PHARMACOLOGY MATTERS

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

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Navigating the threat of antimicrobial resistance

Bacterial resistance | Global impact | New treatments | Biologics

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Editorial

What must medicine have been like back in the dark ages, where treatable infections and injuries killed? According to UK Prime Minister David Cameron (who brought up the issue at the G7 Summit of leader in Brussels in June), and the World Health Organization (WHO), this is a scenario that could happen if we do not find new and improved antibiotics to combat 'superbugs' and antibiotic resistance. As David Cameron has recently announced that Britain will take the lead on the development of new antibiotics, it seemed apt to discuss these biologic quandaries within this issue.

The first article, on the issues's theme of 'antibiotic resistance', Enoch, Pai and Brown deliberate what antimicrobial resistance means from a clinical perspective, and how this increasing problem needs to be addressed.

Venter then goes on to discuss the global crisis that antibiotic resistance is causing, and the fact that drug-resistant bacteria poses one of the greatest risks to human health. She elegantly describes just how bacteria develop their resistance, and what we can do to try to win this 'war'.

William and Wain look at the challenges and solutions in discovering new antibiotic drugs. They identify the development of more selective antibiotic agents targeted to the pathogen, or 'simply', drugs that replace antibiotics altogether. This idea was covered recently in The Times (4 November 2014), the article reported on scientists within the biotechnology company Micreos who have developed the very first drug to replace antibiotics. A sign of things to come?

CEO of the British Society for Antimicrobial Chemotherapy, Tracey Guise, and Director of Antibiotic Action, Laura Piddock share their perspective on the dual crises of antibiotic resistance and a depleted antibiotic discovery pipeline. They talk optimistically about the future, furnished by the efforts of a growing international group of learned societies and organisations that are working tirelessly in this area.

Finally, Ubah, Porter and Barelle, raises our awareness of biologics, which currently dominate the top 10 blockbuster drugs.

This collection of five articles outlines clearly what the WHO is calling 'one of the most significant global risks facing modern medicine: antibiotic resistance'. It is evident that input is needed from every level, as Dr Jeremy Farrar (Director of the Wellcome Trust) said "this is not just a scientific and medical challenge, but an economic and social one too".

As we move into a New Year, I am looking for budding and eager writers. Is this you? If so, I should very much like to hear from you, so please get in touch (*hom@bps.ac.uk*). Maybe you feel you would be an asset to the Editorial Board, if so, please get in touch, or perhaps your talent is art, and you should like to share your images or create requested images for *Pharmacology Matters*. If so, I want to hear from you!

As 2014 passes, I would like to thank BPS and the *Pharmacology Matters* Editorial Board for welcoming me as Editor-in-Chief, and for their continuing support and enthusiasm for *Pharmacology Matters*.

Lastly, it only remains for me to wish you all a very Merry Christmas and a wonderful New Year.

Felicity

Felicity Gavins
Editor-in-Chief
Pharmacology Matters

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Your BPS

Jono Brüün
BPS Chief Executive

Many of you will have accessed this issue of *Pharmacology Matters* directly (and with a much reduced carbon footprint!) from our website, newsletter or via social media and some of you may have picked it up at the BPS stand during our flagship annual meeting: *Pharmacology 2014*. However you come to read this magazine, I hope you enjoy its mix of pharmacology, Society and membership news.

As we reach December, I thought it would be worth reviewing some of the progress and development made at BPS over the course of the year.

I want to begin my review with one of the year's most recent events. In early November, BPS launched a report highlighting the value of clinical pharmacology and therapeutics (CPT) in the NHS, at an event at the House of Lords, hosted by Lord Robert Winston. *A Prescription for the NHS: Recognising the Value of Clinical Pharmacology and Therapeutics* (*bit.ly/CPT_NHS*) is a considerable achievement for the Society's Clinical Section, under the leadership of its Chair Professor Munir Pirmohamed and Vice President Dr Patricia McGettigan, with support in the BPS office provided by Ruth Meyer.

The report sets out a clear and cogent argument that the NHS will be better served by training and employing 150 CPT consultants by 2025 – up from the current cohort of 77 – with resultant contributions to the health of patients and the wealth of the NHS. I was delighted to see this report coming together, as it relates directly to our charitable objective to promote pharmacology and clinical pharmacology in the UK, and because I firmly believe in the critical role CPT has to play in patient safety and care. We will be working hard in 2016 to support these recommendations among policy and decision makers in the NHS, and will keep you updated with progress.

Another step was made earlier in the year, when BPS bid successfully to host the IUPHAR World Congress of Basic and Clinical Pharmacology in 2022. WCP2022 will be held in Glasgow with two senior Society members at the helm: Professor David Webb will act as President of the Congress, while Professor Amrita Ahluwalia will be its Secretary General.

From a personal standpoint, I really enjoyed seeing my team of staff working with their Officer, Trustee and volunteer counterparts, to create an irresistible bid for the right to organize the meeting on behalf of world pharmacology. I am confident BPS will do a terrific job of hosting and welcoming the international pharmacology community in 2022.

Other developments were perhaps not so visible to our members, but will have a positive impact on the Society in the years ahead.

Council has, over the course of 2014, been reviewing the constitution of the Society and has recommended a revised set of governing documents to the membership. It is hoped that, by slimming down the Society's committee structure and allowing clearer delegation of authority from members to their elected representatives and staff, we will be able to work smarter in the coming years. This is a big deal for any charity, and has been completed with input from a number of senior members. My thanks go to all those who have given their time and efforts to produce our updated governing documents.

We launched our new member database in June after 18 months of deliberation, negotiation and preparation. The database is at the heart of any member organization and we hope the enhanced functionality will provide the foundation for a much better experience for all members, and will give us the information we need to 'greater match the Society's activities to the needs of the Membership', to paraphrase one of our strategic objectives.

My thanks go to all those who were involved in this mammoth project, but Carol Medal and latterly Peter Wright, who were at the coalface in the BPS office, deserve a special mention.

Work also began in 2014 on a new BPS website and a review of our visual identity. As we seek to balance the needs of a member organization – i.e. to be welcoming to old and new members alike – we need to be aware of the value of the Society in the outside world. An updated brand will allow us to protect and grow the Society's already strong reputation, while ensuring a professional and friendly experience for those who come across us. Watch out for further developments next year!

The BPS office in Angel Gate received a bit of a facelift over the summer. Some careful planning allowed us to create more desk space for staff – enabling us to expand in future if there is a demand – and a new and flexible Members' Room and Welcome Area. With photographs of founding members on display next to shots from recent outreach events, I hope the office now reflects BPS as an organization that is steeped in history and has an exciting future. Our meeting rooms are available for you to book as a benefit of membership, so please do not hesitate to contact Paul Tizard (*paul.tizard@bps.ac.uk*) for further information.

Finally, I should note some staff changes in the past year. Jess Strangward, our Head of Education left BPS in November after over three years in post. Jess oversaw a period of significant expansion and development in the Society's education function in the time she was with us, bringing BPS into contact with more members of the public than ever through outreach and engagement programmes, spearheading the Society's co-management of the Prescribing Safety Assessment, and driving our *in vivo* policy and funding work. I'd like to thank Jess for her contribution over that time and wish her all the very best.

Meanwhile, two other members of staff are taking time out from BPS to tend to other important issues: Carol Medal (IT Manager) and Chinara Rustamova (Executive Assistant) went on maternity leave. Carol and her partner Nick's baby, Marnie, was born on 2 July while, as I write, Chinara and her husband are still waiting for their new arrival! We look forward to welcoming Carol and Chinara back to BPS in 2015.

ASCEPT-BPS
JOINT SCIENTIFIC MEETING

ASCEPT

BPS BRITISH PHARMACOLOGICAL SOCIETY

Tomorrow's medicines: pharmacology, patients and populations

19-21 May 2015
University of Hong Kong

On behalf of ASCEPT and BPS we invite you to attend the Joint ASCEPT-BPS Scientific Meeting to be held at the University of Hong Kong from Tuesday 19 to Thursday 21 May 2015. The meeting represents the first joint meeting between the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT) and the British Pharmacological Society (BPS) and will be held in association with the Hong Kong Pharmacology Society (HKPS) and the Asia Pacific Federation of Pharmacologists (APFP). The theme for the meeting is **Tomorrow's medicines: pharmacology, patients and populations**.

This meeting will showcase the world class research undertaken by ASCEPT and BPS members, as well as members and researchers from other pharmacological societies and countries in the Australasian region. Importantly, this meeting offers the opportunity to network with colleagues and other leading international and national scientists and academics during both social and scientific sessions of the programme.

The meeting will include eleven topical symposia, four stimulating plenary lectures, a number of relevant oral paper and poster sessions, and a trade display, as well as a welcome reception and meeting dinner at a famous Hong Kong landmark!

Important dates

- Abstract submission – **now open**
- Registration – **now open**
- Abstract submission deadline – **30 January 2015**
- Early registration deadline – **31 March 2015**

Confirmed symposia include:

- Immunopathogenesis and therapeutics of atherosclerosis
- Novel targets harnessing the therapeutic potential of NO: Nitroxyl, soluble guanylate cyclase and beyond
- Frontiers in neuropharmacology: Molecular targets and translational opportunities
- Phenotyping vs genotyping – choosing the right tool for dose individualisation
- Ion channels as therapeutic targets
- Dimerization and biased signalling of GPCRs
- Toll-like receptor 4: Breaking down the barriers
- Improve ethnic bridging to foster clinical development in China/Asia
- Efficacy and safety: The yin and yang of Chinese and herbal medicines
- Pharmacology education in the 21st Century – to cyberspace and beyond
- Understanding and optimising the effects of multiple medicines in old age

Download the full programme at: www.ascept-bps2015.com

Sponsor and exhibitor opportunities

A range of sponsor and exhibitor opportunities are available for the meeting. To obtain a copy of the prospectus, please visit the website or contact the meeting secretariat, Expert Events.

For more information about the meeting

Please visit www.ascept-bps2015.com
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Antimicrobial resistance in bacteria; a clinical perspective

David Enoch, Sumia Pai and Nick Brown

Clinical Microbiology and Public Health Laboratory
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Antimicrobial resistance (AMR) is a threat to the effective prevention and treatment of an ever-increasing range of infections caused by bacteria, parasites, viruses and fungi. The World Health Organization describes it as an increasingly serious threat to global public health [1]. This article describes the history and clinical effects of AMR and then proceeds to describe what has been done, and what needs to be done to combat this threat.

History

Resistant strains of microorganisms naturally evolve. This occurs when microorganisms replicate themselves erroneously or when resistant traits are exchanged between them. AMR emerged as soon as antimicrobial agents were introduced. The use and misuse of antimicrobial drugs accelerates the emergence of AMR. Poor infection control practices, inadequate sanitary conditions and inappropriate food-handling encourage the further spread of AMR.

Clinical effect

Individuals can become colonized with resistant organisms, in which they have no clinical symptoms or signs of infection. Colonization, however, can precede infection. Infections caused by resistant organisms are associated with increased mortality, morbidity and costs. This may be due to delays in appropriate therapy (leading to worsening condition), and second / third line agents are often be not as good as first line agents. This is the case in MRSA (meticillin resistant *Staphylococcus aureus*), where flucloxacillin is more effective than vancomycin for treating susceptible strains of *S. aureus*. Flucloxacillin is better tolerated than vancomycin. *S. aureus* is typically a skin organism, so screening and decolonisation with topical agents has been shown to reduce colonisation and subsequent infection.

Some organisms normally reside in the bowel. These include Gram negative bacilli such as *E. coli* and *Klebsiella spp.* which belong to the class Enterobacteriaceae. These organisms are the most frequent cause of urinary tract infection but can also cause bowel and biliary tract infections. β-lactamases (enzymes that destroy β-lactam antibiotics such as penicillins) soon emerged, but the pharmaceutical industry also evolved and developed new antibiotics with increasing spectra of activity.

