO, 2009). The epidemic is being driven by two factors, namely the close and deadly association between HIV and TB, and the emergence of multi-drug-resistant TB (MDR-TB) (and more recently, virtually untreatable extensively drug-resistant (XDR-TB)). In the long-term, the way to bring the epidemic fully under control is to break the cycle of transmission of *Mycobacterium tuberculosis*, the bacterium that causes TB. Unfortunately, the bacterium spreads easily from one individual to another through aerosol droplets created when someone with active disease coughs.

Perhaps the greatest challenge lies in the often-quoted statistic that a third of the world's population is infected with *M. tuberculosis*. This latent infection is defined simply by the observation of a TB antigen-specific T cell response but with no clinical symptoms of disease. Over the course of a lifetime, up to 10% of infected individuals will develop disease (this risk rises to 10% per annum in HIV-positives) and will spread it to, on average, 15 of their contacts before they are diagnosed and placed on treatment. Thus, to interrupt transmission, we must treat the latently-infected population and seek to cure them of infection before the bacterium has a chance to reactivate. Such a treatment exists: nine months of therapy with the front-line anti-TB drug isoniazid has been shown to effect cure, but the lengthy period of treatment and the concomitant side effects result in poor compliance.

It was with this knowledge in mind that a team led by Professor Douglas Young of Imperial College London set out to discover a new, more potent and rapidly-acting treatment for latent TB, addressing one of the "Grand Challenges in Global Health" (www.gcgh.org). Young assembled a multi-disciplinary team of researchers in academia, research institutes and industry from around the globe capable of tackling the problem in a systematic and integrated fashion (Barry et al, 2009). Now in its fifth year, this research consortium has demonstrated that by working together closely, more rapid progress has been made towards achievement of its specific goals than might have been expected had a set of individual grants been made.

At the core of the programme is exploration of the hypothesis that latent *M. tuberculosis* resides in lesions that are hypoxic, and that, in order to

survive, the bacterium adapts to this environment by altering its metabolism. By targeting those functions that are critical for survival under hypoxic conditions, the team hopes to sterilize the latent lesions much more rapidly and effectively than with today's drugs. The research programme consists of three major activities, namely the characterization of latent lesions from humans and non-human primates, a drug discovery programme exploiting this new knowledge of the biology of latent *M. tuberculosis*, and development of tools that will permit the rapid evaluation of drugs for treating latently infected humans.

Our understanding of TB has been hampered by lack of access to infected human tissue samples, and rodent models do not fully recapitulate the pathophysiology of the disease. Therefore, the team chose to gain access to human lesions through the participation of Ray Cho and his colleagues at the Yonsei University College of Medicine, Seoul, South Korea. Tissue was obtained from patients with active disease undergoing lung resection due to MDR-TB that was refractory to treatment, and from patients with TB lesions but no clinical symptoms of TB that were undergoing resection for suspected lung cancer. Lesions were also obtained from a non-human primate model of latency by JoAnne Flynn of the University of Pittsburgh.

The goal was to isolate bacterial Ribonucleic Acid (RNA) from latent lesions and perform transcriptomics using techniques pioneered by Gary Schoolnik and Gregory Dolganov of Stanford University, and by David Sherman of the Seattle Biomedical Research Institute. The technical challenges were formidable given the very small number of bacilli present in each lesion and although it has not yet proved possible to elucidate the full transcript profile, progress has been made in determining the gene expression level of a number of genes representing biochemical pathways of interest, confirming they play a role in latency.

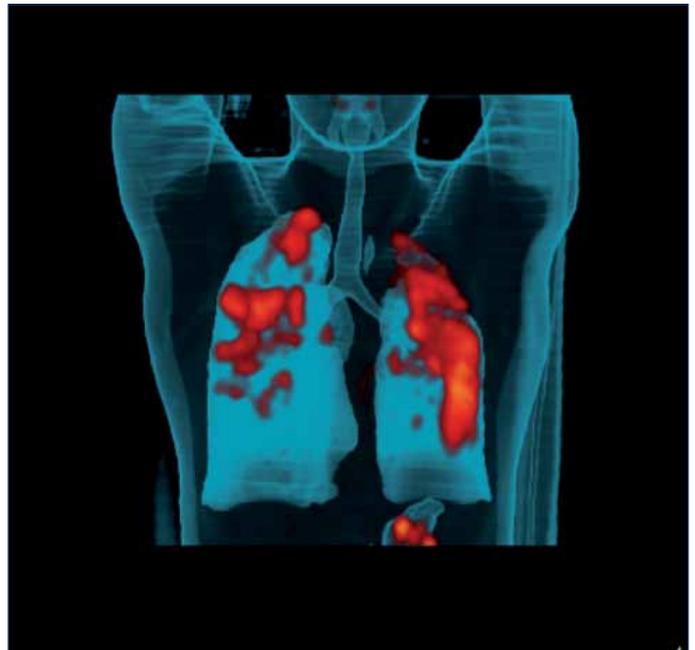
Drug discovery efforts in TB, and in other bacteria, have been hampered by the lack of well-validated targets. Recognizing this, the team put in place a combined genetic and chemical validation strategy before embarking on lead-finding. New *in vitro* assays were developed, suitable for testing compounds for whole-cell activity under low oxygen conditions, by a research team led by Thomas Dick at the Novartis Institute for Tropical Diseases (NITD) in Singapore. Clifton Barry at the Intramural Programme of the US National Institutes of Health (NIH) in Bethesda, USA established biochemical assays for targets of interest, and synthesized chemical inhibitor probes to

demonstrate that inhibition of a specific target activity leads to bacterial killing. Sabine Ehrh and Dirk Schnappinger of Weill Cornell Medical College, New York engineered *M. tuberculosis* strains to express genes under the control of a tetracycline-regulatable promoter and used this to analyze the effect of down-regulating gene expression to mimic the effect of partial inhibition by a drug and hence deduce the vulnerability of a target. Together, the team generated evidence to validate and prioritize a number of drug targets including pantothenate kinase, and the NITD team then generated assays suitable for high-throughput screening which were employed at screening centres within Novartis. From both enzyme-based and whole-cell assays, a number of hits have been identified and lead identification and optimization efforts are now under way. In another approach, a joint effort between the NIH and Novartis laboratories has optimized the anaerobic activity of a series of nitroimidazole compounds and is close to identifying a potential drug candidate.

The third element of the programme is development of new models and tools for evaluation of drugs for latent TB. In studies in MDR-TB patients in South Korea and in non-human primates in Pittsburgh, Barry, Cho and Flynn have followed the effect of treatment with metronidazole (which only has activity on *M. tuberculosis* under hypoxic conditions) on individual lesions by using positron emission tomography and computed tomography (PET/CT) imaging. The goal is to determine whether this method can be used to monitor drug efficacy during clinical trials by determining the effect of a drug on the particular hypoxic lesions which are thought to be rate-limiting for cure. An interesting outcome of these studies has been the observation that latent TB presents as a spectrum of disease on imaging. Finally, groups led by Lourdes Garcia-Garcia of the National Institute of Public Health in Mexico and Robert Wilkinson of the University of Cape Town have studied the human immune response to mycobacterial antigens during the course of isoniazid preventive therapy, and are identifying biomarkers that can be used in field trials to monitor the effect of a new treatment.

So, what are the factors that are critical to the success of an initiative of this type? The stakes are high; failure to capitalize on the opportunity could make funders reluctant to invest again in a bold and relatively risky programme of this type, and yet it is only by undertaking an integrated approach that we are going to make progress in tackling such an intractable problem. Regular, open and honest communication is the key. Professor Young set expectations at the outset, for example by ensuring that interdependent parts of the program were linked through milestones and each sub-grantee is held accountable for deliverables, and by insisting that each sub-grantee participate in a monthly teleconference which came to be known as the “virtual lab meeting”, at which recently generated data is discussed and constructive criticism is invited. The key factor is not only to highlight successes, but also to discuss openly any difficulties that are encountered, issues that may delay progress, and actively seek solutions to problems before they become rate-limiting to the whole programme. Another important point to note is that although the \$20 million funding for this specific project was provided jointly by the Wellcome Trust and the Bill & Melinda Gates Foundation, it would not have been possible to achieve the progress that has been made without substantial additional ‘in-kind’ support provided by both the Intramural Programme of the US NIH and Novartis. Coordination of effort by major funders also contributes to success.

In summary, a consortium of research laboratories encompassing clinical, academic, and industry research disciplines has made significant progress towards the goal of



legend: Positron emission tomography-computed tomography (PET-CT) image of human TB lesions (courtesy of Clifton E. Barry III, NIH)

generating a new therapy for latent TB, and along the way has improved our understanding of and opened new avenues of research into TB latency, setting the stage for major advances in this area in the coming years.

**Ken Duncan, Senior Program Officer, Global Health
Discovery, Bill & Melinda Gates Foundation**

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Tanya Parkinson
Pfizer Global
Research &
Development

Tanya completed her BSc in Microbiology in 1987, and her MSc in Microbiology at Aberdeen University in 1989. Tanya's PhD in yeast molecular biology led her to Pfizer and their Antifungal drug discovery group, responsible for new target identification and lead-seeking. Between 2000-2009 Tanya moved to Pfizer's Antiviral drug discovery group, leading projects on HIV, hepatitis C and respiratory viruses from early target validation through to Phase 1 clinical development. She currently works for the Infectious Diseases Group at Pfizer and is responsible for drug discovery projects for respiratory syncytial virus and neglected diseases (malaria, dengue, human African Trypanosomiasis, Chagas Disease and Leishmaniasis).

Malaria is one of the world's most devastating infectious diseases. Despite a remarkable global effort to tackle the disease, it continues to have a huge impact on global health. In 2008, there were an estimated 243 million cases and 863,000 deaths worldwide (World Health Organization, 2009). Africa suffers the highest burden of disease with ~85% of all cases, the remainder occurring in South-East Asia (10%) and the eastern Mediterranean (4%).

The disease is caused by parasites of the genus *Plasmodium*, with four species causing the majority of human infections. *Plasmodium falciparum* is responsible for most malaria deaths, but *Plasmodium vivax*, once thought to be relatively benign, is increasingly believed to be a significant contributor to malaria disease burden and severity, particularly in Southeast Asia and the western Pacific (Eisele et al, 2007). *P. vivax* is particularly challenging to cure as it forms a dormant hypnozoite form in the liver of patients which is refractory to most drugs and causes re-emergence of disease, sometimes months after initial infection. The other two species, *Plasmodium ovale* and *Plasmodium malariae*, only cause a small number of infections. All four species are transmitted by the bite of the female Anopheles mosquito.

