DDT Vol. 7, No. 20 October 2002

Anti-infectives in the 21st century

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There has been considerable interest in antibiotic resistance as a result of the media attention surrounding recent condemning hospital reports. *Anti-infectives: The Way Forward*, organized by the Institute of Biology and the Royal Pharmaceutical Society, brought together a range of people whose work relates to antibiotic resistance. The meeting was held on 8–9 July 2002 (London, UK).

The problem of resistance

In 1998, the House of Lords produced a report entitled *Resistance to Antibiotics and Other Antimicrobial Agents* [1], which detailed the extent of the problem that we faced at that time. Lord Soulsby of Swaffham Prior (Chairman of the House of Lords Select Committee on Science and Technology; http://www.parliament.the-stationery-office.co.uk) introduced the problem of resistance to anti-infectives and described the venture by the Committee to address this problem. Since the report, there have been several meetings at DEFRA concerning food additives and growth promoters in livestock feed, and the relation of these to the increasing resistance to antibiotics in the human population. The occurrence of new infections, such as *Campylobacter* spread by companion animals, highlights this problem. Antibiotics were one of the most important medical advances of the 20th century but the ever-increasing bacterial resistance is alarming. Important requirements for the control of this scourge are its surveillance and a co-ordinated effort to minimize its spread.

The national problem of resistance was addressed by David Livermore [Antibiotic Resistance Monitoring and Reference Laboratory, Public Health Laboratory Service (ARMRL, PHLS); http://www.cphl.phls.org.uk]. Resistance in the UK remains lower than in some countries; however, in the case of methicillin-resistant *Staphylococcus aureus* (MRSA), the UK has the highest rate of infection (at ~43%). Livermore stated that the fourth certainty of life (after birth, death and taxes) as that if we use antibiotics, we select for resistance. The Scandanavian countries have low overall rates for resistant bacteria, which reflects their conservative prescribing of antibiotics. One question regarding these bacteria is, 'How do certain strains survive and become resistant, when others do not? Is it all a question of chance, time and opportunity?' in the UK, MRSA is the biggest problem and the reasons for clonal success are still uncertain.

Philip Jenkins from the World Health Organization (WHO; http://www.who.org) gave a global perspective of antimicrobial resistance, with infectious diseases accounting for 45–50% of deaths up to the age of 44 years. The majority of these deaths (85%) are caused by five diseases: respiratory infections, diarrhoeal disease, AIDS, tuberculosis (TB) and malaria. The big problem with resistance is that it is irreversible and the flow of new drugs is drying up, with a timeline of ≥10 years before a new drug comes to market. WHO is aiming to focus on six key areas in an attempt to combat this increasing problem, including access to antimicrobials, appropriate use, increased surveillance and rapid diagnostics.

In the final talk of this session, Tom Humphrey from the Division of Food Animal Sciences at the University of Bristol (http://www.bris.ac.uk) introduced the subject of resistance in animals and whether this was a problem for humans. This risk of developing resistance is greater with herd treatments and it is often found to be cheaper to kill infected animals than to treat them. Guidelines to preventing antibiotic selection is to eliminate the prophylactic use of antibiotics and to introduce minimum requirements for therapeutic use.

New drugs, targets and modalities

Ian Chopra (Antimicrobial Research Centre, University of Leeds; http://www.leeds.ac.uk) gave a brief history of antibiotic discovery, starting with penicillin in the 1930s, which led to the 'golden era' of antibiotic development in the 1940–1960s, to the explosion of the conventional antibiotics in the early 1980s. However, even from the earliest use of these drugs, resistance was known. Ways to develop novel drugs to treat infections were presented: expanding a known class of drug, as achieved using the tetracyclines with third generation drugs currently in Phase II trials; to protect a known class by using a resistance inhibitor, which has the disadvantage of inevitable evolution of inhibitor resistance; develop previous discoveries, such as natural products or synthetic compounds. Alarmingly, all possible molecular targets might already have been screened, which means that the next group of agents could be the last.

Challenges and opportunities in antivirals were presented by Graham Darby (formerly GlaxoSmithKline; http://www.gsk.com) with a focus on new targets for novel antivirals. Of the ~30 drugs that are currently approved in the UK and USA, the majority is for use against herpesvirus or HIV, and are replicase- or protease inhibitors. There are a few recent antivirals against influenza and hepatitis B; however, more of these are needed.