Resistance to third generation cephalosporins (i.e. extended spectrum β-lactamases – ESBL) emerged in *Klebsiella* in the 1980s, typically in hospital intensive care units (ICUs). The resistance mechanism, borne on a plasmid, then spread to other organisms such as *E. coli*. ESBL-producing *E. coli* are now present in increasing numbers of patients in the community [2].This occurs more now that the boundaries between hospital care and community care have become increasingly blurred, in that some patients are treated in both settings, transferred to other institutions, or transferred to nursing / residential homes. The plasmid that carries the ESBL gene also infers cross-resistance to a number of other classes of antibiotics including trimethoprim, fluoroquinolones and aminoglycosides; carbapenems often remain the only treatment available.

Unfortunately increasing use of carbapenems has now selected for the emergence of carbapenem resistant Enterobacteriaceae (CRE). Infections with bacteria expressing ESBL and CRE genes are associated with significantly increased mortality and morbidity compared to susceptible strains of the same organism. Bacteraemias with CRE organisms often have mortality rates approaching 40%. These are proving increasingly difficult to treat. Colistin is occasionally the only antibiotic left to treat infections due to CRE. This antibiotic was introduced in the 1950s but was withdrawn in the 1970s due to concerns with nephrotoxicity and neurotoxicity [3].

Resistance rates in Gram negative bacilli such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii* continue to rise. These organisms typically live in the environment (e.g. taps or dust) and mainly cause infections in patients with significant underlying medical conditions, such as those on ICU or transplant recipients. Another Gram negative bacterium with increasing resistance is *Neisseria gonorrhoeae*, the causative organism of gonorrhoea. This has had significant public health related challenges. Resistance to penicillin and tetracycline are commonly seen, ciprofloxacin resistance is increasing and cefixime resistance is emerging, such that combination therapy is now recommended [4].

Tuberculosis (TB) is a chronic disease that requires patients to take multiple drugs for several months [5]. Multidrug regimens were introduced due to the rapid emergence of resistance when one drug at a time was used (initially streptomycin). However, multidrug resistance (MDR-TB; defined as resistance to rifampicin and isoniazid) emerged when TB rates rose following the rise in HIV cases. XDR-TB (extensively drug resistant TB; defined as MDR-TB as above plus resistant to any fluorquinolone and at least one of the following second-line anti-TB injectable drugs (kanamycin, capreomycin or amikacin)) has subsequently emerged.

What has been done? What needs to be done?

We need to protect the antibiotics currently in use and prevent the emergence and spread of further resistance.

Improvements have been made in terms of understanding the epidemiology of resistant organisms. This has led to interventions such as improved hand hygiene, the use of personal protective equipment, antimicrobial stewardship, active screening for AMR organisms, decolonisation with topical agents (e.g. MRSA), and the use of appropriate empirical antimicrobial agents. Other interventions that reduce the chance of developing an infection are also required; these include good central venous catheter care, urinary catheter care and vaccination.

Antibiotic stewardship aims ensure effective treatment of patients with infection whilst minimizing collateral damage from antimicrobial use [6]. It does this by optimising antimicrobial selection, dosing, route, and duration of therapy to maximize clinical cure or prevention of infection while limiting the unintended consequences, such as the emergence of resistance, adverse drug events, and costs. Education, audit, guidelines and policies, IV to oral conversion and appropriate de-escalation are all necessary, though the roles of combination therapy (except for certain

indications) and antibiotic cycling, where antibiotics are substituted for another in an attempt to transiently decrease selection pressure and reduce resistance to the restricted agent, remain unproven.

Techniques have been developed to help diagnose infection and / or resistance earlier than conventional culture and sensitivity testing. Biomarkers (e.g. procalcitonin) have helped in aiding the diagnosis of infection, thereby potentially reducing unnecessary antibiotic use [7]. Molecular methods such as polymerase chain reaction (PCR) allow earlier detection of organisms (e.g. MRSA) or resistance traits (e.g. in Mycobacterium tuberculosis) much earlier than conventional methods.

Antibiotic use in animals needs to be addressed. The Royal College of Veterinary Surgeons has called for veterinarians to use antibiotics judiciously; these should be different to those used in human medicine.

It is also imperative to reinvigorate the drug development pathways and bring new antibiotics into market. However, bringing new antibiotics to market can give a poor return on investment for a pharmaceutical company, unlike drugs used to treat chronic disease. Antibiotics are used for a comparatively short period of time (typically a few weeks at most) and new agents are used sparingly, often as a last resort to treat resistant organisms. Changes need to occur to help solve the current "innovation / discovery" gap. Suggestions included public-private partnerships could be set up to mitigate the up-front costs of drug discovery, whilst pathogen-targeted approaches need to be developed to optimise efficacy against a single pathogen / resistance mechanism. Changes to orphan drug legislation could help address the issue of needing large numbers of patients thus shortening length of a trial. Other initiatives to improve research and development of new drugs that were suggested included research related tax incentives, patent buyouts, health impact fund and funding translational research.

A large number of initiatives have been implemented in the last decade or so to try and address these from a global political perspective. In 2003 the Infectious Diseases Society of America (IDSA) announced the "Bad Bugs, No Drugs" campaign with recommendations to Congress, the Food & Drug Administration and the National Institute for Allergies & Infectious Diseases [8]. In 2009 the European Union, under the presidency of the Swedish Government, launched the "Innovative Incentives for Effective Antibacterials" campaign [9]. In 2010, the IDSA produced a report entitled "The 10x20 Initiative: Pursuing a Global Commitment to Develop 10 new Antibacterial Drugs by 2020"[10] which aspires to develop 10 new antibiotic agents by 2020. The WHO held a summit called "No action today, no cure tomorrow" in 2011[11]. The New Drugs 4 Bad Bugs initiative is a series of programmes designed to directly address some of the scientific challenges associated with antibacterial drug discovery and development was launched in 2011[12].

The Generating Antibiotics Incentives Now (GAIN) Act was enacted in 2012 in the USA. This provides a payout at the end of the development process with five years of guaranteed market exclusivity and priority review for antibiotics that target certain qualifying pathogens. The President's Council of Advisors on Science and Technology reported about antimicrobial resistance in September 2014[13].

ReAct is a Swedish based action group[14], whilst Antibiotic Action is an independent UK-led global initiative based in the UK [15]. These seek to inform and educate all about the need for discovery, research and development of new antibiotics.

Conclusions

Antimicrobial resistance is an increasing problem that needs to be addressed. There is evidence that momentum is increasing in terms of the realisation that something needs to be done and that something needs to be done now. Whilst we need politicians and the pharmaceutical industry to address the issue of drug development, all clinicians and indeed members of the public, have a responsibility to use the available drugs appropriately – they are a valued resource!

References

1 World Health Organisation. Antimicrobial resistance: global report on surveillance 2014. Geneva. Available at: http://www.who.int/drugresistance/documents/surveillancereport/en/. Accessed 21st October 2014

2 Livermore DM, Hawkey PM. CTX-M: changing the face of ESBLs in the UK. *J Antimicrob Chemother.* 2005 Sep;56(3):451-4. Epub 2005 Jul 8.

3 Li J, Nation RL, Milne RW, Turnidge JD, Coulthard K. Evaluation of colistin as an agent against multi-resistant Gram-negative bacteria. *Int J Antimicrob Agents.* 2005 Jan;25(1):11-25.

4 Chisholm SA, Unemo M, Quaye N, Johansson E, Cole MJ, Ison CA, Van de Laar MJ. Molecular epidemiological typing within the European Gonococcal Antimicrobial Resistance Surveillance Programme reveals predominance of a multidrug-resistant clone. *Euro Surveill.* 2013 Jan 17;18(3). pii: 20358.

5 Mitchison DA. The diagnosis and therapy of tuberculosis during the past 100 years. *Am J Respir Crit Care Med.* 2005;171(7):699–706.

6 Dellit TH, Owens RC, McGowan JE Jr, Gerding DN, Weinstein RA, Burke JP, Huskins WC, Paterson DL, Fishman NO, Carpenter CF, Brennan PJ, Billeter M, Hooton TM; Infectious Diseases Society of America; Society for Healthcare Epidemiology of America. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis.* 2007 Jan 15;44(2):159-77.

7 Schuetz P, Müller B, Christ-Crain M, Stolz D, Tamm M, Bouadma L, Luyt CE, Wolff M, Chastre J, Tubach F, Kristoffersen KB, Burkhardt O, Welte T, Schroeder S, Nobre V, Wei L, Bhatnagar N, Bucher HC, Briel M. Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. *Cochrane Database Syst Rev.* 2012 Sep 12;9:CD007498.

8 IDSA (2004) Bad Bugs, No Drugs. Available at: http://www.idsociety.org/uploadedFiles/IDSA/Policy_and_Advocacy/Current_Topics_and_Issues/Advancing_Product_Research_and_Development/Bad_Bugs_No_Drugs/Statements/As%20Antibiotic%20Discovery%20Stagnates%20A%20Public%20Health%20Crisis%20Brews.pdf Accessed 23rd October 2014

9 European Union (2009) Innovative Incentives for Effective Antibacterials. Available at: https://www.lakemedelsverket.se/upload/nyheter/2009/Rapport%20fr%C3%A5n%20m%C3%B6tet.pdf Accessed 23rd October 2014

10 Infectious Diseases Society of America. The 10 x '20 Initiative: pursuing a global commitment to develop 10 new antibacterial drugs by 2020. *Clin Infect Dis.* 2010 Apr 15;50(8):1081-3.

11 WHO (2011) No action today, no cure tomorrow. Available at: http://www.who.int/dg/speeches/2011/WHD_20110407/en/ Accessed 23rd October 2014

12 ND4BB. Available at: http://www.nd4bb.eu/index.php/project Accessed 23rd October 2014

13 PCAST report. Available at: http://www.whitehouse.gov/sites/default/files/microsites/ostp/PCAST/pcast_carb_report_sept2014.pdf Accessed 23rd October 2014

14 http://www.reactgroup.org/ Accessed 23rd October 2014

15 http://antibiotic-action.com/ Accessed 23rd October 2014

About the authors

David is a Consultant Medical Microbiologist in Cambridge, having previously worked in Peterborough, Cambridge and London in Microbiology and London and the south east in General Medicine & Infectious Diseases. He trained in London.

Nick qualified with the degree of MBChB from the University of Bristol in 1985. He has an MD from the same University and MA from the University of Cambridge. He is a Fellow of both the Royal College of Physicians and the Royal College of Pathologists. Nick is a consultant medical microbiologist at Addenbrooke's Hospital in Cambridge, where he has been Trust infection control doctor since 1997. He is also clinical director in the Public Health England (PHE) Lead Public Health Laboratory providing clinical microbiology services to hospital Trusts in Cambridge and Huntingdon and an associate lecturer at the University of Cambridge. He has a particular interest in the use of antibiotics and antibiotic resistance. He is currently President of the British Society for Antimicrobial Chemotherapy (BSAC).

Sumita is currently a senior specialty trainee in medical microbiology at Addenbrookes Hospital, Cambridge. Her undergraduate training was in Sheffield where she subsequently undertook paediatric training. She has worked in microbiology for the last five years and takes an active role in antibiotic stewardship in the Trust. She regularly audits the resistance rates in the paediatric oncology population and reviews Trust wide antibiotic guidelines (especially those for central nervous system infections). She has an interest in paediatric microbiology, especially Clostridium difficile infections in children and has authored papers on this subject.

The global crisis of antibiotic resistance

Rietie Venter
University of South Australia

The serendipitous discovery of penicillin started a new era in medicine; the era of antibiotics. This was a hopeful, positive time where the action of antibiotics was likened to seeing a miracle happening before your eyes. Today, less than ninety years later, we are bombarded on a daily basis with newspaper headlines about dangerous superbugs, impervious to our best antibiotics and treatments.