In recent years, a number of organizations have launched strategies with the goal of eradicating malaria (Table 1). These include a combination of vector (mosquito) control and drug therapy. In addition to the historic method of vector control involving drainage and insecticide spraying of breeding areas, recent efforts

have focused on protection of individuals within households, generally with two approaches; indoor residual spraying (IRS) of insecticides on household surfaces where the Anopheles mosquitoes often rest after blood feeding and the use of insecticide treated bed nets (ITNs). Both strategies have proved cost effective in reducing malaria infections (Yukich et al, 2008) and when combined are estimated to have a 55% protective efficacy in young children (Thomas et al, 2010). However, insecticide resistance is a growing threat to these approaches (Betson et al, 2009, Dabire et al, 2008). In addition, practical and cultural factors can reduce usage of ITNs. For example, they are often reported to be too hot and to be impractical to put up and take down (Alaii et al, 2003a, Alaii et al, 2003b). For these reasons, the use of antimalarial drugs will be a key component of any elimination strategy.

A number of drugs are currently available for malaria treatment (Table 2), and several more are in clinical and pre-clinical development (Wells et al, 2009). Because of the risk of resistance development, malaria drugs are now always used in combination. The current WHO guidelines for treatment of uncomplicated *P. falciparum* malaria recommend artemisinin combination therapy (ACT), a combination of an artemisinin derivative with a drug from a different class. Unlike *P. falciparum*, *P. vivax* is generally still sensitive to chloroquine and this is used for first-line treatment of *P. vivax* malaria. However, chloroquine resistant *P. vivax* has started to appear in Asia (Price et al, 2009) and in these areas ACT is used. Of concern for both

The Bill and Melinda Gates Foundation	Provides funding to improve global development and health, including a goal of malaria eradication. http://www.gatesfoundation.org/Pages/home.aspx
World Health Organization Global Malaria Programme	Malaria surveillance, monitoring and co-ordination of eradication activities. http://www.who.int/malaria/about_us/en/index.html
World Health Organization TDR	Research and training in tropical diseases, including drug discovery for malaria and other diseases. http://apps.who.int/tdr/
Roll Back Malaria partnership	Malaria eradication through treatment and vector control. http://www.rollbackmalaria.org/
Global Fund to Fight AIDS, Tuberculosis and Malaria	Provides funding to fight HIV, tuberculosis and malaria. http://www.theglobalfund.org/en/
Affordable Medicines Facility for Malaria (AMFm)	Reducing costs for malaria medicines. Managed by the Global Fund above. http://www.theglobalfund.org/en/amfm/
Malaria Eradication Research Agenda (MalERA)	Consultative group, aiming to develop a research and development agenda for malaria eradication. http://malera.tropika.net/
Medicines for Malaria Venture (MMV)	Drug discovery and development for malaria. http://mmv.org/
MEND (Medicine in Need)	Application of delivery and manufacturing technologies for malaria, tuberculosis and HIV drugs and vaccines. http://www.medicineinneed.org/
Program for Appropriate Technology in Health (PATH) Malaria Vaccine Initiative	Acceleration of malaria vaccine discovery and development. http://www.malariaivaccine.org/index.php

Table 1: Key organizations working towards malaria eradication

P. falciparum and *P. vivax* therapy are recent reports of reduced sensitivity to artemisinins in Southeast Asia (Noedl et al. 2008). Therefore new therapies are still needed. One of the key areas for focus is drugs with new mechanisms of action and non-overlapping resistance with existing drugs. The availability of the *P. falciparum* genome sequence, coupled with computational and genetic technologies are helping to identify potential new drug targets (Aguero et al, 2008). This has led to drug discovery programmes targeting for example dihydroorotate dehydrogenase, an enzyme involved in pyrimidine biosynthesis (Gujjar et al, 2009), proteases (Sharma 2007, Ettari et al, 2010) and histone deacetylases (Andrews et al, 2009). Other areas where new drugs could have an impact would be in targeting the dormant hypnozoite form of *P. vivax* to prevent the relapsing disease caused by this species, and drugs which attack the sexual form, gametocytes, which are taken up by the mosquito and lead to transmission of the disease. However, drug discovery in these latter areas are hampered by the lack of reliable high throughput *in vitro* and *in vivo* models and limitations in our understanding of the biology of these forms (Mueller et al, 2009, Williamson, 2008).

is submitted. For a drug in a high commercial value disease, this results in faster time to market and consequently several months extra sales before patent expiry. This provides a direct financial incentive to companies to work on tropical diseases. Currently, most large pharma have active drug discovery and development programmes on neglected tropical diseases, which should speed the delivery of new therapies in the coming years.

Despite these efforts to tackle malaria, significant challenges remain. Malaria has the greatest impact on the poorest families, so it is vital that treatment is low cost, or even free. The Affordable Medicines Facility has been set up to tackle this, by reducing the cost of ACTs in malaria endemic countries. They estimate that the cost of a treatment course will reduce from \$6-10 to around \$0.20-0.30. An additional problem is that the poorest families tend to live in rural communities with limited access to healthcare clinics and pharmacies to obtain medicines. In such communities, the use of community health workers for prompt diagnosis and treatment has been shown to reduce mortality from malaria (Haines et al, 2007).

One of the biggest challenges in the fight against malaria is the abundance of counterfeit medicines, a particular issue in Africa, where it is estimated that on average, 20% of all medicines are fake (Sieter, 2009). In Nigeria, the problem is enormous, with around 70% of all medicines in circulation estimated to be counterfeit (World Health Organization, 2006). The danger with counterfeit malaria medicines is that they can either contain no active drug at all, which leads to unnecessary deaths, or they contain sub-eficacious concentrations of drug which can promote the development of drug resistance. Tackling the counterfeit drug industry is a huge task but

one that must be addressed, ensuring that when people receive malaria drugs they are receiving the right dose of the right drug.

The enormous global efforts to tackle malaria are clearly having an impact on the disease burden. In recent years, the number of reported malaria cases and deaths have fallen by over 50% (World Health Organization, 2009), which is encouraging. Progress is being made in vaccine and new drug development, and vector control strategies are clearly having a positive impact. However, much remains to be done to eradicate the disease and the battle is likely to wage for many years to come.

Tanya Parkinson,
Pfizer Global Research & Development, Kent

References available at www.bps.ac.uk/uploadedfiles/PharmacologyMatters/malariareferences.pdf

Drug class	Examples	Mechanism of action
Amino alcohols/4-aminoquinolines /8-amino quinolines	Quinine, Mefloquine, Lumefantrine, Chloroquine, Amodiaquine, Piperaquine, Primaquine,	Prevent detoxification of haem by the parasite
Anti-folates	Sulphadoxine, Pyrimethamine, Proguanil	Inhibit folate metabolism
Napthoquinone	Atovaquone	Inhibit parasite mitochondrial function
Artemisinin derivatives	Artemisinin, Dihydroartemisinin, Artemether, Artesunate, Artemotil/Arteether	Unclear □ multiple mechanisms proposed.
Antibiotics	Tetracycline, Doxyclyline, Clindamycin	Inhibit parasite apicoplast organelle function.

Table 2: Currently available drugs for treatment of malaria

In addition to small molecule drug discovery, much effort has been invested in trying to develop a vaccine for malaria. Research has been slow because of a poor understanding of the immunological responses to the parasite and the lack of predictive pre-clinical models. However, the first vaccine has now advanced to phase three trials. GlaxoSmithKline's Mosquirix™ vaccine (Vekemens et al, 2009) is being tested in infants up to 17 months of age and if successful, is expected to be submitted to regulatory authorities in 2012 and introduced over the next few years (GlaxoSmithKline, 2009).

Historically, pharmaceutical companies have not invested significant effort in malaria drug discovery because of the lack of commercial returns. However, there are now a number of incentives which make working on malaria more attractive. First, there are a number of opportunities for partnerships with organizations such as the Bill and Melinda Gates Foundation, the Medicines for Malaria Venture and the WHO TDR division, which provide some cost sharing, as well as bringing expertise in running clinical trials in developing countries. Second, the Food and Drug Administration (FDA) have introduced the priority review voucher scheme. When a company has a drug approved by the FDA for a tropical disease (including malaria), they receive a voucher entitling them to an accelerated review of any other new drug that



Mike Curtis, King's
College London



Michael Pugsley,
Johnson & Johnson



Simon Authier,
LAB Research Inc

This review provides a perspective on present therapy and therapeutic need in cardiovascular disease. It bases its statistics largely on the US experience. Our recommendation is that new drugs should be sought by ensuring that disease models are properly validated and applying hypothesis-driven thinking to new target identification. This means combining the best aspects of past successful drug discovery with judicious use of emerging technology and approaches.

Cardiovascular Disease (CVD)

CVD is an intricate, highly integrated class of dysfunction that includes hypertension, coronary heart disease (CHD), heart failure, stroke and congenital cardiovascular defects. According to recent statistics from the American Heart Association it has been estimated that more than one-third of American adults (i.e., >81,000,000) have at least one or more forms of CVD. CVD accounts for more deaths annually for the past 100 years than any other disease in the US. See **Figure 1** for UK comparisons.

Mortality rates have declined (from 1996 to 2006) by ~29%, yet CVD still accounts for ~34% of all deaths in the US annually - more than cancer, chronic respiratory disease, accidents, Alzheimer's disease and HIV/AIDS combined. The economic costs associated with CVD for 2010 in the US is projected to be ~\$500 billion. In the UK, the British Heart Foundation reports similar statistics, with 35% of all deaths annually resulting from CVD, of which half of these result from CHD.

CHD

CHD manifests as myocardial ischaemia and angina pectoris. Myocardial ischaemia is impairment of blood flow through coronary arteries, and angina is the acute chest pain that results from this. If the ischaemic region is sufficiently large then arrhythmias may develop. 'Sudden death' due to lethal arrhythmias is the most common cause of death in economically developed countries. The majority of such deaths, which have remained at a nearly constant ratio since the 1970s are due to ventricular fibrillation (VF). In 2010 it is estimated that ~785,000 Americans will have their first episode of CHD and ~470,000 will have a recurrent attack. The median survival rate after VF is ~21%. The underlying causes arrhythmias associated with CHD are problematic. This is because they are most commonly associated with slowly developing coronary atherosclerosis, with acute severe ischaemia occurring suddenly and unpredictably when a thrombus (blood clot) forms on a fissuring atherosclerotic plaque. Moreover, animal studies show (and clinical statistics confirm) that the first symptom of acute myocardial ischaemia is often death (due to VF). Therefore, intervention requires prophylaxis. Moreover, currently approved

drugs and research efforts have been hindered due to serious drug safety issues and associated difficulties in giving drugs to potential patients who, in the wider population (numerically the largest population 'at risk') are ostensibly well.