Fresh approaches to the problem of multidrug resistance (MDR) are certainly required, with the changing pathogen

  PII: S1359-6446(02)02475-3

spectrum (i.e. TB on the increase and polio almost eradicated), therapeutic advances for immunocompromized individuals and the controversy that currently surrounds immunization (e.g. the MMR triple vaccine), said Peter Taylor (School of Pharmacy, London, UK; http://www.ulsop.ac.uk). New potential approaches include photodynamic therapy, phenotype modification, gene transfer mechanisms, nucleic acid targeting, and reconsideration of bacteriophage therapy.

Case studies

Two case studies were presented: *Challenges in Tuberculosis therapy* by Sunita deSousa (AstraZeneca, India; http://www.astrazeneca.com) and *Antivirals* by Maria Zambon (Enteric and Respiratory Virus Laboratory, PHLS). According to deSousa, therapies that are currently used for TB were discovered 30 years ago. A third of the world is infected and treatment currently lasts for at least six months. Major issues are compliance and resistance. New compounds and novel approaches offer some hope and current genomics and proteomics approaches could help identify novel targets. Zambon spoke about neuraminidase inhibitor (NI) resistance and the burden of the disease caused by influenza. Mutations in viral haemagglutinin reduce the requirement for neuraminidase activity, and decrease the virus infectivity, although it is unclear whether this leads to NI resistance *in vivo*. The future will provide important information on the impact of NI drugs on influenza virus evolution.

State-of-the-art drug development

The final talk of the day, by David Payne (GSK), focussed on genomic screening and the ability to sequence entire pathogen genomes, which enable us to identify genes and gene products that are essential to bacterial growth. From this plethora of targets, the aim is to develop completely new antibacterial drugs with novel molecular architecture and novel modes of action.

In the clinic

The second day of the symposium started with a talk by Stephen Gillespie (Royal Free and University College London; http://www.ucl.ac.uk) who described the changing pattern of MDR. The acquisition of MDR in a hospital environment is a result of widespread antibiotic prescription and lateral gene transfer. Resistance is an ever increasing problem, from the first anti-malaria drug quinine, which was introduced into Europe in the 1640s and remained free from resistance until 1910, to the present situation where resistance can develop in a few years.

Resistant Gram-positive cocci and Gram-negative bacteria were presented by Neil Woodford (ARMRL, PHLS) and Laura Piddock (Department of Infection, University of Birmingham; http://www.birmingham.ac.uk), respectively. Woodford described the evolution of bacteria and how we are doing all the running but are staying in the same place in terms of combating this problem. Since the evolution of MRSAs, two strains (EMRSA-15 and -16) have been particularly problematic in the UK, but the reason for their success is unknown. Genomics approaches have identified 96 possible candidates, on the *S. aureus* genome, for novel antibiotic discovery. Piddock described fluoruinolone resistance in *Campylobacter*, which is the most common cause of gastroenteritis in developed countries with half a million cases per year. The *Campylobacter* genome has been sequenced and was found to be a quarter of the size of that of *Escherichia coli*, with genes being used for multiple functions.

Prescriptions and resistance

The practise of prescribing antibiotics was addressed Peter Davey (Medicines Monitoring Unit at Ninewells Hospital; http://www.dundee.ac.uk) who spoke about hospital prescribing in UK hospital settings. Progress of the European Surveillance of Antibiotic Consumption (ESAC) project (http://www.uia.ac.be/esac/index.html) was reviewed and problems with ward-based data analysis were described. The definition of prudent antibiotic prescription was, 'the use of antimicrobials in the most appropriate way for the treatment, or prevention, of human infectious diseases…'. Targets for action by ESAC include educating main prescribers, implementing support systems and the surveillance of antibiotic use.

Nick Barber from the School of Pharmacy (London, UK) enrolled a volunteer to partake in an enlightening role-play of a patient–doctor consultation, where antibiotics were prescribed almost unnecessarily. Prudent community prescribing depends on the balance between three issues: the scientific properties of the drug, patient requirements and the 'greater good' (this includes the overall reduction in resistance and maintaining patient–doctor relationships).

The clinical impact of veterinary prescribing was reviewed by David Burch (Octagon Services; http://www.octagon-services.co.uk). Food producing animals are treated with growth promoters and antimicrobials, and companion animals are given increasing amounts of antibiotics like their human counterparts. The emergence of a vancomycin-resistant strain of *S. aureus* as was recently reported in the national press is an ill omen of times to come.