We are heading towards a post-antibiotic era

Drug-resistant infections are costing the medical industry billions of pounds a year and antibiotic resistance is one of the world's most pressing health problems. The World Economic Forum stated in its 2013 Global Risks report that drug-resistant bacteria poses one of the greatest risks to human health[11]. In addition, the World Health Organization has recently released a report on antimicrobial resistance and concluded that *"a post-antibiotic era – in which common infections and minor injuries can kill – far from being an apocalyptic fantasy, is instead a very real possibility for the 21st Century."* [10]

ESKAPE-ing antimicrobials

The most notorious of the drug-resistant organisms are the so-called ESKAPE pathogens: *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumonia, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacter species*[1]. These organisms are hospital-acquired pathogens that cause life-threatening infections such as pneumonia, urinary tract infections, bloodstream infections, and in the case of *P. aeruginosa* fatal infections in people suffering from cystic fibrosis (the most common inherited genetic disease in the UK). The ESKAPE pathogens are all characterized by a very high level of antibiotic resistance. For instance, in some countries antibiotics do not work in more than 50% of people with *K. pneumonia* infections[10].

Most of the ESKAPE pathogens are widespread in nature. *P. aeruginosa* is particularly ubiquitous. In hospitals it can be found in food, sinks, taps, mops, respiratory equipment and worryingly in the disinfectants used to clean hospital wards. *P. aeruginosa* is also a common contaminant of pharmaceutical preparations as it is able to survive many of the preservatives used to limit bacterial growth. In fact *P. aeruginosa* can use parabens (one of the most widely used group of preservatives) as a source of nutrition, not that much nutrition is needed – this organism has very simple nutritional requirements and is notorious for being able to grow in distilled water.

How do bacteria develop resistance?

Bacteria may be inherently resistant to an antibiotic by, for instance, lacking the target of that specific antibiotic. Gram-negative organisms are intrinsically much more resistant than Gram-positive organisms as they have a double membrane, which acts as a permeability barrier against antibiotics. For example, vancomycin is one of the few antibiotics that is still active against methicillin-resistant *Staphylococcus aureus* (MRSA). However, Gram-negative organisms are completely resistant against vancomycin as the antibiotic cannot penetrate through their outer membrane.

Figure 1: Summary of the different mechanisms by which bacteria can acquire antibiotic (AB) resistance

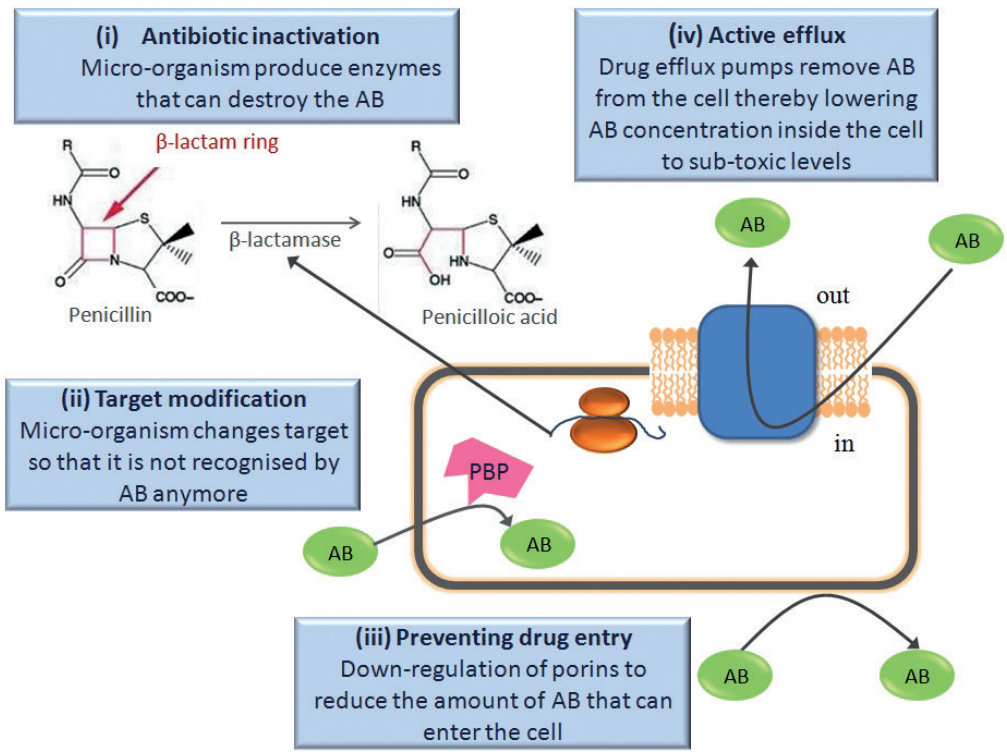
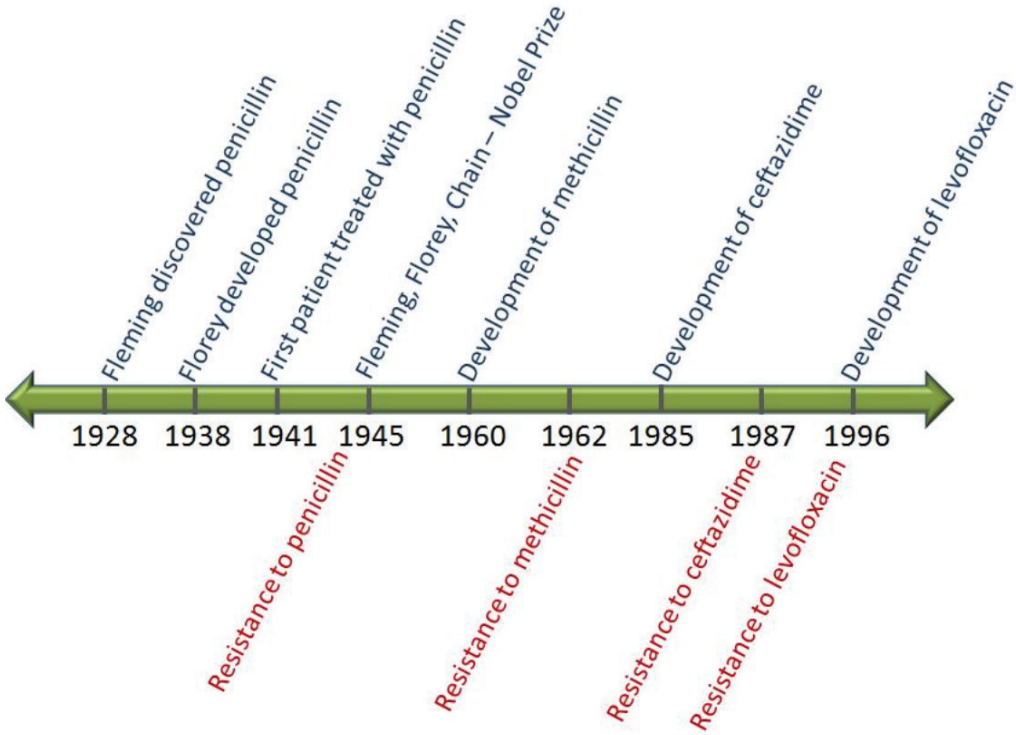


Figure 2: Historical timeline for penicillin and the development of some antibiotics resistance events.



Bacteria can also develop resistance mechanisms to deal with specific classes of antibiotics (Figure 1). Acquired resistance can be divided according to mechanism into:

- Antibiotic inactivation (e.g. pathogens secrete β-lactamases that hydrolyses and deactivates β-lactam antibiotics such as penicillin).
- Target modification/alteration (e.g. MRSA uses a different penicillin binding protein (PBP) which are not a target for penicillin and related compounds).
- Preventing antibiotic entry – Pathogens can down-regulate the expression of porins in their membrane to reduce the amount of antibiotics that can enter in the first place.
- Antibiotic efflux – Removal of antibiotics from the bacterial cell by drug efflux pumps.

Drug efflux pumps confer multi-drug resistance

Drug efflux pumps are protein assemblies that span the membrane of bacteria and actively pump antibiotics from the cell, thereby lowering their concentration inside the cell to sub-toxic levels (Figure 1). An intriguing aspect of drug efflux proteins is their ability to recognize and expel a wide spectrum of structurally unrelated compounds[6]. The clinical implication of this substrate promiscuity is the development of multidrug resistance i.e. the ability of pathogens to survive many different classes of antimicrobials[7].

Drug efflux pumps are also implicated in bacterial pathogenesis, virulence and biofilm formation[8]. In addition, functional efflux pumps are necessary for the selection of drug resistant bacteria. When bacteria are first challenged with an antibiotic, their non-specific constitutively expressed drug efflux pumps provide emergency resistance until they have adapted sufficient mechanisms to deal with the particular antibiotic via more specific means, such as drug inactivation.

Due to the crucial role of drug efflux pumps in multidrug-resistance and virulence, efforts could be concentrated on developing inhibitors for these proteins as this would prevent other mechanisms of resistance from developing. Finding ways to reverse drug resistance or lower virulence could also be better in terms of the development of resistance. If the organism is not killed outright by the drug, but rather rendered non-pathogenic, the selective pressure to develop resistance would be lowered.

In Gram-negative organisms drug efflux pumps form assemblies of three different proteins that span the double membrane as well as periplasmic space to effectively remove antimicrobials and confer resistance. Due to the complexity of these macromolecular assemblies, progress on elucidating their structure and function was slow. The structure of a functional, fully-assembled tripartite drug efflux pump from a Gram-negative bacterium has only very recently been reported[4]. Advances such as these offer hope for the development of new classes of antibiotics aimed at novel targets.

Antibiotics have a short lifespan

The development of resistance to antibiotics was always going to happen. Under ideal circumstances bacteria can divide every 20 minutes. Compare that to the average human lifespan of about 70 years and it is clear that bacteria has an enormous evolutionary advantage. They are incredibly adaptive and can alter their gene expression and subsequent protein expression in order to survive and cope with the treatments that we confront them with.

In fact, antibiotic resistance is ancient. The genes that code for resistance mechanisms against β-lactams, tetracycline and vancomycin was found in 30,000 year old sediments[3]. Therefore, the average antibiotic has a very short lifespan and in most cases resistance to an antibiotic emerge within 1–4 years of its introduction to the market (Figure 2).

As with any other drug it is a long and expensive process to develop a new antibiotic. However, unlike many drugs for chronic conditions, such as high blood pressure which are taken the rest of a patient's life, most courses of antibiotics are only taken for 1–2

weeks. Moreover, if an antibiotic is extremely effective, its use will be limited to last resort only in order to prevent development of resistance [5,9]. These factors, combined with the short life span of average antibiotics, mean that the development of new antibiotics is not a very attractive target for pharmaceutical companies, who tend to concentrate their efforts on less risky prospects[2]. It is no wonder then that in the past couple of years more hair loss products made it to the market than antibiotics.

What should we do?

Even though we cannot stop the development of resistance, we could significantly slow it down with good antibiotic stewardship to limit the inappropriate use of antibiotics. There is an urgent need for funding of collaborative research programmes into the causes of and remedies for antibiotic resistance. We also need to raise awareness worldwide with education and training programmes. Antibiotic resistance is a global problem and it would need a global approach to preserve the miracle of antibiotics and stem the tide of drug-resistant, untreatable infections.