Antiarrhythmic drugs and CHD

In the mid-1980s, development of Class I and Class III drugs (that target sodium and potassium currents, respectively) was undertaken. All these drugs showed activity in a range of animal models of arrhythmias, and initially showed efficacy in the clinic against *non-life-threatening* arrhythmias. This predicated their evaluation in larger Phase III clinical trials as prophylaxis against *lethal VF* under the assumption that efficacy against any arrhythmia predicted efficacy against any other (the 'Cardiac Arrhythmia Suppression Hypothesis'). The Cardiac Arrhythmia Suppression Trial (CAST) tested this hypothesis by examining whether sudden cardiac death in survivors of acute myocardial infarction (MI), could be reduced by Class I drugs that suppress minor ventricular arrhythmias: flecainide, encainide and, later, moricizine (in CAST-II), and mexiletine (in 'IMPACT'; International Mexiletine and Placebo Antiarrhythmic Coronary Trial). The results were catastrophic, with an abnormally high incidence of death in drug treated patients when compared to placebo controls.

Remarkably few sodium channel blocking antiarrhythmic drugs are used clinically today to suppress arrhythmias (of any sort). This is partly the result of drug unsuitability for long term use owing to adverse effects. For example, quinidine, a Class 1 antiarrhythmic with a propensity to evoke arrhythmias by virtue of off-target actions, was shown to increase the incidence of mortality in patients with potentially lethal arrhythmias. It is also partly due to unsuitability of route of administration: lidocaine, which must be given intravenously, may suppress lethal arrhythmias in hospital but it cannot be routinely self-administered by patients out of hospital, so it is unsurprising that, in follow-up, lidocaine had no effect on one year survival after MI.

The class II (β -blocking) antiarrhythmic agents, typified by propranolol, atenolol and esmolol (an ultrashort-acting β adrenergic receptor blocker) are the only antiarrhythmic drugs that have been consistently shown to suppress ventricular arrhythmias and to improve survival post MI (although the two effects are not necessarily related).

The class IV antiarrhythmics (calcium channel blocking agents) have, in contrast, exhibited poor results in MI survivor patients in clinical trials.

Because of the lacklustre performance of Class I antiarrhythmic drugs, development subsequently focused on drugs that alter the action potential duration and prolong refractoriness, i.e. possess class III antiarrhythmic actions. This was facilitated by emerging data in the early 1990s for effectiveness of sotalol and amiodarone in the clinical setting and the results of long-term studies with amiodarone which suggest that it may decrease arrhythmic death after MI. Repolarisation and the configuration of phase 3 of the action potential in cardiac tissue are governed by the complex interaction of many potassium channels, which are heterogeneous in gating and permeation properties as well as susceptibility to modulation by neurotransmitters and intracellular ions. The potassium channels regulate cell function by establishing the resting membrane potential and controlling cell repolarisation. Individual potassium currents overlap in their contribution to the total membrane current during the action potential. The relative importance of each may vary under different conditions such that changes in normal cell electrophysiology during ischaemia may modify the action potential response and alter channel contribution to cardiac function.

The heterogeneity of potassium channels was thought to provide for a large potential for the development of a diverse number of compounds with channel blocking properties. These agents delay the process of repolarization without slowing intracardiac conduction (a potential hazard in an already compromised heart). Sotalol, and amiodarone are Class III agents that block several potassium currents. All block I_{Kr} , the rapid component of the delayed rectifier potassium current. However, while these drugs produce an effective reduction in arrhythmia incidence and mortality, their hallmark repolarization delay (manifested as QT interval prolongation) is associated with a tendency to facilitate the appearance of a syndrome known as torsades de pointes (TdP), which includes in its presentation a potentially lethal ventricular arrhythmia. Amiodarone inhibits Na^+ , K^+ and L-type Ca^{2+} currents as well as I_{KACh} current from atrial and sinoatrial nodal tissue, and antagonises α - and β -adrenoceptors. Amiodarone is the

only class III agent with proven minimal risk for inducing TdP. This has been suggested to be a consequence, paradoxically, of a lack of selectivity for potassium channels, whereby the 'mixed' ion channel blocking actions (particularly block of cardiac L type calcium channels) surmount the torsadogenic liability, while the ability to suppress VF via potassium channel blockade persists. Its analogue, dronedarone a non-iodinated derivative, and racemic (d,l)-sotalol may share this characteristic although this is uncertain and untested.

After the CAST trial, enthusiasm for the potential benefits of amiodarone and sotalol prompted development of potent and more selective second generation Class III agents. These drugs include dofetilide, ibutilide and azimilide. These agents have been confirmed to possess antifibrillatory effects, albeit against atrial fibrillation, and not VF. Dofetilide selectively blocks I_{Kr} . Related drugs such as ibutilide not only blocks I_{Kr} but also augments sodium current. Azimilide blocks multiple potassium currents, IKr and the slow component of the delayed rectifier potassium current (I_{Ks}).

Class III agents are effective at low heart rates at maintaining their primary action, a ventricular repolarization delay caused by prolongation of ventricular action potential duration (APD) and concomitant QT prolongation in the ECG. However, at high heart rates the effectiveness of these agents diminishes. This "reverse use-dependence" limits their effectiveness during tachycardia - when their effects are needed the most. Only amiodarone has a heart rate-independent ability to prolong QT and ventricular APD.

Second generation Class III drugs have been assessed in clinical trials. However, in the SWORD (Survival With Oral D-sotalol) trial d-sotalol (which is highly selective for IKr , unlike the racemate) was found to increase mortality (5.0% vs. 3.1% in placebo) in patients with left ventricular dysfunction after MI. In the Danish Investigations of Arrhythmias and Mortality on Dofetilide clinical trials, dofetilide was shown to exhibit minimal adverse events in patients with left ventricular (LV) systolic dysfunction (DIAMOND), heart failure (DIAMOND-HF)

Figure 1: Absolute number of deaths by disease type, England and Wales, 2008

	Male	%	Female	%	All	%
Total	243014	100	266076	100	509090	100
Cardiovascular total	80846	33.3	87392	32.8	168238	33.0
Hypertension	1805	0.7	2668	1.0	4473	0.9
Ischaemic heart disease	43462	17.9	33523	12.6	76985	15.1
Acute myocardial infarction	16691	6.9	12639	4.8	29330	5.8
Atherosclerosis	198	0.08	369	0.14	567	0.11
Cerebrovascular	17805	7.3	28641	10.8	46446	9.1
Aortic aneurysm	4415	1.8	2958	1.1	7373	1.4
Other heart disease	10166	4.2	14543	5.5	24709	4.9
Cancer	73702	30.3	67437	25.3	141139	27.7
Mental (incl dementia)	5965	2.5	12472	4.7	18437	3.6
Nervous system disease	8127	3.3	9394	3.5	17521	3.4
Diabetes mellitus	2649	1.1	2892	1.1	5541	1.1
Renal failure	1147	0.5	1571	0.6	2718	0.53
Respiratory total	32810	13.5	38950	14.6	71760	14.1
Asthma	322	0.13	749	0.28	1071	0.21
Chronic obstructive pulmonary disease	13032	5.4	11784	4.4	24816	4.9
Influenza	14	0.006	25	0.009	39	0.01
Pneumonia	11531	4.7	17396	6.5	28927	5.7
Other infection/infestation	2919	1.2	3580	1.3	6499	1.3
Liver disease	4726	1.9	2791	1.0	7517	1.5
Pregnancy/childbirth/postpartum			44	0.017		
Sudden infant death syndrome	102	0.04	74	0.028	176	0.035
External causes	11023	4.5	7025	2.6	18048	3.5
Accidents	6754	2.8	5477	2.1	12231	2.4
Suicide	2663	1.1	775	0.29	3438	0.7
Assault	233	0.10	105	0.04	338	0.07

Adapted from Office of National Statistics: <http://www.statistics.gov.uk/pdfdir/dthreg0809.pdf>

and those with a recent myocardial infarction (DIAMOND-MI). However, TdP was observed in dofetilide groups in each study at an incidence rate of 2.1%. Thus the lack of sufficient safety margin has resulted in the removal of several second generation Class III agents from the market (including almokalant, d-sotalol and terikalant).

Thus clinical trials with Class I and III antiarrhythmic agents have provided a valuable lesson, at an unfortunately high price, as to the complex interrelationship that exists between the antiarrhythmic drug, the arrhythmogenic substrate, and efficacy. Additional evidence since the completion of these clinical trials in additional human and animal arrhythmia studies shows that 'selective' sodium and potassium channel blocking antiarrhythmic drugs have predictable proarrhythmic tendencies.

Suptaventricular arrhythmias

In contrast to the problems with drugs for ventricular arrhythmias, recently, marketing approval has been provided for novel antiarrhythmics for use in atrial (supraventricular) arrhythmias. Selective targeting of supraventricular arrhythmias has a perception of reduced risk of ventricular adverse effects (i.e., TdP).

Atrial fibrillation (AF) and atrial flutter, are not immediately life-threatening but are the most common cardiac arrhythmias encountered by cardiologists (partly because half of VF victims die before reaching hospital) and by general practitioners. AF is maintained by re-entrant waves (self-propagating irregular circles of electrical excitation). It is well established that prolongation of atrial refractoriness (by prolongation of the atrial APD) prevents propagation of re-entrant electrical circuits in the atrial tissue. In the human atria I_{to} , a current responsible for early atrial repolarization, and I_{Kur} , which is important in both the early and plateau phases of repolarization, are the major repolarizing currents. Although the channel responsible for I_{Kur} (generated by the $K_v1.5$ gene) is expressed at both the mRNA and protein levels in human ventricular tissue, albeit at low levels, its function appears to be restricted to the atrium.

The channel responsible for the rapid early repolarization current, I_{to} , which is observed in both atrial and ventricular myocytes, is now thought to be a gene product of the $Kv4.2/4.3$ and $Kv1.4$ subfamily. The channel possesses rapid activation and inactivation kinetics and contributes to the "spike and dome" appearance of the ventricular action potential. Channel density and distribution differences amongst cell type results in a variable action potential morphology in various regions of the heart. However a comparison of atrial and ventricular I_{to} reveals significant differences in rates of inactivation and recovery, which can affect drug selectivity for atria versus ventricles.