Future implications

The final session of the day focussed on holistic approaches and complementary medicines and questioned our approach to this ever-increasing threat. Jeremy Hamilton-Miller (Royal Free) spoke about the treatment of the whole person, including mental and social factors and described antibiotic resistance as 'evolution in action'. In 1950, the emergence of resistance was described by L.P Garrod, so it should not have come as a great surprise when problems were seen in the 1980s. The use of complementary medicines was also emphasized, with

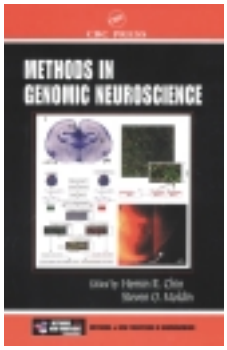
physicians keeping an open mind regarding treatment practices: homeopathy, herbal medicine and dietary supplements. On an optimistic note, Hamilton-Miller said: 'We can beat bacteria…we have the brains and the technology'.

S. Amyes (Medical School, University of Edinburgh; http://www.edinburgh.ac.uk) examined whether we are doing enough to stop the increase in resistance. New antibiotics will come either from serendipity, as with penicillin, by the modification of old drugs, or by novel techniques such as genomics.

Finally, the conference was summarized in a session led by Richard Wise (City Hospital, Birmingham, UK). Governments had addressed this issue 30 years ago but since then only one new class of antimicrobials has been introduced. The output from genomics is slow, with a 10–12 year lead-time for new drugs. The barrier to going forwards in this fight is the resistance itself.

Reference

1 House of Lords Science and Technology – Seventh Report (1998) *Resistance to Antibiotics and Other Antimicrobial Agents.* (Available online at http://www.parliament.the-stationery-office.co.uk/pa/ld199798/ldselect/ldsctech/081vii/st0701.htm)



Methods in Genomic Neuroscience

Edited by Hemin R. Chin and Steven O. Moldin
CRC Press, 2001,
Price: $119.95,
ISBN 0-8493-2397-5

Over the past two decades, advances in molecular genetics have increased exponentially, leading to an enormous wealth of genomic information resulting in the publication of the complete genome of several organisms including *Caenorhabiditis elegans* and *Drosophila melanogaster.*

The arrival of the first working drafts of the human genome, hailed as the 'book of life', has, in particular, created major excitement. Novel ways of using this new information are emerging, with the hope that many unsolved problems in basic and clinical science can be more fully explored, no more so than in the field of neuroscience.

Methods in Genomic Neuroscience, edited by Hemin Chin and Steven Moldin, both eminent scientists in genetics as applied to neurobiology, is part of the *Methods and New Frontiers in Neuroscience* series of books that attempts to present new and exciting experimental techniques and concepts to the neuroscientist. This particular volume explores the application of molecular genetic techniques to neuroscience and contains chapters contributed to by 46 experts in the field.

The first section of the book introduces the basic concepts of inheritance, mutations and genetic manipulation in a clear and simple way that is easily understood by the novice molecular biologist. In particular, the various types of transgenic mice and methods of generating them are clearly described in the chapter by Mark Mayford and Eric Kandel, with some interesting case studies to illustrate the points.

The next section covers the application of genome-wide mutagenesis strategies such as *N*-ethyl-*N*-nitrosurea (ENU) and telomeric repeat amplification protocol (TRAP), and how these techniques can be used to enhance our understanding of several aspects of neuroscience, from brain development and axon projections to complex behaviours. The chapter by Mitchell *et al.*, is accompanied by beautiful illustrations of the effects of various mutations in developmental genes in mice, such as ADAM 23 and KST27, as well as axon guidance defects in EphA4 mutants.

The development of high-throughput systems to measure expression profiles of the entire genome in a global fashion, namely cDNA arrays, has been a major technological advance in the field of molecular biology. This book adequately acknowledges the power of this emerging technology and describes it in a detailed and thoughtful way, covering all aspects from constructing the arrays to analyzing the enormous amount of data that is generated, and pointing out the many pitfalls along the way! cDNA expression arrays have already been used to analyze the gene expression differences in patients with schizophrenia as described by Mirnics, Lewis and Levitt, and no doubt will be an important technique in the study of a variety of other neurological diseases with some genetic susceptibility such as multiple sclerosis as demonstrated recently by Lock *et al.* [1].

The following section (Section Four) contains an eclectic collection of topics ranging from methods of delivering genes to neural tissue to the use of neural stem cells in genetic analysis and brain repair. Although the majority of chapters in this book contain limited methodological descriptions, the chapter by Hida *et al.* consists almost entirely of an experimental protocol for the generation of a full-length cDNA library, making it stand out from the rest. The book concludes with two interesting chapters, which look at identification of disease susceptibility genes and the analysis of individual genetic variation in complex traits, which could provide a foundation for the development of individually tailored drug targets and interventions, so called 'pharmacogenomics'.

  PII: S1359-6446(02)02400-5