References

1. Boucher HW, Talbot GH, Bradley JS, Edwards Jr JE, Gilbert D, Rice LB, Scheld M, Spellberg B, & Bartlett J. Bad Bugs, No Drugs: No ESKAPE! An Update from the Infectious Diseases Society of America. *Clinical Infectious Diseases 2009*, 48:1–12.
2. Cooper, MA & Shlaes, D. Fix the antibiotics pipeline. *Nature 2011*, 472:32.
3. D'Costa VM, King CE, Kalan L, Morar M, Sung WWL, Schwarz C, Froese D, Zazula G, Calmels F, Debruyne R, Golding GB, Poinar HN & Wright GD Antibiotic resistance is ancient. *Nature 2011*, 477:457-461.
4. Du D, Wang Z, James NR, Voss, JE, Klimont E, Ohene-Agyei T, Venter H, Chiu W & Luisi BF. Structure of the AcrAB–TolC multidrug efflux pump. *Nature 2014*,. 509:512-515.
5. Hogberg LD, Heddini A and Cars O. The global need for effective antibiotics: challenges and recent advances. *Trends in Pharmacological Sciences 2010*. 31:509-515.
6. Lomovskaya O, Zgurskaya HI, Totorov M. & Watkins WJ. Waltzing transporters and'the dance macabre'between humans and bacteria. *Nature Rev Drug Discov 2006*, 6:56-65.
7. Piddock, LJ. Clinically Relevant Bacterial Chromosomally Encoded Multi-Drug Resistance Efflux Pumps. *Clinical Microbiology Reviews 2006a*. 19: 382-402.
8. Piddock, LJ. Multidrug-resistance efflux pumps? not just for resistance. *Nature rev Microbiol 2006b*, 4:629-636.
9. Silver, LL. Challenges of antibacterial discovery. *Clinical Microbiology Reviews 2011*. 24:71-109.
10. WHO. Antimicrobial resistance: global report on surveillance 2014. www.who.int/drugresistance/documents/surveillancereport/en/
11. World Economic Forum Global Risks 2013. Section 2: 28-33

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Resurrection of a therapeutic area - problems and solutions in the discovery of new antibiotic drugs

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Antibiotic resistance represents a global problem that threatens the progress made in healthcare provision. Nearly every area of medicine will feel the impact of untreatable infection. For example, all surgical procedures, even currently straightforward 'routine' out-patient procedures, will carry the risk of treatment-induced complications; the immunosuppression of patients, undergoing chemotherapy or organ transplants, will leave them vulnerable to opportunistic environmental bacteria and the management of elderly patients would become focused on preventing infection. Indeed the risk from bacterial infection could become the greatest threat to the successful management of many patient groups. This threat is reinforced by the large number of deaths already due to antibiotic-resistant bacteria (over 40,000 per year in the US and Europe) and the far greater number of people suffering long term or multiple infection-related hospital stays or disablement. To prevent this worrying future from becoming a reality we need to learn from history and improve the way we use antibiotics, but this is not enough – we also need new antibiotics.

Antibiotics have been used successfully in medicine to treat bacterial infections since the 1930s. The initial antibiotic chemical class (chemotype) sulfonamides were followed in the 1940s by the first beta-lactam penicillin antibiotics. The introduction into clinical use of both classes (and all of the subsequent twenty or so chemotypes) was rapidly pursued by the problem of drug resistance, a process where bacterial evolution overcomes the drug's efficacy, rendering it ineffective.

These first two antibiotics were examples of a fully synthetically-derived drug (sulphonamide) and one isolated from a natural fungi source (penicillin), and demonstrate a theme echoed by all later drugs where no single chemotype can overcome the threat of resistance. Resistance may already exist before the antibiotic is used by man, preserved in the gene pool. For example, resistance to the beta-lactam class of antibiotics (the penicillins) has existed in nature for at least half the age of the earth[1]. Resistance can also arise through spontaneous, or induced, mutation and be selected for by the use of the antibiotic. In many cases resistance can easily be passed between bacteria of the same or different species.

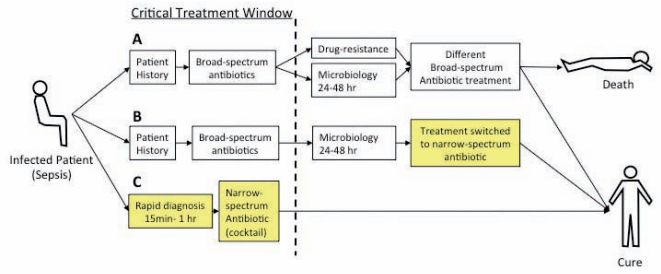
One of the advantages in the early days of the anti-bacterial era was the broad spectrum nature of antibiotics. This meant that limited or no diagnosis of the specific infection was required prior to treatment. In addition, drugs could be used prophylactically to prevent potential infection in complex surgical procedures or diseases with infection risk such as cystic fibrosis.

Whilst the advantages of broad spectrum antibiotics are clear, there are also major problems with their widespread use. The human bacterial flora or microbiome weighs approximately 1kg and is composed of thousands of different bacterial species with chromosomes that contain many more times the DNA of the human genome. When treating a single pathogen with a broad spectrum antibiotic, parts of the microbiome are also exposed to an antibiotic which is toxic to them. This results in the obliteration of susceptible members and the proliferation of those with inherent, or acquired, resistance. Scientific research (and for many of us personal experience) has shown that resistance to antibiotics can be easily transferred between bacteria in the microbiome, providing both a survival advantage and a reservoir of resistance genes for pathogens[2]. Furthermore, the 'collateral damage' caused by alteration in the microbiome from the broad spectrum antibiotic can cause disease directly. A notable example being colonisation of the gut by *Clostridium difficile*, leading to life-threatening disease, involving swelling of the bowel and inflammation of the colon, after severe reduction of the gut microbiome. Some broad spectrum antibiotics have been deselected by the NHS because their use is associated with a high risk of *C. difficile* infection.

The appeal of broad spectrum antibiotics has been historically attractive, yet the discovery of new chemotypes has been painfully slow with only a handful of these coming to market over the past forty years. Drug development pipelines continue with modifications to existing scaffolds to help overcome bacterial resistance, improve pharmacokinetics or extend antibacterial profile, but not providing a long-term solution to drug resistance. One of the reasons for this current situation has been the issue of return-on-investment for pharmaceutical companies with research and development costs not being recouped by expectations on drug pricing and short market life. These metrics, along with company mergers, led to a general withdrawal from the area by the pharmaceutical sector.

The companies still actively engaged in research embraced the emerging molecular, genetic and synthetic chemical technologies of the 1990s in their attempts to generate new broad spectrum antibiotics. Unfortunately these methods were largely unsuccessful for two reasons. The first was that there had been a rationalisation of pharmaceutical company compound screening collections based on strict adherence to physicochemical criteria recommended for identifying orally active drugs. Unfortunately, these criteria defined by Lipinski *et al*[3] were too widely adopted and not designed to accommodate antibacterial molecules, which meant that potential new antibiotic chemotypes were discarded or new ones not included as collections were grown or renewed. The second reason for antibiotic discovery failure was the move to *in vitro* target-based screening. Proteins essential for bacterial growth were identified from genomic sequencing as potential targets conserved across multiple bacteria and were screened against compound libraries in isolation to find blocking ligands. These ligands were optimised using medicinal synthetic chemistry resulting in some cases in very active (picomolar potency) compounds. Unfortunately, the optimisation process could not include the unknown rules of getting chemicals through the cell wall structure of bacteria, so they were inactive against whole cells[4]. Whole-cell screening was also used to look for new compounds that killed bacteria, with some success, however methods were not available to triage the many less-potent hit compounds for rational synthetic chemistry programmes: an embarrassment of hits with nowhere to go.

Figure 1



Potential treatment options for blood-borne infection (sepsis) where every hour's treatment delay is a major threat to life. Patient will die within critical treatment window (A & B) if inactive (drug resistant) antibiotic given. Yellow boxes show future-proof treatment options only possible with new antibiotic funding/payment models

An attractive solution to the lack of antibiotics, which would also reduce the problems of cross-resistance and effects on the natural microbiome, is the development of more selective antibiotic agents targeted to the pathogen. This concept – One Bug, One Drug – increases the potential hit rate in screening campaigns, as compounds don't have to hit multiple bacteria and improves the chances of finding a potential drug. Importantly this concept also aids in chemical optimisation, allowing scientists to steer the chemistry towards one pathogen-specific macromolecular target, not worrying about the more complex task of making a molecule bind to several related, but slightly different, binding sites. More focused chemistry also reduces the risk of compound off-target toxicity.

Several companies are now working on this new approach: Debiopharm with specific compounds targeting *S. aureus*; Polyphor targeting *P. aeruginosa*; Summit plc targeting *C. difficile* and Discuva with an antibiotic discovery 'engine' being used for many different pathogens. The approach used by Discuva uses a combination of advanced techniques including huge collections of gain- and loss-of-function function bacterial variants, next-generation sequencing and enormous bespoke data processing capabilities. Combined this 'platform' provides a method of triaging hits identified from whole-cell bacterial screens providing a route to drug development. The platform output is the identity of the hit compound macromolecular target, associated biochemical pathways involved in the compound mechanism-of-action and potential resistance mechanisms that could arise and allow the bacteria to evade the actions of the compound. This wealth of information is essential for choosing, with confidence, the right compound to progress; providing somewhere to go for the relatively small proportion of hits most likely to make it to the clinic as drugs.

One barrier to this optimistic future of using targeted antibiotics is the need to know the cause of the infection before treatment can be instigated. There is currently a revolution driving the development of new diagnostic technology for infectious disease. Rapid PCR based identification of pathogen and resistance genes has been available, and used for the diagnosis of viral infections for decades, but not implemented for many bacterial infections because of the lack of susceptibility data to guide treatment[5]. The newest technology, nanopore sequencing, combined with rapid sample preparation promises to detect resistance and identify the causal agent directly from clinical samples. Commercial exploitation of this technology will improve the clinical management of infection and open up markets for targeted antibiotics.

The next big battle in the area is establishing a new antibiotic cost model that works for both the pharmaceutical companies and healthcare providers.

The huge success of antibiotics has led to complacency in the economic models where antibiotic price expectations do not match the cost of their development or their economic benefit to society, meaning there are currently no financial drivers for creating new antibiotics[6]. Efforts both in Europe and the US are now focused on fixing the model, by reducing the size and costs of clinical trials and providing financial incentives for entry into this much needed therapeutic area. Such incentives include antibiotic patent life extensions, license agreements for product access or voucher schemes, where provision of a marketed antibiotic could allow a patent extension of a drug in another more financially lucrative therapeutic area.

The UK government recently commissioned a study led by the economist Jim O'Neill in collaboration with the Wellcome Trust to provide a financially-robust solution to this problem. Such a model must include the use of new antibiotic combinations, an approach used so successfully to combat HIV infection, which could lead to a mix-and-match approach combining new non-toxic targeted medicines to stay ahead of antibiotic resistance and prevent the dawn of a post-antibiotic era.

References

1. Hall BG, Barlow M. Structure-based phylogenies of the serine beta-lactamases. *Journal of Molecular Evolution* 2003. **57**(3): 255-60.
2. Modi SR, Collins JJ, Relman DA. Antibiotics and the gut microbiota. *The Journal of Clinical Investigation* 2014. **124**(10): 4212-8.
3. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Advanced Drug Delivery Reviews* 2001. **46**(1-3): 3-26.
4. Payne DJ, Gwynn MN, Holmes DJ, Pompliano DL. Drugs for bad bugs: confronting the challenges of antibacterial discovery. *Nature Reviews Drug Discovery* 2007. **6**(1): 29-40.
5. Livermore DM, Wain J. Revolutionising bacteriology to improve treatment outcomes and antibiotic stewardship. *Infection & Chemotherapy* 2013. **45**(1): 1-10.
6. Spellberg B, Rex JH. The value of single-pathogen antibacterial agents. *Nature Reviews Drug Discovery* 2013. **12**(12): 963.

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Square peg, round hole? Addressing the need for new treatments for bacterial infections whilst using antibiotics carefully

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Antibiotics have, without doubt, transformed healthcare and have brought unprecedented health benefits worldwide. Within two decades of Sir Alexander Fleming's discovery of *Penicillium* mould in 1928, healthcare progressed more than in the two millennia prior to their discovery. It is beyond question that antibiotics are the mainstay of human medicine. In the presence of effective antibiotics almost anything is possible; they are life-saving, life-enhancing, life-extending and enabling agents, without which medicine (as most know it) would not exist. They are the platform on which most, if not all, modern healthcare therapies and procedures stand. Through them our expectations for health and wellbeing are met, with treatments for common and rare infections enabling survival to adulthood and old age. Antibiotics can extend life for those with chronic conditions such as cystic fibrosis. Antibiotics also enable complex surgical transplant procedures and joint replacements to take place, and are vital to successful cancer therapy regimens.

Global health is facing a dual crisis of antibiotic resistance and a depleted antibiotic discovery pipeline. There has been ample warning of the crisis we now face, with physicians and scientists predicting the rise in antibiotic resistance for over a decade. Over 90 inquiries, reports and recommendations, including several by the World Health Organization (WHO), were published globally between 1998 and 2013. The reports were well-received, reported on and acknowledged in medical and scientific circles, but the public remained largely unaware of the problem pending. It has been frustrating for those involved across research, clinical practice and academia especially when other therapy areas reliant on antibiotics have apparently thriving discovery and development pipelines. Imagine the outcry if there were so few new cancer treatments in the pipeline globally, yet the potential size of antibiotics available to defeat a growing number of multidrug-resistant bacterial infections is undeniably small.