While peak or 'fast' I_{Na} (Nav1.5 channel) current underlies excitability and conduction in the heart, the late non-inactivating or slowly inactivating I_{Na} current is thought to play a role in APD. This channel responsible for this current has not been cloned, but likely results from altered kinetics of the gating (transitions a channel makes on its way to opening) of the Nav1.5 channel. Thus, it manifests because a proportion of the Nav1.5 channels do not fully inactivate, according to probability. In the presence of some drugs there is apparent "preferential" block, but it is probably only a consequence of the channel gating (i.e., where a repeated re-opening of the channel occurs) combined with the use-dependence of blocking properties of the drug. Rapid drug block of I_{Na} (because of the short APD in atrial tissue) provides supraventricular selectivity.

Presently several drugs can be used to prevent AF. However these drugs (including flecainide, propafenone, d-sotalol, amiodarone and azimilide) may increase mortality due to a variety of adverse events that range from non-cardiac side effects (pulmonary fibrosis) to ventricular arrhythmias (and TdP). A number of companies are currently developing selective atrial channel blockers. Aventis has AVE 0118, S-9947 and S-20951 which block atrial $Kv1.5/Kv4.3$ channels and Nissan Chemicals is developing NIP-142 which blocks atrial $Kv1.5$ channels.

In the Dronedarone Atrial Fibrillation Study After Electrical Cardioversion (DAFNE) clinical trial, dronedarone (400 mg, twice a day) benefit against AF was intriguingly accompanied by reduced death rates, hinting at a possible effect on VF too. However, the Antiarrhythmic Trial with Dronedarone in Moderate-to-Severe Congestive Heart Failure Evaluating Morbidity Decrease (ANDROMEDA) trial was stopped due to an increase in heart failure in the dronedarone group. Regardless, dronedarone was approved for use in Europe and the US in 2009 for the maintenance of sinus rhythm in patients with AF or atrial flutter with ejection fractions >35%.

Celivarone and budiodarone are non-iodinated amiodarone analogs currently in clinical development. Celivarone has similar electrophysiological and hemodynamic properties to amiodarone and in Phase IIb studies, at doses up to 300mg/day, patients show a reduction in recurrence of AF. Budiodarone also has an electrophysiological profile similar to that of amiodarone; however, it is rapidly metabolized by plasma and tissue esterases which advantageously alters the pharmacokinetic profile. This physicochemical change allows for a reduction in drug half life (to ~7hrs), preserving efficacy (i.e., reduced AF burden) but enhancing safety.

Ranolazine is an antianginal drug that reduces the frequency of angina, improves exercise performance and in non-ST elevation acute coronary syndrome patients prevents recurrent ischaemia while reducing the incidence of atrial fibrillation and ventricular arrhythmia. Ranolazine inhibits the late phase of the inward cardiac sodium (I_{Na}) current during repolarization which may be responsible for its beneficial actions. Ranolazine additionally blocks I_{Kr} resulting in prolongation of the QT interval on the ECG. However there have been no reports of TdP or other proarrhythmia observed to date in patients. Thus, in 2007 ranolazine was approved for use in patients with chronic angina.

Vernakalant is a blocker of the ultra-rapid delayed rectifier (I_{Kur}) and transient outward (I_{to}) K^+ currents in atrial myocytes. Since I_{Kur} is of little or no relevance in human ventricular tissue, I_{Kur} blockers are anticipated to provide atrial-selective antiarrhythmic effectiveness and obtain major therapeutic advantage in atrial fibrillation (AF) patients. Vernakalant has also been shown to block the late component of the sodium current (an effect similar to that of ranolazine) and also I_{KAch} involved in parasympathetic autonomic regulation of heart rate in atrial cells. The intravenous formulation of vernakalant was recommended for approval by the FDA (December, 2007) for conversion of recent-onset atrial fibrillation, yet remains to garner full authorization approval.

Other novel antiarrhythmic drugs in various stages of development include the peptide rotigaptide (ZP123), a gap junction enhancer currently in Phase IIa. The anticipated benefit derives from the drug's ability to facilitate low resistance cell-cell coupling under circumstance where conduction velocity is slowed.

Vagal nerve tone plays an important role in AF. In cardiac tissue there is a 'co-existence' between the muscarinic acetylcholine receptor subtype-2 (M2) and $I_{K_{ACH}}$. In patients with chronic AF, studies indicate constitutive activation of $I_{K_{ACH}}$ (i.e., increased expression and open probability of the channel). NTC-801 is a novel ion channel blocker that selectively inhibits atrial $I_{K_{ACH}}$ and is currently in Phase I development in Japan for the maintenance of normal sinus rhythm in patients with AF.

Despite intensive research with antiarrhythmic drugs over several decades, the decline in mortality associated with CHD is primarily due to implementation of other medical therapies and changes in lifestyle and environmental risk factors (such as smoking cessation and reduced dietary salt intake).

Hypertension

Hypertension (high blood pressure) is clinically defined as a systolic blood pressure >140mmHg or a diastolic blood pressure >90mmHg. Approximately 33.6% of Americans are hypertensive. While the prevalence of hypertension is comparable between genders, it varies between Caucasians and African Americans. African American adults have amongst the highest reported rates of hypertension in the world (~45%).

The renin-angiotensin-aldosterone system (RAAS) plays a pivotal role in blood pressure regulation and the pathogenesis of hypertension. RAAS consists of a series of interactive enzymatic reactions within the blood that uses renally-secreted renin to convert angiotensinogen, produced by the liver, to angiotensin I. Angiotensin-converting enzyme (ACE) primarily located on the endothelial cells of blood vessels, converts angiotensin I to angiotensin II (A-II). A-II is a powerful peptide hormone responsible for numerous effects in many different tissues.

There are two primary receptors for A-II, denoted AT_1 and AT_2 , that mediate effects on the cardiovascular system.

The AT_1 receptor mediates the pathologic effects of A-II that contribute to hypertension including blood vessel constriction, water and electrolyte retention, and cellular hypertrophy and proliferation. The physiological role of the AT_2 receptor remains enigmatic. However, studies generally show that its activation opposes the effects mediated by AT_1 receptors.

AT_1 receptor blockers (valsartan, olmesartan), known as ARBs, are effective therapeutics used to treat all aspects of hypertension including progression to secondary disease presentation as well as regulation of high blood pressure. Note however that this is not the only class of drugs used to reduce blood pressure; others include β -adrenergic blockers (atenolol, metoprolol), calcium channel blockers (amlodipine), angiotensin converting enzyme (ACE) inhibitors (captopril, ramipril), nitrovasodilators (glyceryl trinitrate + hydralazine) and renin inhibitors (aliskiren).

However, unlike most of these agents, ARBs are effective antihypertensive agents that have a limited adverse event profile. In addition to effective blood pressure reduction, reports demonstrate that antihypertensive drugs may play an important role in the treatment of heart failure, ameliorating microvascular and macrovascular complications and providing benefits to end-stage renal disease (ESRD) patients with and without type 2 diabetes mellitus.

Aliskiren is a direct, oral renin inhibitor which has been the most recent drug introduced into the algorithm for the treatment of hypertension. Aliskiren has a comparable

antihypertensive activity to other RAAS inhibitors and is likely to be another useful drug in the antihypertensive armament. Recently it was approved for use in combination with valsartan. When given in combination, several clinical trials have shown a greater reduction in blood pressure than with the individual component drugs.

Congestive heart failure

Congestive heart failure (CHF) is the most common reason for hospitalization of the elderly, and cardiomyopathies, primary disease processes of the heart muscle, are highest in elderly persons. Regardless of the nature of the myopathy (e.g., dilated, hypertrophic, restrictive or right ventricular) the final common endpoint is a reduction in heart function characterized by altered electrophysiological, metabolic and structural changes to cardiac muscle. These effects can be acute (resulting from exposure to toxic drugs or myocardial infarction) and chronic in nature (resulting from myocardial ischaemia or infarction or hypertension).

The mechanism(s) responsible for failure are rarely certain in individuals, but the common feature is reduced cardiac output. This acutely lowers blood pressure, and homeostasis leads to increased sympathetic drive to the heart, redistribution of blood flow to vital organs, and expansion of vascular volume. Unfortunately in the long term the chronic effects of these changes include cardiac hypertrophy, underperfusion of skeletal muscle, venous congestion and oedema (including potentially lethal pulmonary oedema), cardiac arrhythmias and further impairment of cardiac output. This represents a chronic maladaptation (adverse remodelling) to an acute pathological event.

While the mainstay of therapy involves use of agents to reduce venous congestion (volume overload), improve cardiac output (myocardial dysfunction) and prevent arrhythmias, the drugs used are largely palliative and many have severe adverse effects (some being lethal), limited effectiveness, and little preventive value except in terms of limiting adverse remodelling in the case of angiotensin converting enzyme (ACE) inhibitors and beta blockers, leading to high readmission rates. Primary intervention includes use of digitalis glycosides (digoxin) and diuretics (furosemide and torsemide). Additional drugs that are used in heart failure include renin angiotensin and aldosterone system (RAAS) inhibitors such as aldosterone antagonists, ACE inhibitors, angiotensin receptor blockers (ARBs) and nitrovasodilators (e.g., isosorbide dinitrate). Adrenergic receptor antagonist (β -blockers such as carvedilol and metoprolol) reduce enhanced autonomic sympathetic tone that accompanies CHF thereby improving left ventricular ejection fraction in patients, and possibly limiting adverse remodeling.

Nesiritide, an endogenous brain-derived peptide from the natriuretic peptide family (consisting of atrial and brain natriuretic peptides (ANP and BNP) and C-type natriuretic peptide), is approved for use in acutely decompensated heart failure with dyspnea. This family of peptide hormones are potent diuretic, natriuretic and vasodilators. BNP reduces cardiac and pulmonary pressures, reduces systemic vascular resistance and increases cardiac index.

Urocortins are a family of hypothalamic corticotrophin-releasing hormone (CRH) peptides that have been shown to increase cardiac output and reduce left atrial pressure and peripheral vascular resistance in normal and pacing-induced non-clinical models of CHF. A specific human urocortin 2 (h-UCN2) peptide with high affinity and specificity for the CRH type 2 receptor (CRHR2) has been studied in non-clinical models as well as CHF patients and shown to increase left

ventricular ejection fraction and improve cardiac output (CO). Further clinical trials are needed to characterize efficacy and safety.