The pharmaceutical industry, duty bound to provide a return to its investors, does seem to have been listening, being only too aware of the damage caused by antimicrobial resistance and of the downward impact it had on the life-span of the antibiotics they had developed. As the financial impact of rising resistance rates was felt, the regulatory environment was becoming increasingly complex, and in turn expensive, which saw the development of antibiotics become a high-risk-low-return activity. The consequent effects have been significant and have brought antibiotic discovery and development to its knees. Multiple mergers has seen the number of pharmaceutical companies diminish; with those producing new antibiotics reduced significantly. The golden era of antibiotic development was over. Sixteen systemic antibacterial agents reached market from 1983–1987 compared to the two approved for human use from 2008–2012. Even these are not adequate to meet current needs, with new drugs reaching the patient being predominantly those active against Gram-positive bacteria such as MRSA or minor modifications of previous agents, and this trend continues in the current pipeline.

This is of critical concern in the face of the continued emergence of new types of resistance and spread around the world, particularly in Gram-negative bacteria including *Escherichia coli* and *Klebsiella pneumoniae*, for which there are few – and sometimes no – effective treatments. In April 2014, WHO published its first report on the global status of antimicrobial resistance, indicating that this problem is widespread.. Averting this crisis under current regulatory and economic arrangement is akin to putting a square peg into a round hole. Simply repeating past practices in the hope of success have proved futile, and until recently there was little evidence of progress or political impetus necessary to bring about change.

There is now hope on the horizon, furnished by the efforts of a growing international group of learned societies and organizations that have worked continuously and tirelessly to raise the profile of the dilemma faced and influence those in the research, political, economic and public arenas through education and continued pressure for action. Amongst these organizations are ReAct and Antibiotic Action (BPS signed the Antibiotic Action Petition, supporting the need for effective antibiotics, in 2013) in Europe and the Alliance for Prudent Antibiotic Use, CDDEP and the Pew Trust in the US. These influential organizations and others like them have provided the resources and motivation necessary to kindle action that will hopefully bring about change. Their collective messages are finally being heard and there are definite signs that the landscape is at last changing, with professional interest and campaign action helping accelerate the pace of change worldwide.

Political recognition is also growing. In 2009 the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) was established by US Presidential declaration, issuing its first report in September 2012, identifying the need for intensified cooperation between the USA and the EU. The USA Food and Drug Administration also announced the formation of a task force to support development of the Antibacterial Drug Development Task Force (ADDTF) to assist in developing and revising guidance related to antibacterial drug development, as required by the Generating Antibiotic Incentives Now (GAIN) and Food and Drug Administration Safety and Innovation Act (FDASIA), that was signed into US law on 9 July 2012. In September 2014, President Obama issued an Executive Order 'Combating Antibiotic-Resistant Bacteria'. In the EU, as a result of the WHO and EU Action plans on antimicrobial

resistance, both published in 2011, the European Medicines Agency has been reviewing the requirements for clinical trials of antibacterial treatments. The World Economic Forum Global Risks Report 2013 and 2014 also recognized the magnitude of the global burden of antibiotic resistance by its inclusion on the global risks register. In India, publication of the Chennai Declaration led to changes in Indian law aimed at ending the sale of over-the-counter antibiotics.

October 2014 saw the launch of major new European initiative *Driving Reinvestment in R&D and Responsible Antibiotic Use* (DRIVE-AB). DRIVE-AB is a €9.4 million public-private consortium, funded by the EU Innovative Medicines Initiative (IMI). This initiative aims to define a standard for the responsible use of effective antibiotics, and to develop, test and recommend new economic models for pharmaceutical industry investment in producing new ones. This innovative project brings together 17 partner organisations from 11 countries across the EU; the initiative will guard against what has been done in the past and begin to act on what we already know to bring new solutions to market.

The past 18 months have seen unprecedented UK political activity and global leadership. June 2013 saw the establishment of The All Party Parliamentary Group on Antibiotics, chaired by Jamie Reed MP, Shadow Minister for Health, helping to ensure antibiotics remain high on the political agenda. The UK Government's five-year strategy on antimicrobial resistance was also published in 2013. In July 2014, the UK Parliamentary Science and Technology Select Committee reported on the findings of its inquiry into antimicrobial resistance, and in a landmark event antibiotics won public support and was voted the winning topic of the £10 million Longitude Prize. Perhaps of highest political significance, the UK Prime Minister David Cameron declared in July 2014 the need for urgent and global action. This was followed by the launch of a Commission on Antibiotic Resistance under the leadership of the renowned economist Jim O'Neill.

With all this activity, it is hoped that governments will respond as they have to other public health crises such as Alzheimer's disease and obesity, and identify dedicated and properly funded mechanisms that will further the scientific base for understanding the biology, clinical and societal impact of antibiotic resistance (how resistance occurs, how it is spread and the financial cost), facilitate drug development and stimulate economic development. Enabling small and medium-sized enterprises (SMEs), academia and Pharma to work together collaboratively, capitalising on their abilities to accelerate the discovery of new ways to prevent and treat bacterial infections is essential. Regulators and economists must work together across international boundaries to examine and safely redefine the regulatory and financial models that govern the development and marketing of antibacterial agents to facilitate a full return to this market by industry.

Lastly, it is imperative that all stakeholders – professional, political, public, industrial – understand the importance of ensuring antibiotics are used appropriately and with the respect they deserve. Antibiotics are used widely in many settings and so discouraging use other than to treat bacterial infection is essential. Education on appropriate use will include instruction on curtailment of use where there is no bacterial infection and restricting the purchase of antibiotics by the general public, which is widespread in some. Internationally, learned societies must work together so that prescribing of antimicrobial agents is included in the training and education of all prescribers. To assist in this process the University of Dundee and British Society for Antimicrobial Chemotherapy are working with colleagues globally to develop a Massive Open Online Course (MOOC) on Antimicrobial Stewardship. The aim of this course is to pool international expertise and deliver global training opportunities in the responsible use of antibiotics.

The British Pharmacological Society supports the training and education of prescribers through the Prescribing Safety Assessment (www.prescribe.ac.uk/psa/). The assessment question bank contains approximately 200 questions regarding antimicrobials.

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Biologics in disease targeting; a case for "the smaller, the better"

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Biologics, also known as biopharmaceuticals, have a number of definitions but here, they are considered as therapeutic agents of biotechnological origin that contain proteins derived from recombinant DNA technology and hybridoma techniques. Recombinant proteins used in therapy can be derived from cell lines maintained in long-term culture, and more recently from genetically engineered prokaryotic cells (e.g. *Escherichia coli*). Some examples of biopharmaceuticals include biological proteins (e.g., cytokines, hormones, clotting factors), monoclonal antibodies (mAbs) and alternative binding scaffolds, protein/peptide vaccines, even cell/tissue-based therapies. For the purpose of this article we will focus on mAbs and a comparison to the next generation of small single-domain antigen binders that are derived from antibody and non-antibody sources.

Advances in recombinant DNA, protein engineering and phage display technologies, coupled with a greater understanding of disease processes, have resulted in the successful development and production of a growing number of clinically available therapeutic and diagnostic biologics[1,2]. This growth is reflected by the 2012 global spending on new drug development, which was in excess of $80 billion with biopharmaceutical research accounting for about 50% of this total budget.

Biologics currently dominate the top 10 blockbuster drugs (annual revenues of greater than $1 billion), accounting for a market value of $150.1 billion in 2011 and with a predicted revenue generation of $251.8 billion by 2017[3]. Although the USA is currently the biggest player in the biologics market developing countries such as Brazil, India, Russia and China are exhibiting strong growth and gaining a significant position globally [4].

MAbs are currently "top of the leader board" as they represent about 32% of overall revenue (≈ $48 billion). This is expected to reach $90 billion by 2017, giving an estimated compound annual growth factor (CAGR) of 11.8%. As of February 2013, 39 mAbs had been approved for therapeutic use, and over 350 were in clinical development[3,5,6].

It is important to note that chronic inflammatory diseases and cancers are the primary indications for antibody therapy due in part to the systemic accessibility of the target antigen, target specificity and minimal off-site toxicity. Of the 28 USA and Europe market-approved mAbs fewer than half are recognised unique targets, with four targeting TNF-a and CD20 and two each targeting EGFR and VEGF[5]. The inherent advantages of mAbs over small molecules are the chief reason for their current clinical and commercial successes. These advantages include high levels of specificity for targets, reduced off-site toxicity, and the Fc region mediated efficacy benefits of induced cell death and extended serum half-life. In addition, depending on the chosen application of the drug, the potency and pharmacokinetic properties of these mAbs can be tailored via molecular engineering for optimal efficacy[7].

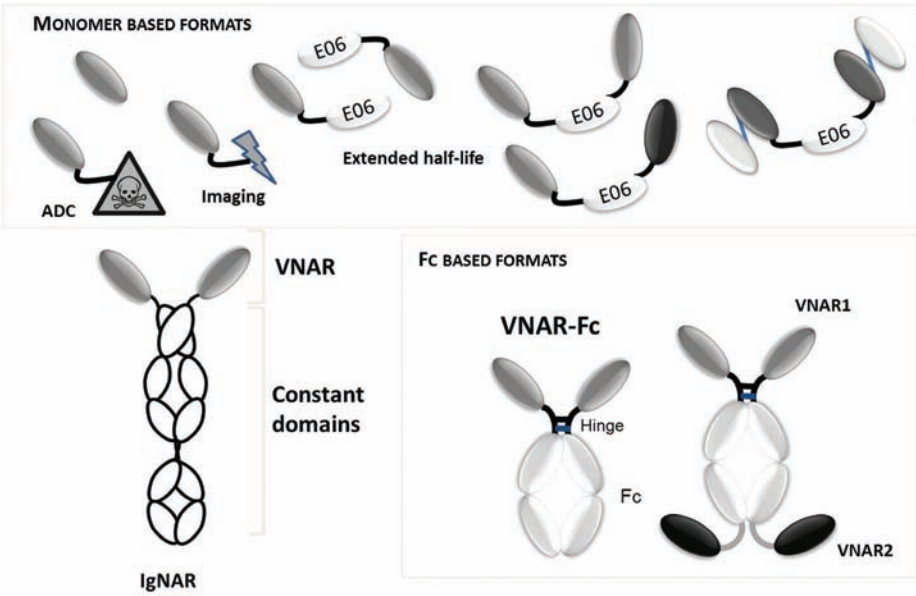
The potential for introducing non-natural but enhanced functionality into mAbs by engineering two different antigen binding sites (bispecific) or conjugating drugs (war heads) was realized decades ago, but the development of marketed products based on these formats has proved challenging[8]. Obstacles relating to design, engineering, manufacturing and preclinical evaluation of these more complex antibody domains have gradually been overcome. This has culminated in a number of new therapeutic platforms capable of generating bispecific antibodies and several antibody-drug conjugates (ADC) that are performing well in late stage clinical studies and attaining approvals. To date, these "double-headed magic bullets" have been utilized with success in oncology primarily for targeting cell-surface receptors involved in tumour cell growth or angiogenesis. They are capable of inducing apoptosis, or immunomodulation and include mAbs that target the same or two different antigens[9].

Although the clinical use of mAbs has undoubtedly changed the therapeutic landscape forever, biological constraints and important economic challenges limit their efficacy for certain indications and reduce their availability to patients[10,11]. Many of these commercial and biological limitations are directly related to the molecular size and complexity of the mAb structures and include: access limited to systemic targets or cell surface antigens following intravenous or subcutaneous administration, minimal tissue penetration or cryptic epitope accessibility, lack of oral availability and high manufacturing costs[6]. This list of limitations has been the driving force behind the discovery and development of "single-domain" drug programmes.

Until recently single chain Fv (scFv) fragments were thought to be the smallest antibody fragment with functional antigen-recognition capabilities. The discovery and subsequent development of the camelid VHHs (nanobodies) and shark variable new antigen receptors (VNARs) was predicated on a belief that a further decrease in the size of the minimal antigen-binding domain below that of the scFv to a single-domain format may deliver both therapeutic and commercial advantages. These novel antigen-binding single-domains, VHH and VNAR, possess an extended CDR3 loop region stabilized by interloop disulphide bridges to enhance stability, solubility and epitope interaction, including the recognition of cryptic binding sites[12,13]. At one-tenth the size of a mAb, they do not undergo spontaneous dimerisation. Their single-domain format, small size and simple molecular architecture makes them amenable to multiple re-formatting. Their single chain composition also delivers high stability under extreme conditions, enhanced tissue penetration, reduced immunogenicity, increased solubility and efficient expression in heterologous protein expression systems[14,15].

The VHHs were "discovered" in the early 1990s as naturally occurring single-domain antibodies in Camelidae (camels, dromedaries and llamas) and were shown to play a role in the adaptive immune system in these mammals[16]. The ability to raise

Figure 1. Schematic representation of VNAR domains illustrating their amenability to re-formatting and fusion at both N- and C- terminals.
ADC, Antibody Drug Conjugate; IgNAR, Immunoglobulin new antigen receptor; VNAR, Variable new antigen receptor; E06, Half-life extension VNAR bio-tool6.



antigen-specific nanobodies through immunization led to the isolation of VHH as possible drug candidates. Ablynx, a Belgium-based biotechnology company, successfully developed VHH domains against a number of targets. There are currently seven nanobodies in clinical trials[5], with more than 25 programmes spanning six major therapeutic areas, including infectious disease, cardiovascular, oncology, immunology, musculoskeletal and respiratory.

VNARs are the "new kids on the block" that exist naturally as high affinity binding domains; and whilst they share similarities in terms of their structure and properties with VHH, they are smaller and more stable proteins that have squeezed a fourth binding loop into their single-domain format. Nanobodies have evolved directly from an IgG lineage but have at some point undergone a truncation of the CH1 region resulting in the direct fusion of the VH domain to the hinge region and loss of their partner VL domain. In stark contrast, VNARs are not antibodies per se and are not derived from an antibody lineage and have never had or lost a partner VL domain. This ancestral difference between VHH and VNAR is not only of interest because it exemplifies an exciting piece of convergent evolution; it also puts the VNARs at a distinct commercial advantage in a complex patent landscape. VNARs are the smallest (known) naturally occurring antigen-specific binding domains in the vertebrate kingdom with a molecular mass of ≈ 12 kDa. They have a truncated CDR2 framework region with a long variable protruding CDR3, additional diversity present in CDR1 and two compensatory hypervariable (HV) regions where CDR2 would be found in an antibody[17]. Together this delivers the highest density of binding loops in any natural domain.

There are currently two established routes to VNAR generation and isolation. Utilizing either shark immunisation or direct selection from large and diverse synthetic VNAR libraries coupled with display technology, high affinity VNARs against multiple targets have been successfully isolated. Some of these targets include, Ebola virus, human serum albumin, TNF-a, ricin, cholera toxin and many others[8]. These studies have demonstrated a number of the advantages of the small VNAR structures such as accessing cryptic sites, reduced immunogenicity and increased stability, highlighting the potential therapeutic benefits such as improved tissue penetration and crossing the blood brain barrier. One important additional feature of VNAR is the ease with which they undergo molecular reformatting, as they are amenable to both N- and C-terminal fusions without any significant loss in activity (Figure 1).

Our team at the University of Aberdeen has successfully isolated VNAR domains against high profile therapeutic and half-life extension targets. The VNAR-based half-life extension bio-tool has the capability to increase the serum circulating time of a fusion VNAR partner from a few hours to weeks. This domain known as E06 was isolated form a spiny dogfish immunized with HSA and has shown efficacy across three different pharmacokinetic (PK) models[18]. Reducing administration frequency and dose of a drug is desirable for both patients and healthcare providers as it improves compliance, and limits therapeutic failure and the infection risk associated with multiple injections of biologics drugs.

To conclude, whilst biologic drug development, in particular mAbs, has begun a period of domination in developed world economies,we believe that a new wave of next-generation domain therapeutics based on small, stable and flexible drug scaffolds will deliver exciting opportunities in areas outside of the "sweet-spot" of traditional biologic therapies. VHHs are already in the vanguard of this biologics revolution with a number of candidate molecules performing well in later-stage clinical trials. Just as VHH will replace mAbs in certain areas, we also predict that VNARs derived from sharks may eventually supersede their VHH cousins for a number of clinical indications by offering further improvements in size, structure and stability, and commercial opportunity through the exploitation of non-antibody based patents.

Maybe one day, developing countries may also be able to enjoy the clinical benefits of the current biologics revolution we enjoy in the developed world as next generation single-domain biotherapeutics become more affordable, stable (in temperate regions) and even orally bioavailable.

Declaration of interest

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The authors declare no competing financial interest.

References

1. Cohen SN, Chang AC, Boyer HW, Helling RB. Construction of biologically functional bacterial plasmids *in vitro*. *Natl Acad Sci* USA 1973. 70:3240-4; PMID: 4594039.
2. Kohler G, Milstein C. Continuous cultures of fused cells secreting antibody of predefined specificity. *Nature* 1975. 256:495-7; PMID: 1172191.
3. Highsmith J. Biologic therapeutic drugs: technologies and global markets. BIO079B, BCC Research, Wellesley, MA 02481, USA; 2013.
4. Bosklopper E. Antibody drugs:technologies and global markets. BIO016H, BCC Research,Wellesley, MA 02481, USA; 2012.
5. Reichert JM. Marketed therapeutic antibodies compendium. *mAbs* 2012. 4:413-415.
6. Kovaleva M, Ferguson L, Steven J, Porter A, Barelle C. Shark variable new antigen receptor biologics – a novel technology platform for therapeutic drug development. *Expert Opin Biol Ther* 2014. (0):1-13.
7. Presta LG. Molecular engineering and design of therapeutic antibodies. *Curr Opin Immunol* 2008. 20:460-470.
8. Reichert JM. Bispecific antibodies and ADCs; Once and future kings? *mAbs* 2011. 3[4]: 329-330.
9. Demarest SJ, Hariharan K, Dong J. Emerging antibody combinations in oncology. *mAbs* 2011. 3[4]:338-351.
10. Chames P, Van Regenmortel M, Weiss E, Baty D. Therapeutic antibodies: successes, limitations and hopes for the future. *Br J Pharmacol* 2009. 157(2): 220-233.
11. Hansel TT, Kropshofer H, Singer T, Mitchell JA, George AJ. The safety and side effects of monoclonal antibodies. *Nat Rev Drug Discov* 2010. 9(4):325-338.
12. Desmyter A, Thomas R, Transue MAG, Minh-Hoa DT, Freddy P, Hamers R, Serge M, Lode W. Crystal structure of a camel single-domain VH antibody fragment in complex with lysozyme. *Nat Struct Mol Biol* 1996. 3(9): 803-811.
13. Greenberg AS, David A, Marianne H. A new antigen receptor gene family that undergoes rearrangement and extensive somatic diversification in sharks. *Nature* 1995. 374:168-173.
14. Roux KH, Greenberg AS, Greene L, Strelets L, Avila D, McKinney EC, Flajnik MF. Structural analysis of the nurse shark (new) antigen receptor (NAR): molecular convergence of NAR and unusual mammalian immunoglobulins. *Proc Natl Acad Sci* 1998. 95(20): 11804-11809.
15. Griffiths AD, Duncan AR. Strategies for selection of antibodies by phage display. *Curr Opin Biotechnol* 1998. 9:102-108.
16. Hamers-Casterman CTSGCENR, Atarhouch T, Muyldermans S, Robinson G, Hammers C, Bajyana Songa E, Bendahman N, Hammers R. Naturally occurring antibodies devoid of light chains. *Nature* 1993. 363(6428): 446-448.
17. Stansfield RL, Dooley H, Flajnik MF, Wilson IA. Crystal structure of a shark single-domain antibody V region in complex with lysozyme. *Science* 2004. 305:1770-1773.
18. Müller MR, Saunders K, Grace C, Jin M, Piche-Nicholas N, steven J, O'Dwyer R, Wu L, Khetemenee L, Vugmeyster Y, Hickling TP, Tchistiakova L, Olland S, Gill D, Jensen A, Barelle CJ. Improving the pharmacokinetic properties of biologics by fusion to an anti-HSA shark VNAR domain. *mAbs* 2012. 4:673-685.

About the authors

Obinna graduated from School of Pharmacy, University of Benin, Nigeria in 2006. He obtained his clinical internship training at the Federal Medical Centre Umuahia, Nigeria. After completing his one year compulsory national service he joined Boehringer Ingelheim in 2008. In 2010, he decided to return to his "first love" which is academia/research. Obinna was offered a place at the University of Aberdeen to study an MSc Clinical Pharmacology and Toxicology, which he completed in 2011 and he is currently a 3rd year doctoral candidate in biomedical sciences at the University of Aberdeen, supervised by Andy and Caroline.

Andy is Professor of Biotechnology and Director of the Scottish Biologics Facility, University of Aberdeen. His current research focuses on development of binding proteins from sharks (VNARs) and their use as site-delivered treatments for inflammatory disease and as protein drug conjugates for cancer therapy.

Andy was founder and CSO of Haptogen Ltd, acquired by Wyeth in October 2007. In 2005 he was made the Ernst and Young Plc, UK Science and Technology Entrepreneur of the Year. Andy is also on the Board of the University of Aberdeen spin-out NovaBiotics Ltd, an anti-infectives company that has two antimicrobial products in Phase II. In 2013 NovaBiotics announced a global licensing deal for its lead product with the US pharmaceutical company Taro Inc.

Caroline leads a team of senior scientists at the University of Aberdeen developing shark single-chain domains from initial lead isolation through to clinical candidate identification. Prior to setting up this team, Caroline was Head of Shark IgNAR Development in Pfizer and Wyeth where she was responsible for establishing robust platforms for the isolation of these binding domains and progressing pipeline candidates. Her first experience of developing shark domains was during her time with the antibody engineering spin-out company, Haptogen, where she was Programmes and Alliance manager. Caroline obtained her PhD in biochemistry at the University of Aberdeen and an MBA from Robert Gordon's University, Business School.

Will universities display logic about the importance of the Impact Factor? IF only!

Richard Green
University of Nottingham

The Impact Factor of the *British Journal of Pharmacology* (brjpharmacol.org) has now been published for this year and is 4.990, down from last year (5.067). Is that important? Most of us would question the significance of the third decimal place, and perhaps even the second, so rounding of these values to 5.0 and 5.1 demonstrates that the journal has continued to perform well and consistently and reaffirms its position as the best placed general pharmacology journal by far. However being below the arbitrary figure of 5.000 does influence those less able to evaluate the importance of these figures – university administrators – and this has an impact on scientists.

For some time major universities have demanded publication in 'top' journals, some using an arbitrary figure such as 5 to be the benchmark IF, and some are now even intimating that promotion might be linked, in part, to publication in journals possessing this magic figure. There are several points that should be made to refute this nonsense.

All established scientists have a good feel as to whether their work is likely to be accepted by a 'premier' journal or, although being interesting and solid, is more suited to a lower IF journal with a good reputation and appropriate readership. However universities' obsession with IF now means that work must first be submitted to a high IF journal, even if the scientists involved feel it is unlikely to be accepted. Consequently such journals are now flooded with papers that will never make the cut and as a result they are becoming more and more arbitrary about their decisions from the outset. I was recently told by a fellow pharmacologist that his paper was rejected by a major psychopharmacology journal, but was consoled by the editor with the comment that "at least it did go to reviewers"; some 70% of papers being rejected in an initial triage by the editors. Of those going to review only 10% were then accepted. That means a total acceptance rate of 3%.

Many papers to major journals are now being rejected for trivial reasons, since revision is often frowned upon because of the sheer number of submissions being dealt with. Consequently authors are unable to rectify or refute even small criticisms that could have been easily handled in the past. I would guess that editors of such journals would claim that its high IF attests to the quality of their approach; but since they can have absolutely no idea as to how often rejected papers might have been cited if revised and published, this is a spurious claim.