Stroke

Acute ischaemic stroke (AIS) is the third leading cause of mortality after heart disease and cancer, and the major medical cause of serious, long term disability, in developed countries. A stroke can result from either a blood clot occluding an artery (ischaemic stroke) or from the rupture of a cerebral blood vessel (hemorrhagic stroke). Of the more than 795,000 new or recurrent stroke victims per year in the US, about 87% suffer from a stroke due to a blood clot and if left untreated 36% will sustain moderate to severe disability within 3 months.

Plasminogen activators (PAs) are naturally occurring proteases that function in converting plasminogen into plasmin, thus initiating the process of fibrinolysis. Fibrinolysis is an important, 'housekeeping' process that removes small blood clots which can be potentially life-threatening. The optimal use of PAs in AIS has yet to be realized since many of these thrombolytics are encumbered by lack of proven efficacy and/or safety issues. The ideal PA for AIS would be safe, highly fibrin-selective, and easy to administer and would provide rapid reperfusion of ischaemic tissue.

Currently, tissue-type plasminogen activator (t-PA, also known as alteplase) is the only approved thrombolytic for AIS in the US, Canada, and European Union; however, administration of t-PA is restricted to a narrow 3-hour treatment window after the onset of AIS symptoms due to the approximately 16% increase in risk for intracerebral hemorrhage (ICH) associated with its use beyond this timeframe. Given that only about 17% of AIS patients arrive at hospital within 3 hours of stroke symptom onset, most stroke victims will be left untreated. In fact, it has been estimated that only 1-6% of stroke sufferers receive treatment with tPA. Thus, the need for a fibrinolytic agent with improved safety and efficacy, as well as an extended time-to-treatment window, is critical for the successful outcome of stroke survivors.

Thrombolytic therapy with recombinant tissue plasminogen activator (rt-PA) is effective in treating AIS within the first 3 hours after symptom onset. Recombinant *Desmodus* salivary plasminogen activator $\alpha 1$ (rDSPA $\alpha 1$, also known as desmoteplase), is a novel PA derived from the saliva of the vampire bat *Desmodus rotundus* that has been shown to treat AIS up to 9 hours post-stroke onset with a positive risk:benefit ratio not shown in previous trials with rt-PA when treating patients beyond 3 hours. It is currently in Phase II clinical development.

Diabetes/Obesity

Diabetes Mellitus (DM) is a chronic disease that continues to grow in prevalence in North American and around the world. A majority of those afflicted have type 2 onset diabetes mellitus (T2DM). The American Diabetes Association statistics show that a staggering 24 million children and adults (~8% of the population) are diabetic while an estimated additional ~6 million remain undiagnosed with 57 million more exhibiting 'pre-diabetic' signs that include higher than normal blood glucose levels.

The World Health Organization (WHO) predicts that within the next 20 years an astounding 350 million people will suffer from T2DM. As with diabetes, the prevalence of obesity, another leading cause of death, continues to increase worldwide. According to estimates in the US, obesity affects ~97 million adults and according to the WHO ~1.6 billion

adults are overweight. The number of overweight people globally is projected to increase to ~2.3 billion within the next 5 years, with more than 700 million obese. The US Centers for Disease Control (CDC) predict that obesity-related deaths will soon surpass smoking-related illness as the leading cause of preventable death in the United States. Overweight and obese individuals are at increased risk for chronic health problems such as cardiovascular disease, hypertension, T2DM, digestive disease, cerebrovascular disease (stroke and transient ischaemic attacks), and variant forms of cancer.

In 2007 the total economic cost of diagnosed diabetes in the US was estimated to be \$174 billion; however, when costs associated with pre-diabetes, undiagnosed diabetes and gestational diabetes are included the total cost of diabetes in the United States is estimated to be \$218 billion.

Type 2 diabetes mellitus is characterized by two major defects: resistance to the action of insulin in various tissues (muscle, liver, and adipose) and decreased secretion of insulin by the pancreas. These altered physiological processes result in impaired glucose uptake at the cellular level. Chronic hyperglycemia leads to progressive impairment of insulin secretion and to insulin resistance in peripheral tissues which further worsens the control of blood glucose levels. In addition, chronic hyperglycemia has been demonstrated to be a major risk factor for complications, from heart disease, retinopathy, nephropathy, and neuropathy. Aggressive glycemic control has been demonstrated to decrease microvascular and possibly macrovascular complications intimately associated with glucose toxicity.

Various classes of orally available antihyperglycemic agents (OHAs) are now used to target different pathophysiologic factors that contribute to diabetes. Alpha (α)-glucosidase inhibitors such as acarbose delay intestinal carbohydrate absorption. Biguanides such as metformin target hepatic insulin resistance by decreasing the amount of glucose made by the liver while increasing glucose uptake by target tissues. Sulfonylureas (SUs) are insulin secretagogues that increase pancreatic insulin secretion. Insulin sensitizers (e.g., thiazolidinediones, TZDs) target adipocytes and muscles to decrease insulin resistance and increase cellular utilization of glucose. Several new glucose-lowering agents have been recently approved or are under review by US and EU regulatory authorities for the treatment of T2DM. These work by increasing the actions of incretin hormones such as glucagon like peptide-1 (GLP-1) and glucose dependent insulinotropic peptide (GIP). These therapeutics include the injectable GLP-1 analogue, exenatide, and the orally-administered dipeptidyl peptidase IV (DPP-IV) inhibitors, vildagliptin and sitagliptin. These new agents may enable patients with type 2 diabetes to achieve glycemic control while reducing the risk of hypoglycemia and weight gain. Anti-obesity therapy induces weight loss by non-pharmacological (dietary, behavioral, and/or physical) or pharmacological methods.

Current drug therapies include centrally-acting appetite suppressants and an inhibitor of gastric and pancreatic lipase (e.g., orlistat). These compounds have modest effects on weight loss and may have side effects such as increased heart rate and blood pressure, insomnia, irritability, (for appetite suppressants), or steatorrhea and abdominal cramps (for lipase inhibitor).

The cannabinoid receptor type 1 (CB1) antagonist, rimonabant (Accomplia), an anorectic, anti-obesity drug that is an inverse agonist for CB1 was authorized for use by the European

Commission in 2006 for patients with high Body Mass Index (BMI) with risk factors including T2DM and dyslipidemia. However, in 2009, the EMEA concluded that drug benefits did not outweigh its risks (suicidality, severe depression) in these patients and the drug was subsequently withdrawn from the market.

Conclusion

Cardiovascular disease remains a leading cause of debility and death, and poses a major challenge for pharmacologists. The major aspects of difficulty are similar to those faced in other therapeutic areas. Target validation and identification of new chemical entities (NCEs) that hit the target are the main consideration. Target validation is difficult because this is driven by hypothesis, based on clinical speculation and animal model data. Clinical speculation is often driven by biomarker identification.

This can amount to little more than finding something that changes in a disease state in the absence of a drug. And since seeking a drug is the objective here, there will be no drug to use to validate the biomarker. Pharmacogenomics is another basis for clinical speculation. The same considerations apply. Animal model data is potentially more productive, given that a disease model allows NCE testing for potential drug identification. However, diseases that most require drugs are diseases for which no curative drugs exist.

Therefore models cannot be validated by showing the 'standard' therapy works in the model. This creates a scenario where NCEs with hypothetical value as putative drugs are tested in models that are not validated because there is no available drug that works in humans. Progress in this scenario requires a good hypothesis and dogmatic diligence. This is the 'Black approach' that gave us propranolol and cimetidine. The modern approach is more oriented towards mapping the molecular biology of disease processes with a view to revealing druggable targets as a research byproduct. It is too early to say whether this will provide a better route to drugs.

A greater degree of concern about adverse drug effects has served to limit the momentum of drugs discovery, much as the greatly enhanced approaches to vehicle safety have limited the speed of formula one racing cars. In neither milieu is 'death or glory' appropriate, so we must wait for innovation to catch up with safety in drug discovery, and hopefully the medicines pipeline will begin to thrill us again, just as the sight of Button and Hamilton thrills us now at the Grand Prix.

Michael K Pugsley¹, Simon Authier², Michael J. Curtis^{3*}

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1. Department of Toxicology/Pathology, Johnson & Johnson PRD, OMP 2357, 1000 Route 202 South Raritan, NJ 08869
2. LAB Research Inc. 445, Armand-Frappier Boul.
Laval, Qc H7V 4B3
3. Cardiovascular Division, Rayne Institute, St Thomas' Hospital, King's College London, London SE17EH, UK

*Author for correspondence



David Back,
University of
Liverpool

David Back has a personal chair in Pharmacology at the University of Liverpool. He established the HIV Pharmacology Research Group at the commencement of the antiretroviral era more than 20 years ago. Here he looks back over the remarkable success of antiretroviral therapy and discusses where the likely advances will be seen in the next few years.

According to the 2009 UNAIDS/WHO AIDS epidemic report, there were an estimated 33.4 million people worldwide living with HIV in 2008, including 2.7 million who were newly-infected with HIV. Over 2 million people were estimated to have died from AIDS that year, including 300,000 children (www.unaids.org/en/KnowledgeCentre/HIVData). Globally, the spread of HIV appeared to peak in 1996 when 3.5 million infections occurred; therefore the latest figure for new infections is about 30% lower than at the peak. However there is no cause for complacency. Although progress has been made in preventing new HIV infections and lowering AIDS-related mortality, leading to a stabilization of the epidemic in many regions of the world, there are still areas where prevalence continues to increase - particularly in Eastern Europe and some parts of Asia. And all the time hanging over us is the knowledge that Sub-Saharan Africa carries more than 70% of the total HIV burden.

Twenty-five years after the discovery of the anti-viral effects of azidothymidine (AZT; ZDV) there are now 25 approved single antiretroviral drugs in six classes (nucleoside/nucleotide reverse transcriptase inhibitors, NRTIs; non-nucleoside reverse transcriptase inhibitors, NNRTIs; protease inhibitors, PIs; entry inhibitors, EIs; Chemokine receptor antagonists, CCR5 antagonists and integrase inhibitors; **Table 1**).

Although HIV infection cannot be cured with the current treatments and all patients have to face the prospect of receiving antiretroviral therapy for life, there have been dramatic, and in many ways unprecedented advances in the drugs available.