We should also question the ability of editors and referees to appraise the importance of papers they accept. A few years ago when I was a Senior Editor of the *British Journal of Pharmacology*, an experiment was conducted whereby referees and editors were asked to score the possible importance of each submitted paper, not for the purposes of acceptance/rejection but so that the score could be compared with the number of subsequent citations following publication (where 1= low importance; 2=medium and 3 = high importance). Subsequent analysis showed that, while there was a good correlation with medium score 2, there were an impressive number of proposed low importance papers being cited frequently, and many papers that the reviewers thought to be of high importance received embarrassingly few citations over the next few years. I doubt that the ability of reviewers and even editors to spot winners has now improved.

I would suggest that assessing the ability of research scientists by the journals in which they are able to publish is severely flawed. In my area of psychopharmacology there are several excellent journals with IF values well below 5, partly because top quality papers are spread out among them. However they are required reading for all psychopharmacologists. Surely if we are to judge a scientist by his publications it is the number of times the work is cited that is important, not the IF of the journal in which it is published? To illustrate this consider scientist A who publishes a paper in a journal with IF >5 that is cited three times over the next three years, versus scientist B who publishes a paper in a journal with an IF of 4 that gets cited 30 times over the same time period. I certainly know which scientist I think has made more of an impact. Furthermore the 'value' of a scientist publishing as one of a large team of authors in a high IF journal may be less than one publishing as, say, one of three authors in a journal with a slightly lower IF.

In the category pharmacy and pharmacology only 20 journals have an IF above 5.0 (versus neuroscience where 45 breach that figure). This means the number of top journals that any pharmacologist can select in their category is severely limited; particularly because only nine of the 20 are not review journals. The *British Journal of Pharmacology* is by far the highest general pharmacology journal ranking in the list at 21/245. The importance of general pharmacology journals is their wide availability and readership so their influence is substantial.

The Journal Citation Reports® also list other metrics and these reveal other impressive statistics for the journal. The five-year impact factor, surely a more valid figure than a one-year snapshot, is 4.994 ranking the journal 16/245. The Article Influence® score which measures the influence of each article over five years puts it in the top 20, while the EigenFactor® score which measures journals' total importance to the scientific community, puts it into the top five pharmacy and pharmacology journals. Finally, only five journals ranked above the *British Journal of Pharmacology* have a longer half-life (> 7.5) and only one (a clinical journal) is not solely a review journal, so work published in our journal remains important and citable to other pharmacologists for a long time.

The big problem for university pharmacologists is that administrators love numbers because they assume numbers give credence to their decision-making processes, and this includes 'measuring' the importance of research. Sadly in the case of the IF number this is not strictly true. From talking to others I suspect many of us realize this; the problem is getting the message across to the administration block.

About the author

Richard is honorary Professor of Neuropharmacology at Nottingham University, having previously worked for the MRC, Astra and AstraZeneca. He has been a member of BPS for over 40 years and was awarded an honorary Fellowship last year. He is a President Emeritus of the Society and is currently a Trustee.

BPS Meetings update

Barbara McDermott
Vice President-Meetings

Karen Schlaegel
Head of Meetings and Events

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

The British Pharmacological Society was represented by speakers, delegates, officers and a team from the Schild Plot at the congress in beautiful Cape Town. As a Gold Sponsor of the congress, the Society supported three symposia:

- Communicating with the public and the policy community
- Regulatory challenges In herbal and traditional medicines
- Using clinical toxicology studies to improve biomarkers and regulatory decisions

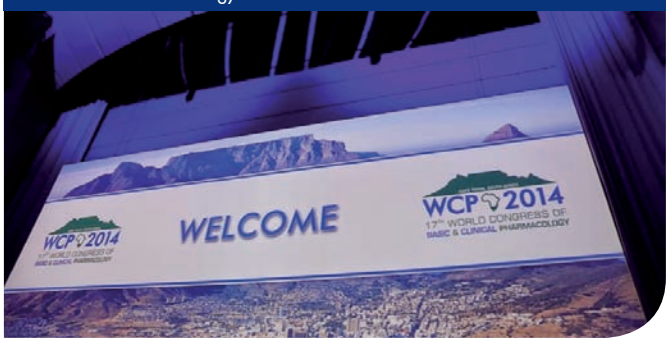
As well as plenary lectures by:

- Professor Simon Maxwell
- Professor Munir Pirmohamed
- Professor Salvador Moncada
- Professor Nicholas White

The BPS stand in the exhibition hall was busy throughout the congress and provided a great opportunity to catch up with members as well as providing information about the Society, and membership in particular, to delegates from all over the world.

The highlight was of course President-Elect, David Webb's presentation of the Society's successful bid to host the 19th IUPHAR World Congress of Basic and Clinical Pharmacology in 2022. Team BPS was delighted with the result and is now looking forward to organizing the congress in Glasgow in eight years' time.

BPS was a gold sponsor at the 17th IUPHAR World Congress of Basic and Clinical Pharmacology



David Webb presented the Society's successful bid to host the 19th World Congress of Basic and Clinical Pharmacology in 2022

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

Following on from the successful 2011 meeting *Biologics for the new millennium,* around 100 delegates came together in Cambridge to discuss the pharmacology of biologics for the treatment of respiratory disease. Internationally renowned speakers covered topics including molecular engineering of biologics, the utility of biomarkers for patient stratification and the clinical pharmacology of respiratory disease, and gave updates on recent clinical trials.

On the evening of the first day, the BPS Industry Committee organized a networking event. Steve Bates, CEO of the BioIndustry Association, and Ann Hayes, chair of the Industry Committee welcomed the delegates. Andrew Sandham, Partner of Syncona Partners LLP, a healthcare specialist investment company and independent subsidiary of the Wellcome Trust, gave a short presentation on "What is required to set up a biotech company/spin-out – perspectives from a healthcare investment company".

Feedback from speakers and delegates has been very positive and we would like to thank the Organizing Committee for delivering another excellent meeting!

Pharmacology 2014, 16–18 December 2014

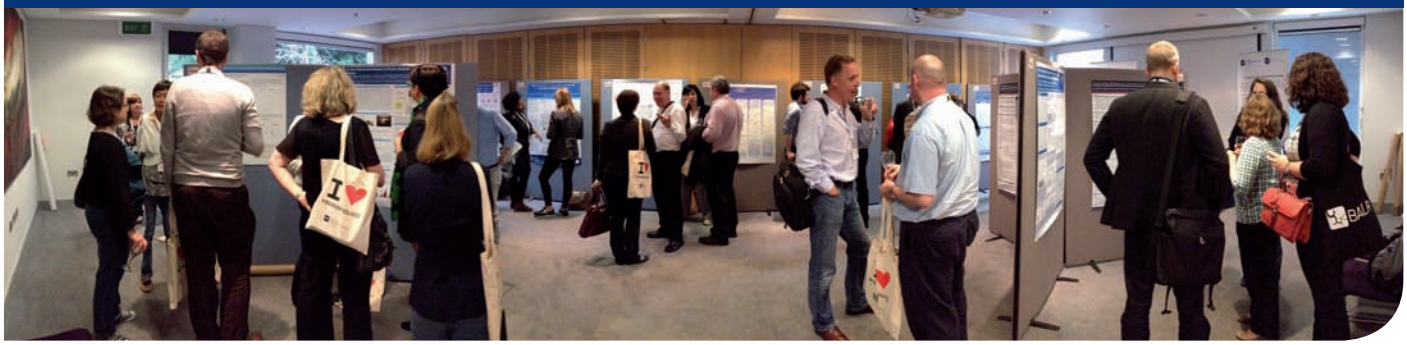
This year's meeting to be held again at the Queen Elizabeth II Conference Centre in Westminster has attracted a record number of abstract submissions – over 370 abstracts have been submitted by authors from 37 countries – confirming that the poster and oral presentations continue to be a valued component of the meeting. The abstract review process with view to publication on *pa2online* will take place on site and we would like to encourage all delegates to visit the poster and oral sessions and interact with the presenting authors.

We would also like to thank the sponsors and exhibitors – many of whom have been supporting the meeting for a number of years now. A special thanks to our Gold partner (Abcam®), our two Silver partners (Hello Bio and The Royal Society of Chemistry) and our four Bronze partners (ASPET, AstraZeneca, DMT and Wiley).

The programme incorporates twelve symposia on current topics in basic, translational and clinical pharmacology, and the following four plenary lectures:

- Lilly Prize Lecture: Clinical pharmacology in the poisons unit
  Professor Nick Bateman, University of Edinburgh
- AstraZeneca Women in Pharmacology Prize Lecture:
  Breaching barriers: Junctures and junctions in inflammation
  Professor Sussan Nourshargh, Queen Mary University of London
- Gaddum Memorial Award Lecture: Receptors as an evolving concept: From switches to biased microprocessors
  Professor Terrence Kenakin, University of North Carolina
- Gary Price Lecture: Agonist efficacy — the view from the single receptor
  Professor Lucia Sivilotti, University College London

Delegates came together to discuss the pharmacology of biologics for the treatment of respiratory disease



BPS Affinity Groups

The Meetings Committee recently launched the following seven Affinity Groups:

- Cardiovascular and Respiratory
- Drug Discovery, Development and Evaluation
- Education and Skills
- Integrative and Systems Pharmacology
- Molecular and Cellular Pharmacology
- Neuropharmacology
- Toxicology

The process of appointing co-chairs for each of them is currently taking place. Thank you to everyone who has sent in an application. The Meetings Committee along with the appointed chairs will then develop a strategy as to how the Affinity Groups can help encourage and support member involvement with the Society's activities and keep members up-to-date with development in their research areas. All members can sign up to one or more of the Affinity Groups relevant to them in the Members' Area of the website (*services.bps.ac.uk*).

The year ahead:

Festival of Neuroscience, 12-15 April 2015, Edinburgh

BPS is again a partner society at the British Neuroscience Association Festival of Neuroscience and is supporting the session *Brain cannabinoid system: a new therapeutic frontier in brain repair* organized by Francisco Molina-Holgado.

Focused meeting: Exploiting the new pharmacology and application to drug discovery, 20-21 April 2015, Edinburgh

This meeting will focus on new concepts and developments in pharmacology and how these can be exploited in drug discovery including: new strategies for targeting calcium channels, tyrosine kinases, microRNAs, epigenetics, new developments in monoclonal antibodies, allosteric modulators, biased signalling, and receptor structure. The meeting will include invited expert speakers, contributed free communications and poster presentations – with prizes for young investigators.

Joint ASCEPT-BPS Scientific Meeting: Tomorrow's medicines: pharmacology, patients and populations, 19-21 May 2015

Online registration and abstract submission are now open for this joint meeting, which will be held at the University of Hong Kong and in association with the Hong Kong Pharmacology Society (HKPS) and the Asia Pacific Federation of Pharmacologists (APFP). Adina Michael-Titus, from Barts & The London Medical School, will be opening the meeting with the BPS keynote lecture on *Neuroprotection: challenges for the 21st century.*

Bursaries are available for BPS members presenting at the meeting – so remember to submit your abstract before the deadline of 30 January 2015. Further information can be found at *http://ascept-bps2015.com/*

Other meetings

Two further meetings will also be held: one with the Austrian Pharmacological Society in Graz in September and the other with the British Toxicology Society in October 2015. Next year will end with the flagship annual meeting *Pharmacology 2015*, of course. Please visit the BPS website (*www.bps.ac.uk*) for further information.

Last but not least we would like to highlight the bursaries that BPS makes available for members presenting at BPS meetings as well as at external, pharmacology-related meetings. BPS aims to give financial support to all eligible applicants and gives out £50,000 in travel awards each year (applicants are expected to have been a member of the Society for at least a year). The Meetings Committee is also running a sponsorship scheme for external meetings. All information regarding the application process and deadlines can be found at *www.bps.ac.uk*.

As always, if you have any questions or suggestions or would like to get involved with the BPS meetings, please do not hesitate to contact us at *meetings@bps.ac.uk*.

We look forward to seeing you at *Pharmacology 2014* in London!