There has been a 10-fold increase in the last five years in the number of HIV+ people in low and middle-income countries gaining access to therapy. So where the drugs are available we have a chronic treatable infection; the challenge is to ensure that all people living with HIV receive treatment (listed as one of the key priority areas for the UNAIDS Outcome Framework 2009-2011). Zidovudine, the first drug approved for treating HIV by the FDA in 1987, is still in use today. The early monotherapy studies established a 'proof of concept' that treatment with an antiretroviral could slow the progression of HIV, but unfortunately both the monotherapy and dual NRTI therapy studies of the late 80's and early 90's failed to show more than a transient effect on disease progression. The big breakthrough came in 1996 with the introduction of protease inhibitors and subsequently non-nucleoside reverse transcriptase inhibitors used as part of a triple combination regimen (Highly Active AntiRetroviral Therapy; HAART). For the clinical pharmacologist each class of drug had significant challenges. NRTIs require intracellular phosphorylation and therefore to understand the overall disposition and PK-PD relationships meant measuring the active anabolite (a triphosphate) inside the target cells [Barry et al 1994]. Of the 10 protease inhibitors all except one are peptidomimetic and undergo rapid first pass metabolism (substantially mediated by CYP3A4 but with some transporter involvement).

The big breakthrough with this class of drugs was the finding that ritonavir, an active antiretroviral at a dose of 600 mg twice daily, could at low doses (100 mg twice or once daily) 'boost' the plasma concentrations of the other PIs (the so called 'pharmacokinetic boosting'). This immediately resulted not only in improved pharmacokinetic profiles but reduced doses and therefore tablet burden [Hill et al 2009]. But there was a trade off, since inhibition of CYP3A4 and other proteins by ritonavir meant that there was a marked potential for drug-drug interactions with other co-medications. Ask any HIV healthcare professional today and they will tell you that dealing with drug-drug interactions remains one of the greatest challenges in antiretroviral therapy. The Liverpool HIV research group recognized that there was a need for readily available information on drug-drug interactions and established the HIV Drug Interactions website (www.hiv-druginteractions.org) see **Figure 1**. This is now recognized as the key drug interaction resource for the HIV practitioner [Armstrong & del Rio 2009]. However it is not only the protease inhibitors that give rise to the interaction problem since the non nucleoside reverse transcriptase inhibitors efavirenz and nevirapine are relatively potent inducers of several enzymes and transporters.

Approved Antiretroviral Agents at January 2010			
Approved Drugs With Intracellular Mechanisms of Action			
NRTIs*	PIs	NNRTIs	Integrase Inhibitors
Abacavir	Amprenavir	Delavirdine	Raltegravir
Didanosine	Atazanavir	Efavirenz	
Emtricitabine	Darunavir	Etravirine	
Lamivudine	Fosamprenavir	Nevirapine	
Stavudine	Indinavir		
Tenofovir	Lopinavir/ritonavir		
Zalcitabine	Nelfinavir		
Zidovudine	Ritonavir		
	Saquinavir		
	Tipranavir		

Approved Drugs With Extracellular Mechanisms of Action	
Fusion Inhibitors	
Enfuvirtide	
Maraviroc	

*Not listed are NRTI co-formulations:
abacavir/lamivudine
emtricitabine/tenofovir DF
zidovudine/lamivudine
zidovudine/lamivudine/abacavir

Table 1

Within the last few years there have been significant advances in drugs acting on new targets, particularly the integrase enzyme and the CCR5 receptor. Probably the most exciting drugs are the integrase inhibitors which are designed to stop HIV replication through inhibition of the virus-encoded integrase which is the key to viral genes being incorporated into the DNA of the host cell. Recent data, comparing the efficacy of the integrase inhibitor raltegravir and efavirenz both in combination with 2 N(t)RTIs in adults with HIV infection naïve to therapy, showed a rapid viral decay with a high percentage of patients with plasma HIV RNA below the limits of assay detection at 96 weeks [Murray et al 2007]. So looking back we have to acknowledge the extraordinary advances with a person commencing antiretroviral therapy at the age of 20 or 30 now facing a further 30 or more years of life. Once daily regimens (even one pill once a day) and drugs with less drug interactions (raltegravir) are important contributors to patient compliance which is a critical factor in ensuring sustainability of viral load suppression.



Figure 1

But major challenges remain. All the drugs can cause serious adverse effects. One recent study from the Swiss HIV Cohort found a high rate of adverse effects that were sufficiently serious to result in a change or discontinuation of treatment (22.4 modifications per 100 person years) [Elzi et al 2010]. We need to understand better the underlying mechanisms of adverse effects so that we can inform the next generation of antiretrovirals. Another challenge is resistance. Replication of HIV is highly error prone. Once resistance to a drug is established will there be options remaining for the patients? Clearly we need new drugs with non overlapping resistance profiles and thankfully there is a pipeline of drugs both within existing classes and acting at new targets (attachment inhibitors and maturation inhibitors).

However to benefit from antiretroviral therapy you must know you are infected! It is estimated that approximately a quarter of infected persons in the USA do not know they are infected [Katz 2010], and similar or higher figures will be found in other parts of the world. Hence there needs to be increased access to rapid HIV testing so that patients receive prevention counselling and care is initiated. Despite the effective treatments it would be better to prevent a person becoming infected in the first place. There are currently ongoing studies of pre exposure prophylaxis with daily administration of reverse transcriptase inhibitors. In addition, programmes of needle exchange and opiate replacement therapies are two effective prevention strategies. And then there is the whole vaccine arena which certainly from a theoretical perspective could make huge inroads into the HIV pandemic. However

here we always seem to be hit with disappointment and it is very unlikely that an effective vaccine is within grasp [Virgin & Walker 2010]. Which takes us back to the drugs! Without question there have been incredible advances in treatment. Who could have foreseen how far we have progressed? But can we do better than HAART? We know that we can suppress HIV RNA below the limits of detection and restore immune function. However, there is still the problem of latent replication-competent provirus in resting CD4+ T cells and strategies to attack this reservoir are required if there is any hope of effecting a cure. To meet this challenge an HIV Latency Collaboratory Venture has been proposed (Richman et al 2009) which brings together pharmaceutical companies, academic institutions, government bodies and healthcare professionals.

Clearly there is much work to be done but as Richman et al point out 'if novel scientific insights can be brought to bear in clinically effective ways then the era marked by the benefits of HAART may be followed by one in which HAART is no longer a lifelong necessity'.

David Back, Department of Pharmacology, School of Biomedical Sciences, University of Liverpool

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Robin Hiley,
Vice-President
Meetings

After several years on the south coast, the BPS Winter Meeting returned to London and was held in the Queen Elizabeth II Conference Centre in Westminster. The Winter Meeting is the flagship event of the Society and it brings together the Clinical and Basic sciences, together with a wide range of symposia proposed by the Special Interest Groups and individual members. The BPS would like to take this opportunity to thank our sponsors MEDA Pharmaceuticals, Tocris Bioscience and Matrix Biologicals Ltd.

An important part of the meeting is the opportunity for younger pharmacologists, including undergraduates nominated by their departments, to discuss their science with the more established members of the Society. For the second year in a row, the second day was designated “Young Persons’ Day” and it included a stimulating symposium on ‘Translational Pharmacology’ organized by the Young Pharmacologists’ Committee and supported by GSK. It aimed to explore the optimization of partnerships between industry and academic centres and the drug discovery theme followed on from the morning’s symposium on ‘The kinetics of drug/receptor interactions: the benefit to drug discovery’. The Tocris Lecturer, nominated by the Young Persons’ Committee (YPC) was Alice Tuff of Sense about Science who gave an insightful account of the issues involved in conveying complex science to the general public. After this, Professor Sir Nicolas Wald gave the President’s Lecture in which he dealt with the difficult issue of ‘Pharmacological auto-compensation’. Sadly, some members seem to have missed one of these lectures in the mistaken belief that the lunch bags could not be taken into the lectures.

Young Pharmacologists’ Day was ‘topped and tailed’ by poster sessions in which medical students and basic science students presented their research alongside their more senior colleagues in the Poster Sessions. These sessions provoked much informed and enjoyable discussion and I, for one learned much.

Traditionally, the first day of the meeting sees the Clinical Section’s symposium which, this year, was entitled ‘Delivering safe prescribing in the NHS’ (all health systems want safe prescribing and I hope it was of interest not only to our UK members). This was organized by Simon Maxwell and related to the Society’s initiatives on Safe Prescribing. Tuesday morning also saw symposia on ‘Cannabinoid signalling in brain repair’ and ‘Chemokine antagonists as therapeutic agents’. After the quiet start to the meeting last year, we started at 10 o’clock, and the result was improved attendance at the start of these symposia, the hypothesis that it was due to better accessibility, rather than a recognition that pharmacologists aren’t ‘morning people’ has still to be tested.

The evening included the Specialist Registrars’ Session, which this year was on ‘The many faces of CPT’ and saw leaders in the NHS, academia, the regulator and industry explain the career opportunities for clinical pharmacologists.

Those who fancied a different challenge were invited to a river cruise, organized by the Young Pharmacologists Committee (YPC) and sponsored by Novartis and MedImmune, featuring karaoke, a quiz on London landmarks and a Limerick competition (though I understand these will not be published in *Pharmacology Matters* owing to uncertainty about their academic merit). The next day people were buzzing with the success of the cruise.

The Annual Dinner and Prize Giving on Wednesday was held in what had been the library of the National Liberal Club, under the gaze of British statesman of the 19th and early 20th centuries. Congratulations were given to the large number of prizewinners receiving awards, and we warmly thanked the retiring President, Jeff Aronson, for his time in leading the Society during which he worked hard to increase the prominence of Clinical Pharmacology, particularly, in the eyes of government and the life of the country.

The final day’s programme was again diverse, with something to interest most people. There were symposia on ‘Antibody therapeutics’, ‘Targeting the endocannabinoid system for gastrointestinal diseases’ and ‘The histamine H4 receptor’, all of which contained much material for thought. Our ASCEPT visitor, Professor Alastair Stewart (University of Melbourne), presented a lunchtime lecture on “Glucocorticoid-resistant inflammation and tissue remodelling” which he argued persuasively was a driver for anti-inflammatory drug discovery. After-lunch posters and oral communication sessions served to bring this meeting to a close. It saw increased attendance throughout and a 20% increase in registrations, which suggests the experiment of coming back to London was a success.

However, $n = 1$ is not good enough, and so, this year, we are returning to the Queen Elizabeth II Conference Centre, 14-16 December. The Society extends a warm invitation to all its members and its guests to come and participate in what is one of the biggest and diverse annual meetings of pharmacologists in the world. I hope to see you there.

Robin Hiley, Vice-President Meetings



Jane Mitchell,
Chair of the Young
Pharmacologists'
Committee

It was my pleasure to take over from Professor Robin Plevin as chair of the Young Pharmacologists' Committee for the BPS in January 2010. As Professor of Cardiothoracic Pharmacology and Director of Postgraduate Research at Imperial College London I have had the advantage of working with young pharmacologists for many years. Interestingly, it transpires that I became a member of the BPS before some of the younger members were even born! Which brings me to an important point: the Young Pharmacologists' events are not just for the young, but also for the 'young at heart'!