Feedback from speakers and delegates who attended Inspired Biologics has been very positive

Young Pharmacologists update

Maria Fernandes
Editor, *Pharmacology Matters*

Young Life Scientists Symposium

In early October, the British Pharmacological Society along with the Biochemical Society and Physiological Society supported a Young Life Scientist Symposium, organized by early career researchers at King's College London. The symposium *Current progress on the physiology and pharmacology of TRP channels* had an excellent scientific programme and included a fascinating lecture on outreach activities – including sending experiments to the International Space Station! One of the organizers, Dr Khadija Alawi provided an overview:

> *"We had over 80 delegates attend, and the day was packed with exciting seminars and lectures. We even went to Masala Zone after the symposium to keep up the 'TRP' theme and it was an enjoyable and delicious evening. We learned how challenging it is to organize a conference, how to successfully liaise with companies for sponsorship and how to efficiently plan our time."*

Teaching awards

Our 3rd annual Welcome Reception will take place during *Pharmacology 2014* on 16 December 2014 at Church House. The reception will include the inaugural Excellence in Pharmacology Teaching Awards, where students from four shortlisted universities across the UK will try to convince the judging panel why their choice of lecturer should win! Good luck to all nominees: Dr Christine Edmead, University of Bath, Dr Kirsten Pugh, Cardiff University, Dr Sohag Saleh, Imperial College and Dr Ian McFadzean, King's College London. Buy your ticket for the Welcome Reception when you register for *Pharmacology 2014* to see who will win! The evening will also offer a chance to network, including canapés and classical musical from a string ensemble.

The importance of communicating our research: The bigger picture

Earlier in the year, after finishing his PhD in pulmonary pharmacology, Young Pharmacologists Committee member Dr Dan Reed was invited to speak at a patient conference for patients with pulmonary hypertension. Despite having an excellent scientific experience during his studies with Professor Jane Mitchell, he was not prepared for meeting patients:

> *"My experience at this meeting was something very different to any other meeting I had attended and, in many ways, has changed my view of what it means to be a research scientis. Pulmonary hypertension is a devastating and fatal disease. Of course, I knew this from my reading and thought I understood what that meant. However, in meeting patients with this disease I was humbled, touched and inspired. This experience and the feedback I have received has truly changed my perspective on why we do research and how we communicate what we find."*

Get involved!

Since its inception, the Young Pharmacologists Committee has fundraised for World Congress of Basic and Clinical Pharmacology bursaries, created videos on how drugs work, contributed symposia to *Pharmacology 2014*, attended Society strategy meetings and parliamentary receptions, and judged symposia and award applications. Getting involved doesn't have to be a huge commitment, but it can provide so much experience and helps to widen your network particularly for early career researchers. If any of these activities take your interest consider volunteering for the Society, whether that be contributing to an outreach event or applying to join a committee. Update your profile at *services.bps.ac.uk* or contact *info@bps.ac.uk* for more information.

Prize winners from the Young Life Scientists Symposium. From left to right: Tue Banke, Rebecca Clarke, Antonio Soares, Caitriona O'leary and Hannah Wilson

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Student Contribution to Pharmacology Prize

The British Pharmacological Society's Education and Training Committee has established a number of university-based prizes. The prizes are intended to enable universities offering medicine or undergraduate bioscience degrees, containing substantial amounts of pharmacology, to recognise the efforts of a final year student who has contributed most to the discipline of pharmacology.

The type of contribution might include involvement in a student society or volunteering at outreach or open day events. The Society is dependent on members who are enthusiastic about their discipline and willing to contribute to the activities of the society. These prizes reward altruistic tendencies in our student members.

The winners of the Student Contribution to Pharmacology Prize 2014 are:

Mike Daniels, Leeds University who was nominated by Dr Dan Donnelly

Mike Daniels was an excellent final year student representative for the Pharmacology cohort that graduated in 2014. His enthusiasm for the subject of Pharmacology was clear to both staff and students throughout his time at Leeds. Mike had a very successful placement year at MedImmune, where he met two other pharmacologists (from Glasgow and Bath) and set up "OpenBio" (www.openbio.co.uk/), with the aim of making breakthroughs in the biological sciences intelligible to other students and to the general public. There are even ambitions for an OpenBio Journal where undergraduate and graduate students can share some of their original research.

Ana Martinez Carron, King's College London who was nominated by Professor Sue Brain

Ana graduated in July 2014 with a first class degree in Pharmacology and Molecular Genetics with extramural year. Over 50% of her degree involved pharmacology courses. Ana has been Treasurer of the student pharmacology society for 2013/14. Her aim was to make the society financially self-sufficient, which had not previously been possible. She attracted funds, including from BPS. She provided a rigorous approach towards finance, ensuring that the Society produced an interesting programme whilst staying in budget. Ana and her colleagues delivered a well-attended programme and a legacy for the incoming society officials.

These prizes will be awarded by the recipient universities at degree or graduation ceremonies.

If you would like to award this prize to a student in 2015, please contact the BPS Education team (*education@bps.ac.uk*).

Ana Martinez Carron and family celebrate her winning the Student Contribution to Pharmacology Prize

Ana Martinez Carron (far right and celebrating with her family) received her Student Contribution to Pharmacology Prize at the King's College London prize giving ceremony

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ETRIS: Facilitating research and training in *in-vivo* pharmacology

Dave Lewis
University of Leeds

Considerable funds have been provided over the last ten years by the *British Pharmacological Society*, the pharmaceutical industry, Research Councils, charities and Government to address the shortage within the UK of individuals with the knowledge, skills and expertise to undertake *in-vivo* pharmacological research. These funds have been utilised for initiatives which include the provision of "New Blood" lectureships, capacity building Centres of Integrative Mammalian Biology, additional funding to support PhD studentships, short courses in *in-vivo* physiology and pharmacology and support for undergraduate *in-vivo* education modules[1].

However, whilst funding for the majority of these initiatives has either ceased or is coming to an end, there is still a need to provide an education and training in *in-vivo* pharmacology, not only for colleagues new to the discipline but also established researchers. Both EU Directive 2010/63/EU[2] and the amended Animal (Scientific Procedures) Act, 1986[3] require continued on-the-job training and CPD throughout an individual's career. Whilst the use of research animals for training and the maintenance/improvement of skills for all researchers is now a permissible purpose under the amended Act[3], this use should be only where absolutely necessary and following other training methods. Initial or refresher training could also be provided through the use of digital learning objects or open educational resources.

Whilst many excellent *in-vivo* e-learning resources have been developed, significant numbers are locked behind the websites of institutions, commercial or professional organisations, only available to members or subscribers. Those that are freely available are often unknown to the community. To address this problem of lack of awareness, ETRIS (Educational and Training Resources in *In-vivo* Sciences, *www.etris.leeds.ac.uk*), a website which directs individuals to free, open access, or open educational *in-vivo* e-resources was developed. ETRIS is an open access website, free to use, with no registration or login required; its objective to provide education, training or to facilitate research in *in-vivo* pharmacology. Resources were discovered following an open call to colleagues, searches of educational and animal welfare websites and resource repositories, ETRIS's developers' own knowledge of available resources and an online search. To promote adoption and use by colleagues, individual resources are accompanied by a descriptive paragraph which outlines what is in the resource, its provenance, copyright or access restrictions and suggested usage or audience. Resources are grouped into thirteen categories including animal handling and restraint, genetically modified animals, minor procedures, ethics and the 3Rs. Additional categories will be added as the website expands.

Individual resources are vetted using my knowledge and expertise in *in-vivo* pharmacology, animal welfare, ethics and the 3Rs, and current legislation prior to inclusion to ensure compliance with best practice in the 3Rs and animal welfare legislation. The reputation and standing of the resources author in the field is also taken into account in this process.

Get involved

Our vision is for ETRIS to be a living repository which grows as colleagues submit more resources for inclusion, increasing its usefulness. If you have any e-learning or training resources, including, but not restricted to, videos, podcasts, guidance notes, software or educational protocols that you are willing to share or know of any relevant resources on open access websites, please contact me, Dave Lewis at: *3Rs@leeds.ac.uk*. Resources do not have to fall within existing categories. To realize the maximum benefit of the repository, we also want ETRIS to be adopted and, more importantly, used by *in-vivo* pharmacologists and physiologists across the globe. Therefore please use ETRIS, link to it from your Institutional or company Biomedical Services or Home Office websites, share the site with your colleagues in the UK and abroad. Your feedback on the site or individual resources would also be appreciated.

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References

1. Collis M.G. (2006) *Nature Reviews Drug Discovery* 5, 377-380
2. European Union (2010) Directive 2010/63/EU. Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:276:0033:0079:en:PDF
3. Home Office (2012) Animal (Scientific Procedures) Act, 1986. Available at: http://www.legislation.gov.uk/ukpga/1986/14/contents

About the author

Dave is Senior Lecturer in Neuroscience and Bioethics at the University of Leeds. After graduating in Pharmacology from the University of Leeds, he undertook PhD and post-doctoral studies investigating the central pathways controlling the cardio-respiratory systems with John Coote at the University of Birmingham. Returning to Leeds, his research centred on the hindbrain pathways controlling the gastrointestinal system. More recently, he has focused on student education and public engagement activities, developing innovative, research-led teaching, which is not normally found in the curriculum, yet addresses a clear demand from employers.

Dave has substantial involvement in the development of education and training in in-vivo pharmacology. He Chairs the IUPHAR IOSP initiative, the BPS In-vivo Pharmacology Training Group and is a council member of LASA. He was awarded a University of Leeds Teaching Fellowship in 2010, the BPS Rang Prize in 2012 and the Physiological Society's Otto Hutter Teaching prize in 2013.

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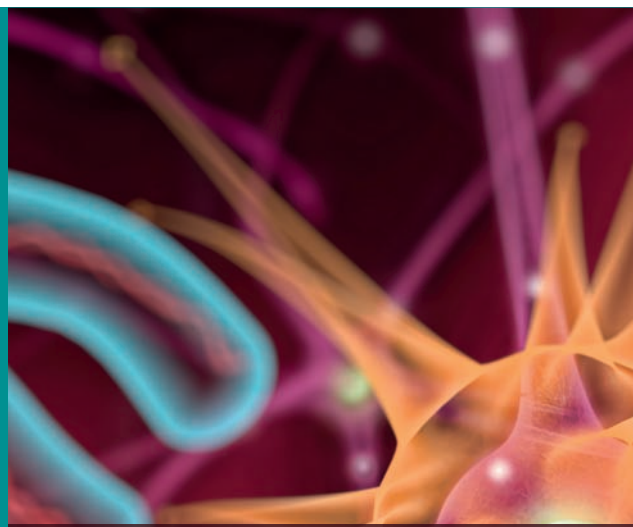

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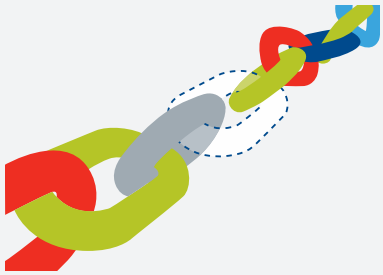
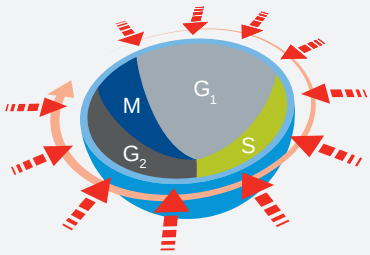
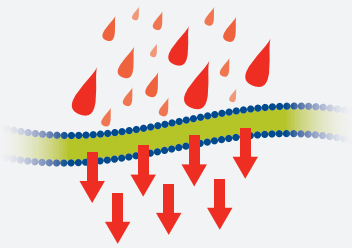


Low compromise to protein-protein interactions

Range of selectivity

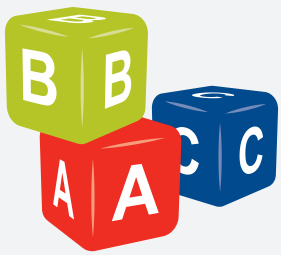


Rapid effects for temporal control



Cell-permeable and blood-brain barrier permeable options

Reversible and long-term effects



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