The BPS Young Pharmacologists' Committee exists to provide a platform for our younger members, enabling them to access activities and forums within the core of the society. This results not only in raising the profile of our younger members but also in real benefit to the Society's activities as a whole. I have been inspired by the

professionalism, enthusiasm and dedication of the Young Pharmacologists' Committee, which not only organizes social events but also scientific and PR activities, as you will see in more detail in the following report from Sara Barnes.

I am very pleased to announce that the Committee was successful in its symposium bid for this year's BPS Winter Meeting. The symposium, entitled 'Pharmacology of Lipid Mediators in Health and Disease', will bring together leaders from various fields of lipid mediator pharmacology and see younger members contributing as both chairs and speakers in the session. I very much look forward to working with the committee over my coming term as Chairperson.

Jane Mitchell, Chair of the Young Pharmacologists' Committee



Sara Barnes,
Young Pharma-
cologists' Editor

2009 Round Up

2009 was an active year for the Young Pharmacologists' Committee with our first-ever symposium at a Winter Meeting. Entitled Translational Pharmacology-optimizing academic/industry partnerships, this event included two talks by young BPS members who discussed their experiences of the benefits and pitfalls associated with academic-industrial collaborations.

In addition to organizing the Tocris lecture given by Alice Tuff from Sense About Science (who was mentioned in Simon Singh's latest best-seller *Trick or Treatment: Alternative Medicine on Trial*), the Committee also ran two well-attended social events at the Summer and Winter Meetings, including a cruise along the river Thames. One young pharmacologist said "The Thames cruise was a really great way to get to meet fellow undergraduates, postgraduates and researchers alike, which meant there was always a friendly face to be seen the next day at the conference!"

Young Life Scientists' Symposium

2010 saw the Young Pharmacologists' committee building on the strengths of 2009 with the Young Life Scientists' symposium on 26 May. Styled The next generation of asthma and allergy research-Tackling a 21st century epidemic, this symposium was a fantastic opportunity for young pharmacologists to present their work and gain valuable feedback and inspiration from others. This fully booked one-day conference for PhD students and early-stage postdocs was jointly organized with the Biochemical and Physiological Societies.

WorldPharma 2010 Social Event

WorldPharma kicks off in Copenhagen this summer and the Committee is organizing an evening social event on Tuesday 20 July for young pharmacologists from around the world to get together and try a few of the local bars in the New Harbour district.

BPS-sponsored Talks

In 2010, also look out for more BPS-sponsored talks at universities around the UK. Societies at King's College London and the universities of Bath, Cambridge and Leicester, amongst others, have all successfully applied for BPS bursaries to invite a guest speaker to give a talk. Upcoming talks, can be found on the Meetings section of the BPS website.

Bursaries for Undergraduates to attend the BPS Winter Meeting 2010

Looking ahead to the Winter Meeting 2010, the Committee will continue offering bursaries of up to £200 to undergraduates attending the Meeting and presenting a poster. Any undergraduate doing a pharmacologically relevant degree will be eligible to apply.

For more details on bursaries and sponsored talks please contact Karen Schlaegel at ks@bps.ac.uk.

We hope to see you in December!



Jeff Aronson,
President Emeritus
BPS

Introduction

The last four years (2006-9) have seen a large number of positive developments in clinical pharmacology in the UK, beginning to reverse the effects of a long period of decline. One of these developments, all of which I have detailed elsewhere [1], was a report of a working group of the Royal College of Physicians of London (RCP), entitled 'Innovating for Health: Patients, Physicians, the Pharmaceutical Industry, and the NHS'. The final recommendation in the report was that 'The RCP should create a Pharmaceutical Forum . . . Ways to trigger a renaissance of clinical pharmacology should be a priority issue for this Forum' [2]. A forum, called the Medicines Forum, has since been established and has reaffirmed that priority; I am currently chairing a working party of that Forum, looking into ways of furthering this aim. One of the many suggestions for further activity that have emerged is that the BPS should publish a manifesto. Such a manifesto has now been published in full [3], and here I present its essential components.

A manifesto is defined in the Oxford English Dictionary as 'a public declaration or proclamation ... esp. a printed declaration, explanation, or justification of policy'; and in extended use 'a book or other work ... propounding a theory or argument'. This manifesto is based on the way that academic and health service clinical pharmacology is practised in the UK. It also recognizes the importance of basic academic pharmacology and of clinical pharmacology in commercial companies and regulatory authorities. Its perspective is for the most part a UK one; however, most of the discussion is relevant to clinical pharmacology wherever in the world it is practised, and it could be used to develop a manifesto elsewhere.

The manifesto consists of:

- A proposed definition of a clinical pharmacologist
- Two complementary definitions of clinical pharmacology, presented as visual representations of (a) the topics that together comprise the discipline (Figure 1) and (b) the inter-relationships among those topics (Figure 2)
- A description of what clinical pharmacologists should be expected to do
- A model of how expertise in clinical pharmacology should be disseminated

A definition of a clinical pharmacologist

A clinical pharmacologist is a medically qualified practitioner who teaches, does research, frames policy, and gives information and advice about the actions and proper uses of medicines in humans, and implements that knowledge in clinical practice.

The scope of clinical pharmacology

The complete scope of clinical pharmacology is illustrated in Figure 1. The heart of it is a list of topics that the subject covers (second column from the right, blue). This list, which shows how principles are translated into practice (left-hand column, red), is based on the paradigm in the second column from the left (green), which shows how molecular mechanisms are translated into the clinical effects of medicines ('from molecules to medicines'). In this paradigm, effects at the molecular level are translated into cellular or tissue effects, which produce organ effects, in turn resulting in effects in the individual; the sum of those individual effects can also be measured in the population.

This paradigm outlines a framework for the ways in which the pharmacological (including toxicological) properties of medicines can be studied:

Molecular pharmacology

- pharmacodynamic effects mediated through receptors, autacoids, enzymes, transporters
- pharmacokinetics (e.g. protein binding)

Cellular and tissue pharmacology

- pharmacodynamics (pharmacology, biochemistry, physiology)
- pharmacokinetics (e.g. drug distribution) and [the biochemistry of] drug metabolism
- the pharmacodynamic and pharmacokinetic effects of genetic variants

Organ pharmacology

- pharmacokinetics (e.g. organ clearance)
- pharmacodynamics
- adverse drug reactions and interactions

Whole body (individual) pharmacology

- pharmacodynamics
- adverse drug reactions and interactions
- practical drug therapy, including prescribing, n-of-1 studies, and monitoring therapy
- clinical toxicology
- psychological and behavioural factors that affect therapy (e.g. adherence)

Population pharmacology

- randomized clinical trials and observational studies (such as case-control studies)
- pharmacoepidemiology, including drug utilization studies
- pharmacovigilance
- pharmacoconomics

- social factors that affect therapy
- medicines policy

The various methods that clinical pharmacologists use to study these processes (such as ligand-receptor binding techniques, pharmacokinetic techniques, monitoring techniques, health economics) go ‘from bench to bedside’ (Figure 1, right-hand column, red).

This list of topics progresses from basic pharmacological studies in humans (human pharmacology), to its practical applications in individuals and populations (applied pharmacology). All of this together constitutes clinical pharmacology, defined in terms of its scope.

Clinical pharmacology—an operational definition

It is convenient to arrange this list of topics in a linear fashion, as shown in Figure 1. However, the repetition of certain items at each level, as listed above, shows that the subject does not operate in linear fashion. In fact, like all science, it operates as a network. This observation leads to an operational definition of clinical pharmacology in the systems approach shown in Figure 2. This representation shows that clinical pharmacology consists of four discrete systems (blue and purple ovals), subdivided into two pairs. The top two systems are the basic tools of human pharmacology (left) and applied pharmacology (right); the bottom two are their practical applications in individuals (left) and populations (right). These systems are interconnected in many ways. For example, in pharmacokinetic-pharmacodynamic (PK/PD) studies the pharmacodynamic measurements can be used to investigate the way in which a system behaves that can be taken from any level of drug action—molecular, cellular, organ, or whole body. At the applied end of the scale, the results of clinical trials and observational studies in large populations, including population dose-response curves and pharmacokinetics, inform clinical practice in the individual patient, and here the major feedback link is via evidence-based medicine; this in turn can inform basic science and pose further questions. For the sake of simplicity some arrows have been omitted from the diagram, for example the to-and-fro link between applied pharmacology and practical drug therapy. At the heart of all this, and

providing missing links, are biomarkers, to which all aspects of pharmacology contribute; however, the diagram performs these interactions—the different ways in which a relevant biomarker relates to the pathway that links the actions of a drug to its effects demand different, usually non-linear, models of such interactions. Finally, drug development in all its pre- and post-marketing aspects hovers over the whole structure (grey oval), feeding off all aspects of it.

These two models (Figures 1 and 2) are not mutually exclusive. Each depicts an important aspect of what pharmacology means for both clinical and non-clinical scientists. Both models have something to say about the relation between clinical pharmacology and translational medicine. The model in Figure 1 stresses the extensive scope of the subject. The model in Figure 2 shows how scientific and clinical developments go hand in hand and

talk to each other, information from one area informing research in another, back and forth.

What clinical pharmacologists do

Mentoring

Clinical pharmacologists are mentors, offering support and guidance to others, advising and/or training them. Teaching is the most important aspect of this. Teaching in academic clinical pharmacology includes laboratory science and clinical science, encompassing not only pharmacology, but such subjects, where relevant, as biochemistry, physiology, statistics, and clinical medicine. Teaching also includes all aspects of practical drug therapy as underpinned by the science of pharmacology. Those taught include research students, both clinical and non-clinical, medical students and doctors in training, senior colleagues in other specialties, pharmacists, and nurses.

Clinical pharmacologists also prepare teaching materials, including journal articles, didactic textbooks, reference books, and e-learning materials, sometimes also part of the framing of policy (see below).

Mentoring also includes sponsoring, protecting, and promoting recognition of one’s junior colleagues.

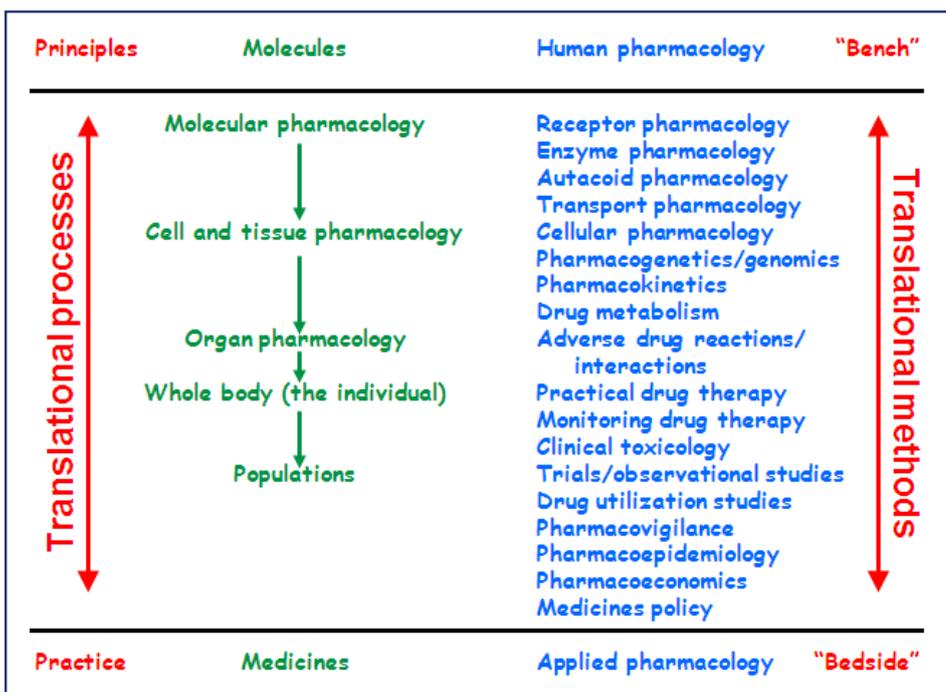


Figure 1: A framework that encompasses the topics covered by clinical pharmacology, from basic pharmacology in humans (human pharmacology) to all aspects of applied pharmacology in individuals and populations.

Research

Clinical pharmacologists are researchers. Academic clinical pharmacologists deal with drug-related problems at any level, from molecular pharmacology to drug therapy in populations, and including all aspects of toxicology; there are also no boundaries to the types of clinical research that they, and their counterparts in drug companies, can undertake, since their interests span all medical specialties in which drug therapy is involved. So, collaborative research is common. Much original research in drug discovery and development goes on in drug companies; clinical pharmacologists play important roles in drug companies and contract research organizations, taking part in all phases of drug development, including pharmacoeconomic assessments.

The methods that are used in this research include not only the tools of pharmacology, but also biochemical, physiological, genetic, statistical, and

epidemiological techniques. They may also involve thought experiments, including definition of terms and classification of systems.

Clinical work

Clinical pharmacologists are physicians and expert prescribers. Clinical pharmacologists who are employed in academic departments or health-care services mostly work as physicians in acute general medicine or clinical toxicology. Many have a special clinical interest, such as hypertension, asthma, or epilepsy, which may feed their research. Some are clinical toxicologists, dealing with poisoning, drugs of abuse, and the toxicology of non-therapeutic drugs and chemicals. In out-patient clinics clinical pharmacologists deal with general medical problems as well as patients with specific drug-related problems. And they will often receive written or telephoned requests, from general practitioners or hospital colleagues, for information and advice about drug-related problems in patients who do not merit direct referral.

Clinical expertise is also important in the design and conduct of drug trials, at all phases of drug development, whether in academic departments, drug companies, or contract research organizations, and in understanding their implications in drug regulation.

Policy

Clinical pharmacologists are policy makers. 'Policy' includes local, national, and international policy related to medicines. These activities take many forms, such as formulary development, medicines licensing, prescribing policies, and development of guidelines. Most are undertaken part time, such as membership or chairmanship of committees. In drug companies work that can be listed under this heading includes preparation and assessment of company dossiers during drug development, pharmacovigilance, and assessment of the benefit to harm balance ('risk-benefit' analysis) and the development of risk management policies.

Some clinical pharmacologists hold permanent positions in regulatory authorities, such as the MHRA, NICE, and the European Medicines Agency (EMA). A few carry out research on medicines policy.

Clinical pharmacologists are also often called upon to give advice outside clinical medicine and areas of medicines policy, and some have set up individual consultancies to provide advice in a wide range of areas related to drug discovery, development, and use. These activities include consultation by drug companies about drug development and advice in legal cases, such as patent disputes or criminal cases involving medicines or drugs of abuse. They may also be called upon by the media to comment on drug-related events of public interest.

A model for the dissemination of expertise in clinical pharmacology

There are currently an estimated 50-60 consultant clinical pharmacologists in UK universities and the NHS. More are needed, not least in order to deliver essential teaching in medical schools, but also to train specialists, both to maintain a critical mass and to provide staff for other organizations, including drug companies and regulatory authorities. The Royal College of Physicians has recommended that 'the workforce requirement for consultants in clinical pharmacology [in the UK] is approximately 200 whole-time equivalents'.

A more realistic expectation would be as outlined in **Figure 3**. It is essential to maintain a core of dedicated academic clinical pharmacologists (inner ring, yellow and purple); a realistic target in the UK would be about 100 such individuals, performing the various activities outlined above, with clinical duties mainly in acute general medicine and toxicology.

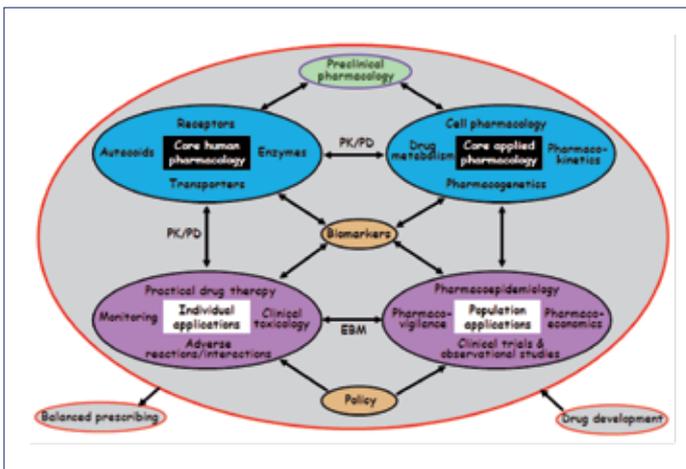


Figure 2: An operational definition of clinical pharmacology (see text for a full description)

Even so, that would not be enough to fulfil all requirements, particularly teaching. The shortfall in the health care services should be made good by a cadre of core clinical pharmacologists working outside academic departments (middle ring, orange and blue), trained in both clinical pharmacology and a second medical specialty, the latter being the career specialty, such as cardiology, geriatrics, or general practice. Others in this group would fulfil the urgent need for clinical pharmacologists in drug companies and contract research organizations and in regulatory authorities.

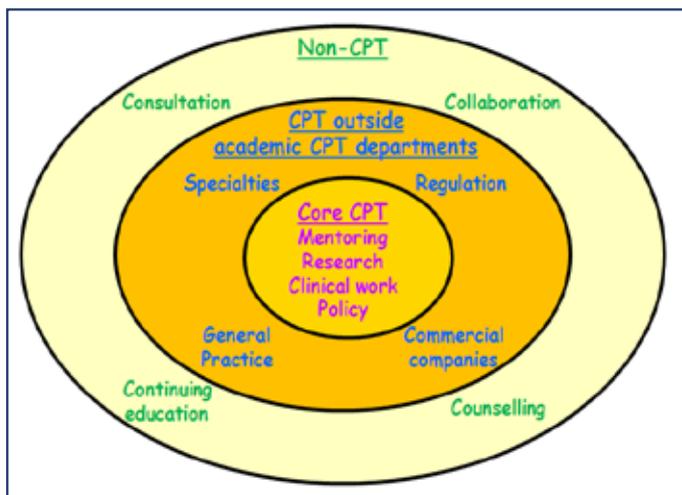


Figure 3: A diagrammatic representation of how expertise in clinical pharmacology should be created and disseminated

As the only clinical specialty that still includes a substantial amount of research training, clinical pharmacology is an attractive option for those who want to pursue a career in academic medicine in no matter what specialty, and should be one of the disciplines used in training Foundation Year doctors on special research programmes and in subsequent Academic Clinical Fellowships.

Those in the two core sectors in this model are in a position to influence the use of medicines in the wider medical and non-medical communities (outer ring, cream and green) by research collaboration, continuing education, clinical consultation, and counselling ('peer mentoring').

Conclusion

Clinical pharmacologists fulfil several different roles, encompassing the complete spectrum of their discipline:

- As laboratory researchers, they rank with other basic scientists as contributors to drug discovery and development
- As reviewers and interpreters of data about medicines they stand beside epidemiologists and statisticians as contributors to drug development and understanding drug action.
- As clinicians they teach their students, inform and advise their colleagues, and complement the activities of their colleagues
in other clinical specialties as contributors to practical drug therapy
- As policy makers they complement the contributions of their colleagues in all fields related to the use of medicines

However, while it is possible for many types of individual, medically qualified or not, to contribute to different aspects

of the discipline, each does it in a different way. Clinical pharmacologists are the only specialists who bring all the important attributes together in the study of the actions of medicines and the application of the basic science of pharmacology to practical drug therapy. And they are, par excellence, medical practitioners and expert prescribers.

Jeff Aronson, President Emeritus, BPS

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Clinical pharmacology in research, teaching and healthcare

In 1970 the World Health Organization (WHO) gathered together a group of experts in clinical pharmacology to produce a guiding document for the discipline. In spite of a number of attempts that document has never been updated and the above titled document has been produced under the auspices of IUPHAR with that purpose.

Professor Folke Sjoqvist and I have acted as editors in bringing together a group of distinguished clinical pharmacologists from Europe, the USA, South Africa and Australia who have contributed articles on the importance of clinical pharmacology in research, teaching (both undergraduate and postgraduate) and healthcare.

There are also sections on the role of Governments and the Pharmaceutical Industry, as well as chapters on the global medicine scene and the contribution that clinical pharmacology makes to global public health.

The document tries to be informative for many people but it is aimed at decision makers who are in a position to increase the role that clinical pharmacology offers to improve healthcare in the world. It will be published in the journal *Basic and Clinical Pharmacology and Toxicology* in July and if you are going to WorldPharma 2010 in Copenhagen you will receive a copy in your registration bag.

We all hope that WHO will develop the document further next year and in the meantime we hope this document will help to increase the growing optimism concerning the future of clinical pharmacology.

Michael Orme, Liverpool University

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